Analysis of Clinical Application of Bronchial Provocation Test Based on Real-World Data (Postprint)

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Date: 2025-03-18T00:00:00+00:00

Abstract

Background Bronchial provocation test (BPT) is a commonly used method for confirming airway hyperresponsiveness (AHR) and is also an important tool for asthma diagnosis and efficacy evaluation. However, departments other than respiratory medicine pay insufficient attention to BPT.

Objective Based on real-world large-sample BPT data, to analyze the implementation status of BPT, positive test rates, and AHR grading among different hospital departments.

Methods BPT reports from the Pulmonary Function Laboratory of the First Affiliated Hospital of Guangzhou Medical University from March 2017 to April 2022 were retrospectively collected, excluding children (<18 years) and reports with missing key indicators. The number of BPT requests, positive rates, and clinical diagnosis categories for each department were recorded. BPT-positive data were divided into pre-methacholine inhalation positive and post-methacholine inhalation positive groups; the former was classified as the extremely severe group, while the latter was subdivided into extremely mild, mild, moderate, and severe groups based on the cumulative methacholine dose (PD20) when forced expiratory volume in the first second (FEV1) decreased by 20% from baseline. Differences in age, height, weight, and baseline lung function parameters among groups were compared. Multivariate Logistic regression was used to analyze risk factors for BPT positivity.

Results A total of 24,034 BPT reports were included, with positive, negative, and suspiciously positive rates of 27.91%, 67.83%, and 4.22%, respectively; 8 cases failed to complete the test. Reports from internal medicine and surgery departments accounted for 86.50% and 3.07% of cases, respectively, with positive rates of 28.30% and 18.70%. Only 2 gynecological patients were included, with 1 positive case. Statistically significant differences were found among BPT-positive groups in age, weight, FEV1, percentage of predicted FEV1 (FEV1%pred), forced vital capacity (FVC), FEV1/FVC, and percentage of predicted FEV1/FVC (FEV1/FVC%pred) ($P<0.05$). FEV1, FEV1%pred, FEV1/FVC, and FEV1/FVC%pred all gradually decreased with increasing AHR grade (all $P<0.05$). Multivariate Logistic regression identified age $ $40 years, female sex, BMI $ $24, clinical diagnosis of asthma, FEV1%pred <80%, and FEV1/FVC%pred <92% as risk factors for BPT positivity ($P<0.05$). There were 51 adverse events (0.21%), including 8 test terminations due to intolerance; all adverse reactions were extremely mild or mild.

Conclusion BPT is the gold standard for rapid clinical diagnosis of AHR and provides significant clinical guidance value. In addition to respiratory departments, internal medicine and surgery departments also show relatively high positive detection rates in patients suspected of having AHR, warranting greater emphasis on BPT. Patients with low baseline FEV1 and FEV1/FVC, particularly females, those aged $ $40 years, and individuals with high BMI, require vigilance for possible AHR. BPT demonstrates good overall safety, though FEV1 changes and adverse reactions should be closely monitored during testing.

Full Text

Clinical Application Analysis of Bronchial Provocation Test Based on Real-World Data

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Abstract

Background The bronchial provocation test (BPT) is a widely utilized method for assessing airway hyperresponsiveness (AHR) and serves as a crucial tool for both the diagnosis and therapeutic evaluation of asthma. Despite its significance, BPT is often underutilized outside the field of respiratory medicine. **Objective** This study aims to analyze the application of BPT across various hospital departments, as well as the BPT positive rate and AHR severity grades, using real-world data from a large sample of BPT cases. **Methods** BPT reports from the First Affiliated Hospital of Guangzhou Medical University, spanning March 2017 to April 2022, were systematically collected for analysis. Reports pertaining to children (under 18 years of age) and those lacking critical indicators were excluded from the study. The analysis focused on the distribution of

