Bronchodilator test in extreme old age: Adverse effects of short-acting beta-2 adrenergic agonists with clinical repercussion and bronchodilator response

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INTRODUCTION

The geriatric population has been increasing in Brasil and worldwide as a result of the decline in fertility and the significant increase in life expectancy³. It is estimated that, by 2050, the “fourth age” population (≥85 years) will have more than tripled worldwide⁵,⁶ and, in Brasil, the extremely elderly population (≥90 years) will go from 394,000 in 2010 to around 3.5 million by 2050³.
The prevalence of respiratory diseases and symptoms, such as cough and dyspnea, increases in the elderly population, so diagnostic investigation is required for the appropriate medical decision-making\textsuperscript{4,5}.

Spirometry is the pulmonary function test most available and used in clinical practice to screen for respiratory diseases, and the bronchodilator test should be an integral part of the spirometry to aid in the diagnosis, treatment, and therapy follow-up of different respiratory pathologies\textsuperscript{6-9}.

The chronological age is questioned as a limiting factor to properly perform spirometry\textsuperscript{10}, and there is some insecurity from the lay population and even from health professionals regarding the use of short-acting beta-2 agonists on elderly people and/or with heart disease\textsuperscript{11,12}, even in a single dose for an additional examination.

The goal of this study was to assess if the chronological age is a limiting factor for performing the bronchodilator test, determine the adverse effects with significant clinical significance of short-acting beta-2 agonists, and evaluate the bronchodilator response of spirometry in the fourth age.

**METHODS**

This is a retrospective study conducted at the University of Tiradentes (Unit), in the city of Aracaju (SE).

The sample was extracted from the database (spirometer and respiratory questionnaire) of a private laboratory of pulmonary function, from January 2012 to April 2017.

The research was approved by the Research Ethics Committee of Unit (CAAE: 67734717.2.0000.5371). There were no conflicts of interest.

The standardized respiratory questionnaire used in the spirometry assessed the anthropometric and demographic factors, respiratory symptoms, smoking, comorbidities, lung diseases and previous heart diseases, professional history, previous surgery and intubation, medications in use, clinical indication, and identification of the physician who requested the exam.

The study included patients ≥87 years of chronological age and excluded those ≤86 years.

In the first stage of the research, to assess the adverse effects of the inhaled bronchodilator, we considered only the first spirometry of each patient.

In the second stage, we evaluated the bronchodilator response of the patients who underwent the bronchodilator test. Based on the diagnosis of the request for the spirometry test by the assistant physician and on the respiratory questionnaire, for purposes of statistical evaluation of the bronchodilator response, the patients were divided into two groups: obstructive respiratory disease and non-obstructive. Then, in order to assess the influence of chronological age on the bronchodilator response and significant adverse effects, patients were divided into two groups, one from 87 to 89 years old, and another ≥90 years. Exams that did not meet the criteria for acceptability and reproducibility were excluded\textsuperscript{6}.

Spirometry tests were performed in the same room, using the same spirometer with a pneumotachograph coupled to a computer (model Microlab-3500; Micro Medical Ltd., Kent, England), where the tests were saved, which allowed to retrieve individual exams stored by means of menu selection. Each exam was evaluated regarding flow-volume and volume-time curves, and the conventional spirometric variables, such as forced vital capacity (FVC), forced expiratory volume during the first second (FEV\textsubscript{1}), FEV\textsubscript{1}/FVC ratio, peak expiratory flow (PEF), and middle expiratory flows\textsuperscript{33}.

The technical rules for examinations, criteria for acceptability, reproducibility, and interpretation of the spirometry test were determined according to the guidelines of the Brazilian Society of Pulmonology and Phthisiology\textsuperscript{8}, and interpreted by the same pulmonologist, associated to the SBPT, and certified on spirometry.

The spirometry results were classified based on the lower limit of normality for the FEV\textsubscript{1}, FVC, and FEV\textsubscript{1}/FVC ratio. The bronchodilator test was considered with a significant variation when there were elevations of the FEV\textsubscript{1} and/or FVC ≥200 ml and 12\%, and variations in volume, flow, or both, in relation to its initial value\textsuperscript{34}.

Soon after the completion of the initial spirometry, the bronchodilator test was performed by inhaling 100 mcg sprays of salbutamol from a inhaler coupled with a spacer, repeated sequentially after an interval of 15 to 30 seconds, between maneuvers, four times, totaling 400 mcg salbutamol. Then, the patient remained at rest for 15 to 20 minutes to repeat the spirometry after the use of the bronchodilator. The following were observed and considered adverse reactions with significant clinical repercus-
sion from the use of salbutamol: induction of heart arrhythmia, coronary failure, heart failure, hypertensive crisis, cardiac arrest, and respiratory failure. The adverse effects were observed immediately after inhaling the bronchodilator drug during the waiting period to repeat the exam and after the exam was completed, when the patients were cleared to go home. Minor adverse effects, without clinical repercussions or increased risk to patients that justified a contraindication to the bronchodilator test, such as tremors, reflex tachycardia, palpitations, flushing, and headache, were not taken into account.