BPT applications across various departments, the rate of positive BPT results, and the classification of clinical diagnoses. Positive BPT data were categorized into two groups: those positive prior to methacholine inhalation and those positive post-inhalation. The former group was designated as the "very severe" category, while the latter was further subdivided into "very mild," "mild," "moderate," and "severe" categories based on PD20 values. Comparative analyses of age, height, weight, and baseline lung function indices were conducted across these groups. Additionally, multivariate Logistic regression analysis was employed to identify risk factors associated with positive BPT outcomes. **Results** In this study, a total of 24,034 BPT reports were analyzed. The distribution of report outcomes was as follows: 27.91% were positive, 67.83% were negative, and 4.22% were suspected positive. Additionally, 8 cases did not complete the test. The internal and surgical BPT reports constituted 86.50% and 3.07% of the total, respectively, with corresponding positive rates of 28.30% and 18.70%. The study included only 2 gynecological patients, of whom 1 tested positive. Significant differences were observed in age, body weight, forced expiratory volume in the first second (FEV1), percentage of predicted FEV1 (FEV1%pred), forced vital capacity (FVC), FEV1/FVC ratio, and percentage of predicted FEV1/FVC (FEV1/FVC%pred) among the BPT positive groups (all P<0.05). Notably, FEV1, FEV1%pred, FEV1/FVC, and FEV1/FVC%pred values decreased progressively with increasing severity of AHR (P<0.05). Multivariate Logistic regression analysis identified several risk factors for positive BPT results, including age over 40 years, female gender, body mass index (BMI) $ $24, clinical diagnosis of asthma, FEV1%pred <80%, and FEV1/FVC%pred <92% (P<0.05). A total of 51 adverse events associated with BPT were recorded, all of which were classified as very mild or mild. Among these, 8 cases were unable to complete the test due to intolerance. **Conclusion** BPT remains the gold standard for the rapid clinical diagnosis of AHR, offering significant value for clinical guidance. The positive rate of BPT in patients with suspected AHR is high not only in the respiratory department but also among other medical departments, warranting increased attention to BPT. Particular vigilance is advised for patients with low baseline FEV1 and FEV1/FVC, especially in females, people over 40 years old, or those with a high BMI. BPT is generally considered safe, but it is crucial to closely monitor changes in FEV1 and any adverse reactions during provocation tests.

Keywords: Bronchial provocation tests; Basic lung function; Methacholine; Hospital departments; Disease attributes

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1. Materials and Methods

Bronchial asthma is a common inflammatory airway disease in clinical practice, with airway hyperresponsiveness (AHR) representing one of its key pathophysiological characteristics [1-2]. The bronchial provocation test (BPT) serves as a commonly employed clinical method for verifying AHR and constitutes an important tool for asthma diagnosis and therapeutic evaluation [3]. While traditional clinical trials represent the "gold standard" for assessing the safety and efficacy of new therapeutic agents, their strict inclusion and exclusion criteria often mean that study populations do not represent the patient populations encountered in clinical practice [4]. Given China' s large patient base and wide disease spectrum, real-world clinical data resources contain tremendous research value, and the mining and analysis of such data can provide valuable references for clinical decision-making [5-6]. As a routinely performed pulmonary function testing technique, BPT has accumulated substantial data in clinical practice. However, due to various factors such as lack of data platform integration, policy support, and patient information protection, collecting and utilizing large-sample real-world data remains time-consuming and labor-intensive. Therefore, this study aims to conduct a retrospective analysis based on real-world BPT data collected through a relatively comprehensive pulmonary function data platform to evaluate the actual implementation of BPT, compare clinical characteristic differences across various AHR severity grades, and provide references for clinical practice.

1.1 Data Collection

In July 2022, BPT data from March 2017 to April 2022 were exported from the Respiratory Health Big Database of the National Respiratory Medicine Center at the First Affiliated Hospital of Guangzhou Medical University. Only the first BPT data for each patient were included. Exclusion criteria were: (1) missing important pulmonary function indicators, such as post-challenge FEV1; (2) termination of BPT due to poor patient cooperation; and (3) patients under 18 years of age.