The statistical analysis was performed using the Statistical Package for Social Sciences, version 21.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were described as mean and standard deviation, and categorical variables were summarized by means of simple and relative frequencies. The chi-square test was used to assess the differences in bronchodilator response between the groups of patients. The significance level adopted was p<0.05.

### RESULTS

Among the 4,126 spirometric tests performed during the period evaluated, 77 (1.86%) were of elderly individuals ≥87 years. Two patients were excluded from this study for having repeated the exam. In total, we selected for this study 75 patients with a mean age of 89.34 ± 0.29 years (CI 95% 88.74-89.94), minimum age of 87 years, and a maximum of 97 years, predominantly females (58.7%, 44/75). There were 61.3% (46/75) non-smokers, 34.7% (26/75) former smokers, and 4% (3/75) active smokers. Table 1 shows the demographic, anthropometric, smoking activity, and comorbidities of the general sample.

The bronchodilator test was performed in 86.6% (65/75) of the patients; 13.3% (10/75) did not undergo the bronchodilator test. One patient (1/75; 1.33%) refused to use the bronchodilator medication, and, in nine tests (9/75; 12%), the assistant physician, when requesting the examination, excluded the bronchodilator test (Figure 1).

The assessment of significant response to the bronchodilator was performed in 63 of the 65 (96.92%) patients who underwent the bronchodilator test; two examinations were excluded because they did not meet the criteria for acceptability and reproducibility and were, therefore, considered inconclusive tests (D Quality), making it impossible to interpret the bronchodilator test.

Among the 63 patients analyzed, 20.63% (13/63) had a significant response to the bronchodilator; two patients (2/63; 3.17%) responded to flow, three to volume (4/63; 6.34%), and seven to flow and volume (7/63; 11.11%). The bronchodilator response was not significant in 79.63% (50/63) of the patients who underwent the bronchodilator test.

After assessing the bronchodilator response per group, a positive response was found in both groups (obstructive: 9/34; 26.47%; non-obstructive: 4/29; 13.79%), with no significant difference between the groups (p<0.11).

The chronological age did not influence the positive bronchodilator response in the groups per age group (87 to 89 years old: 10/44; 22.72%; and ≥90 years: 3/19; 15.78%; p<0.23). No adverse effects were observed with a significant clinical repercussion of the bronchodilator medication during or after the test completion in all patients from both groups, so they were all discharged from the pulmonary function service a few minutes after the spirometry was completed.

### TABLE 1. DEMOGRAPHIC, ANTHROPOMETRIC, SMOKING ACTIVITY, AND COMORBIDITIES CHARACTERISTICS OF ELDERLY INDIVIDUALS ≥87 YEARS

| Variables                     | ≥ 87 years | CI 95%          |
|-------------------------------|------------|-----------------|
| Female, n (%)¹                | 44 (58.7%) |                 |
| Age², years                   | 89.34 ± 0.29 year | 88.74 - 89.94  |
| Height, meters²               | 1.52 ± 0.1 | 1.50 - 1.55     |
| BMI²                          | 27.02 ± 0.58 | 25.86 - 28.18  |
| Weight, Kg²                   | 63.30 ± 1.52 | 60.26 - 66.35  |
| Nonsmokers¹                   | 46 (61.3%) |                 |
| Former smokers¹               | 26 (34.7%) |                 |
| Smokers¹                      | 3 (4%)     |                 |
| Comorbidities, n (%)¹         |            |                 |
| Asthma                        | 20 (26.7%) |                 |
| COPD                          | 22 (29.3%) |                 |
| Allergic rhinitis             | 23 (30.7%) |                 |
| SAH                           | 33 (44%)   |                 |
| Dyslipidemia                  | 17 (22.7%) |                 |
| OSA                           | 16 (21.3%) |                 |
| Diabetes mellitus             | 14 (18.7%) |                 |
| Cerebrovascular               | 6 (8%)     |                 |
| Cognitive deficit             | 7 (9.3%)   |                 |
| GERD                          | 5 (6.7%)   |                 |
| Prostatic Hyperplasia         | 4 (5.33%)  |                 |
| Arrhythmias                   | 4 (5.33%)  |                 |
| Other comorbidities           | 16 (21.33%)|                 |

¹ Values as n (%). ² Values as mean ± SD. CI 95%: Confidence interval; BMI: Body Mass Index, SAH: Systemic arterial hypertension, OSA: Obstructive sleep apnea. Other comorbidities (depression, anxiety, coronary failure, previous breast neoplasia, interstitial lung disease, pulmonary nodule, osteoarthritis, chronic cough, hypothyroidism, auditory deficit). Some patients had one or more comorbidities. Main Author: Saulo Maia d’Avila Melo
DISCUSSION

Even with healthy aging, there is a reduction of the physiological capacity of all organs, in particular of the respiratory system. Elderly patients have an increased risk for respiratory diseases, since the frequent exposure to environmental toxins over a lifetime, particularly to tobacco smoke, environmental pollution, occupational dust, and respiratory infections, predispose to a higher risk of acute or chronic lung disease.