1.2 Methods

Basic information collected included gender, age, height, weight, department of origin, and clinical diagnosis. Baseline pulmonary function indices comprised forced expiratory volume in 1 second (FEV1), percentage of predicted FEV1 (FEV1%pred), forced vital capacity (FVC), percentage of predicted FVC (FVC%pred), FEV1/FVC ratio, and percentage of predicted FEV1/FVC (FEV1/FVC%pred). BPT-related indicators included the cumulative dose of methacholine causing a 20% decrease in FEV1 (PD20) and adverse reactions. Baseline lung function was classified as normal, essentially normal [with normal FEV1/FVC%pred, FEV1%pred, and FVC%pred, and only one of the following three parameters below 65%pred: percentage of predicted maximum midexpiratory flow (MMEF%pred), percentage of predicted maximal expiratory flow after 50% of the FVC has been exhaled (MEF50%pred), or percentage of predicted maximal expiratory flow after 25% of the FVC has been exhaled (MEF25%pred)], mixed ventilatory dysfunction, obstructive ventilatory dysfunction, restrictive ventilatory dysfunction, small airway ventilatory dysfunction, or non-specific ventilatory dysfunction (normal FEV1/FVC%pred and FVC%pred with FEV1%pred <80%). The distribution of BPT applications across clinical departments and clinical diagnoses in adults ($ $18 years) was analyzed. Positive BPT patients were divided into those positive before methacholine inhalation (in whom repeated forced breathing or inhalation of 0.9% sodium chloride solution immediately induced bronchospasm with $ $20% FEV1 decline) and those positive after methacholine inhalation. The former group was designated as the very severe group, while the latter was further subdivided based on PD20 results into very mild (PD20 1.076-2.500 mg), mild (PD20 0.294-1.075 mg), moderate (PD20 0.035-0.293 mg), and severe (PD20 <0.035 mg) groups. Age, height, weight, and baseline lung function indices were compared across these groups [7-8]. Multivariate Logistic regression analysis was performed using gender, age, BMI, clinical diagnosis of asthma, cough of unknown cause, chronic obstructive pulmonary disease (COPD), and baseline lung function indices (FEV1%pred, FVC%pred, FEV1/FVC%pred) as independent variables to explore risk factors for positive BPT [9-10]. Adverse reactions were classified as very mild (resolved with rest only), mild (resolved with bronchodilator inhalation or oxygen only), moderate (requiring steroid treatment), or severe (requiring emergency or hospital treatment).

1.3 Pulmonary Function Testing

Both baseline pulmonary function and BPT were performed using the Masterscreen system from German Jaeger Company. Prior to testing, patients' medical histories were thoroughly reviewed to exclude those with BPT contraindications. Patients were required to discontinue medications affecting test results, such as β-agonists, glucocorticoids, and antiallergic drugs, before testing, and to avoid strenuous exercise, smoking, and consumption of caffeinated foods like cola and coffee. Informed consent was obtained from all participants. Patient parameters including name, gender, age, weight, and height were entered into the pulmonary function equipment. Testing was performed at least three times according to forced vital capacity quality control standards [11], with the best value selected as the baseline for each index. Patients with FEV1%pred $ $60% could proceed to BPT. According to Chinese bronchial provocation test guidelines [8], patients sequentially inhaled 0.9% sodium chloride solution and different doses of methacholine, with pulmonary function repeatedly measured. The test was stopped when FEV1 decreased by $ $20% from baseline or after inhalation of the maximum dose with <20% FEV1 decline. A $ $20% FEV1 decrease indicated a positive result, 15%-20% decline indicated suspected positivity, and <15% decline indicated a negative result. Positive patients required inhalation of a bronchodilator to restore FEV1 to >85% of the pre-challenge value.

1.4 Statistical Methods

Statistical analysis was performed using SPSS 25.0 software. Normally distributed continuous variables were expressed as ($\bar{x}\pm s$), and categorical data were expressed as relative frequencies. Comparisons of 各项指标 among the very mild, mild, moderate, severe, and very severe groups were conducted using one-way ANOVA, with pairwise comparisons performed using the S-N-K method. Multivariate Logistic regression analysis was used to identify risk factors for positive BPT, with missing values imputed using mean imputation. A P-value <0.05 was considered statistically significant.

2. Results

2.1 Data Screening

This study collected 32,479 BPT reports, with valid data accounting for 99.70% (32,381/32,479). After data cleaning and screening (Figure 1 [Figure 1: see original paper]), 24,034 BPT reports from patients aged 18-93 years were included. The analysis included 6,709 positive reports (27.91%), 16,302 negative reports (67.83%), and 1,015 suspected positive reports (4.22%), with 8 cases failing to complete the test. Among positive BPT reports, 5,989 had non-missing PD20 data.

2.2 Department Distribution and Clinical Diagnosis

Regarding department distribution, internal medicine and surgery departments accounted for 86.50% (20,789/24,034) and 3.07% (738/24,034) of reports, respectively, with positive rates of 28.30% (5,883/20,789) and 18.70% (138/738). The overall positive rate was 27.97% (6,021/21,527). Within surgical departments, the positive rates were: thoracic surgery 14.95% (74/495), otolaryngology-head and neck surgery 25.44% (58/228), and other surgical departments 40.00% (6/15). Positive rates for internal medicine departments are shown in Figure 2 [Figure 2: see original paper], where the positive rate represents the number of positive BPT cases divided by the total number of BPT cases. Only 2 gynecological patients were included in this study, with 1 positive case.

The top five clinical diagnoses before testing were: cough of unknown cause (7,733 cases), asthma (2,105 cases), dyspnea (999 cases), and bronchitis.

2.4 Comparison of Indicators Across Groups

After excluding BPT reports with missing PD20 data, 5,989 positive BPT cases were included, comprising 5,684 cases positive after methacholine inhalation and 305 cases positive before methacholine inhalation (i.e., bronchospasm induced by repeated forced breathing or inhalation of 0.9% sodium chloride solution). No statistically significant differences were observed in height or FVC%pred among the very mild, mild, moderate, severe, and very severe groups (P>0.05). However, significant differences were found in age, weight, FEV1, FEV1%pred, FVC, FEV1/FVC, and FEV1/FVC%pred (P<0.05). Notably, FEV1, FEV1%pred, FEV1/FVC, and FEV1/FVC%pred decreased progressively with increasing AHR severity (P<0.05), as shown in Table 1 .

2.5 Multivariate Logistic Regression Analysis of Risk Factors for Positive BPT

Using BPT positivity (assignment: yes=1, no=0) as the dependent variable and gender, age, BMI, clinical diagnosis of asthma, cough of unknown cause, COPD, and baseline lung function indices (FEV1%pred, FVC%pred, FEV1/FVC%pred) as independent variables, multivariate Logistic regression analysis revealed that age $ $40 years (OR=1.246, 95%CI=1.165-1.331, P<0.001), female gender (OR=1.602, 95%CI=1.501-1.771, P<0.001), BMI $ $24 (OR=1.114, 95%CI=1.043-1.190, P=0.001), clinical diagnosis of asthma (OR=2.382, 95%CI=2.148-2.642, P<0.001), FEV1%pred <80% (OR=3.076, 95%CI=2.775-3.410, P<0.001), and FEV1/FVC%pred <92% (OR=4.628, 95%CI=4.297-4.985, P<0.001) were risk factors for positive BPT, as shown in Figure 4 [Figure 4: see original paper].

2.6 Adverse Reactions to Methacholine Challenge

A total of 51 patients (0.21%) experienced adverse reactions during methacholine challenge, primarily including cough, wheezing, dizziness, and chest tightness. Eight cases were terminated due to intolerance resulting in poor quality control. All adverse reactions were classified as very mild or mild, with symptoms resolving after rest or inhalation of 200-400 g salbutamol within 20 minutes.