Inhaled bronchodilator therapy is the basis for the treatment of obstructive respiratory diseases. Spirometry with a bronchodilator test is commonly performed as a fundamental part of the evaluation of pulmonary function and has a preponderant role in the diagnosis, assessment of severity, and estimation of therapeutic response of respiratory diseases.

There is currently a limited number of studies on spirometry in elderly patients and no discussion regarding the use of bronchodilators in the fourth age.

In a recent publication that included more than 97,000 spirometric tests from five continents, in 33 countries, only 0.8% of individuals were more than 80 years old (chronological age), and of these, only 26 were ≥90 years.

We evidence here, in a pioneering way, the importance and the security of bronchodilators in the fourth age, with no adverse effects with significant clinical repercussions. A significant response to salbutamol was observed in 20.63% (13/63) of the patients in both groups (obstructive and non-obstructive), which demonstrates that there are no contraindications, so the repetition of the spirometry after bronchodilation should be routine, with safety, since it useful as a diagnostic aid and in therapeutic orientation, contributing to the clinical decision-making process in this elderly population.

In real life, the cardiovascular side effects of bronchodilators are one of the major concerns, and there is controversy regarding the relative systemic safety of the chronic use of fenoterol and salbutamol. However, the safety of these medications in obstructive lung disease patients in acute crisis (asthma and COPD) is demonstrated in previous research.

The cardiovascular and systemic safety of high doses of inhaled fenoterol and salbutamol has been demonstrated in asthmatic patients in severe acute crisis. In COPD exacerbations, the use of short-acting beta-2 agonists, through inhaling did not increase the risk of fatal or nonfatal myocardial infarction.

Spirometry is an outpatient elective examination in which bronchodilators are used in a single dose or in low doses when compared to those used during crises of acute or chronic lung disease patients. Our patients were not in an acute crisis; therefore, they had a lower probability of triggering cardiovascular complications.

Bronchodilators are safe drugs when used in the recommended doses. In spirometry, it is recommended using a short-acting beta-2 (salbutamol) or a short-acting anticholinergic (ipratropium bromide), preferably in spray, because of its availability, ease of use, and cost. The dose of spray salbutamol, 400 mcg (4 jets of 100 mcg), preferably with a spacer, with a repetition of the examination after 15 minutes, and a

### TABLE 2. CONTRAINDICATIONS OF SPIROMETRY AND BRONCHODILATOR TEST

| Absolute | Relative |
|----------|----------|
| Hemodynamic instability. | Age under 5 to 6 years. |
| Pulmonary embolism. | Confused patient or with dementia. |
| Acute retinal detachment. | Uncooperative. |
| Recent pneumothorax (≤2 weeks). | Recent abdominal or thoracic surgery. |
| Active respiratory infection: viral, tuberculosis, others. | Acute diarrhea or vomiting, nauseated state. |
| Acute hemoptysis. | Hypertensive crisis. |
| Recent myocardial infarction. | Oral or maxillofacial disorders that prevent oral coupling to the device. |
| Thoracic aortic aneurysm >6 cm. | Chest or abdominal pain that prevents ventilatory maneuvers. |
| Unstable angina. | Recent brain, eye, or otorhinolaryngologic surgery. |
| Unstable arrhythmia. | |
| Intracranial hypertension. | |

Relative contraindications for the bronchodilator test Known or likely adverse reactions to the intended bronchodilator. Known heart arrhythmia. Patient’s fear regarding the use of bronchodilators. If there is a contraindication to spirometry, the bronchodilator test should not be performed. The relative contraindications for the bronchodilator test should be assessed individually with changes of the type of bronchodilator and analyzed on a case by case basis, by evaluating the risk-benefit ratio. Table adapted.

### TABLE 3. GENERAL CONTRAINDICATIONS TO THE USE OF SELECTIVE SHORT-ACTING BETA-2 ADRENERGIC AGONIST AND IPRATROPiUM BROMiDE

| Beta-2 adrenergic agonists | Ipratropium Bromide |
|---------------------------|---------------------|
| Hyperthyroidism. / Subvalvular aortic stenosis. / Hypertrophic obstructive heart disease. / Tachyarrhythmias. / Sensitivity to sympathomimetic drugs. / Hypersensitivity to any component of the formulation. | Hypersensitivity to any component of the formulation. / Hypersensitivity to atropine or its derivatives. / Use with caution in narrow-angle glaucoma, bladder obstruction, prostate hyperplasia, and myasthenia gravis. |

Table adapted.
dose of ipratropium bromide, of 160 mcg (8 jets x 20 mcg), with a repetition of the examination after 30 to 45 minutes\textsuperscript{9,14-16}. Ipratropium bromide presents a lower incidence of adverse effects, especially cardiovascular ones, in comparison to beta-2 agonists\textsuperscript{21}.

With there is a contraindication to spirometry, the bronchodilator test, consequently, should not be performed (Table 2).

Research regarding contraindications specific to the bronchodilator test during spirometry is limited\textsuperscript{6,14-16}. We did not find in the literature any absolute contraindication for the bronchodilator test, and important adverse effects (severe cardiac arrhythmia, hypertensive crisis, coronary failure, heart failure, or respiratory failure) triggered by the bronchodilator test.

The contraindications, in general, to bronchodilators used in the bronchodilator test (short-acting beta-2 agonists and ipratropium bromide) are shown in Table 3.

Reports of smaller risks without clinical repercussions, including tremors of the extremities, reflex tachycardia, excitation, flushing, palpitations, headache, and dizziness do not justify a contraindication to the bronchodilator test, since these cause only concern to patients (often due to lack of prior guidance) and health professionals who are not used to the medication. However, spirometry requests that specify the non-use of the bronchodilator test are justified, particularly in elderly patients or with heart disease.

Therefore, when there is no contraindication to spirometry, the bronchodilator test should be performed respecting its contraindications, which should be analyzed on a case by case basis by evaluating the risk-benefit ratio (Tables 2 and 3).

The use of a specific questionnaire to assess adverse effects without significant clinical repercussions, the potassium dose, and the lack of cardiovascular monitoring during and after the completion of the bronchodilator test were limitations of our study because of its retrospective design.

**CONCLUSION**

Our study demonstrated that chronological age is not a limiting factor for bronchodilator tests, that short-acting selective adrenergic beta-2 agonists presented no adverse effects with significant clinical consequences, and that they were useful to assist in the diagnosis and therapeutic orientation of patients in the fourth age.

**Contribution of the authors**

SMAM - Concept, creation, and formatting of the research, literature review, submission to the Research Ethics Committee, database review, discussion of the results and statistics, discussion with the literature, and drafting of the article.

LAO; RAR; JLFW - Literature review, drafting, and review of the database, discussion of the results and statistics, discussion with the literature, and drafting of the article.

**RESUMO**

**OBJETIVOS:** Avaliar se idade cronológica é um fator limitante para realizar prova broncodilatadora, determinar efeitos adversos significativos com repercussão clínica dos beta-2 agonistas de curta ação e avaliar a resposta broncodilatadora na espirometria, na velhice extrema.

**MÉTODOS:** Estudo transversal, retrospectivo. Amostra extraída do banco de dados (espirômetro e questionário respiratório) de um serviço de função pulmonar. Incluídos na pesquisa pacientes com ≥90 anos, sendo avaliados a resposta broncodilatadora e efeitos adversos significativos com repercussão clínica ao broncodilatador.

**RESULTADOS:** Amostra de 25 pacientes com idade de 92,12 ± 2,22 anos (IC 95%; 91,20 – 93,04), idade mínima de 90 anos e máxima de 97 anos, predominando o sexo feminino, com 72% (18/25). A prova broncodilatadora foi realizada em 84% (21/25) dos pacientes. A avaliação da resposta ao broncodilatador foi feita em 19 dos 21 pacientes (90,47%) que realizaram a prova broncodilatadora, uma vez que dois desses exames não preencheram os critérios de aceitabilidade e reprodutibilidade. A resposta broncodilatadora foi significativa em 10,52% (2/19) dos pacientes, ambos portadores de pneumopatia obstrutiva. Não foram observados efeitos adversos com repercussão clínica da medicação broncodilatadora (salbutamol) durante ou após sua realização.

**CONCLUSÕES:** A idade cronológica não é um fator limitante para a realização da prova broncodilatadora, os beta-2 agonistas de curta ação não apresentaram efeitos adversos com repercussão clínica significativa e foram bastante úteis para auxiliar no diagnóstico e orientação terapêutica na velhice extrema.

**PALAVRAS-CHAVE:** Broncodilatadores. Idoso. Envelhecimento. Testes de função respiratória. Espirometria. Longevidade.
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