The classification of baseline lung function and positive rates are shown in Figure 3 [Figure 3: see original paper]. Mixed ventilatory dysfunction showed the highest positive rate, followed by obstructive ventilatory dysfunction. Normal and essentially normal lung function had the highest case numbers but the lowest positive rate. Restrictive ventilatory dysfunction had 256 positive cases, with the top three clinical diagnoses being cough of unknown cause (62 cases), asthma (25 cases), and dyspnea (11 cases).

Discussion

This study found that while surgical patients accounted for a relatively low proportion of cases, the positive rate reached 18.70%. This suggests that the number of BPTs performed in surgical departments needs to be increased. Respiratory symptoms such as wheezing, cough, and chest tightness, along with physiological evidence of AHR and variable airflow limitation, are commonly used for asthma diagnosis [12-13], and positive BPT represents important physiological evidence of airway changes, holding significant diagnostic value for asthma [14]. Currently, electronic medical records are widely used in hospitals at all levels. With advances in information technology and the construction of big data platforms, the mining and utilization of the potential value of large-scale real-world data will become increasingly common. Although there may be some error rates during data export, overall, the accuracy of big data platform data is already very high, with BPT report data export accuracy reaching 99.70% in this study.

This single-center, real-world data study simply analyzed the positive rate of BPT, department distribution, and compared differences in 各项指标 across different AHR grades, providing certain guiding significance for future clinical practice. The department performing the most BPTs in this study was respiratory medicine; however, other internal medicine departments such as cardiology, general practice, emergency medicine, and geriatrics performed relatively few BPTs, with more than 10 internal medicine departments (excluding respiratory medicine) ordering fewer than 20 BPT examinations over the past five years. This suggests that non-respiratory internal medicine departments should also pay more attention to BPT. For patients with unexplained cough or chest tightness, the possibility of AHR should be considered and appropriate tests ordered to promptly detect comorbid bronchial asthma or other diseases causing AHR and to initiate standardized treatment early. Additionally, patients with mixed or obstructive ventilatory dysfunction showed the highest positive rates, indicating that patients with significant airflow limitation on baseline pulmonary function have a high likelihood of AHR. Therefore, for asthma patients, especially children with poor perception, regular baseline pulmonary function testing can be used to monitor AHR and reduce the risk of severe asthma attacks [15]. Conversely, for patients with significant airflow limitation, asthma should also be considered as a possibility, and after treatment to rule out acute exacerbation and when the patient meets the indications for provocation testing, BPT should be performed immediately to evaluate airway reactivity for definitive diagnosis and standardized treatment.

According to previous literature, perioperative bronchospasm due to lack of preoperative airway assessment is not uncommon in surgical departments. LI Guanhua et al. [16] showed that early preoperative screening focused primarily on asthma symptoms, with an intraoperative asthma attack rate of 28% among 100 cases. In later stages, after screening for AHR and providing pharmacological treatment before elective surgery, only 8 cases of asthma attacks occurred among 1,100 patients. REGLI et al. [17] conducted a cohort study of 9,297 children, in which 193 (2.1%) experienced perioperative bronchospasm and 351 (3.8%) experienced laryngospasm. Mechanical stimulation from tracheal intubation, extubation, and suctioning, as well as anesthesia and other factors, can trigger perioperative asthma attacks [18]. Therefore, preoperative assessment of airway function in patients with suspected or confirmed asthma and appropriate management are important measures to avoid intraoperative bronchospasm. It is recommended that, in non-emergency situations, asthma patients undergo BPT assessment at least one week before surgery, with short-acting β-agonists (SABA) and long-acting β-agonists (LABA) commonly used preoperatively to control respiratory symptoms [19].

This study' s multivariate Logistic regression analysis identified age \$ \$40 years, female gender, high BMI, abnormal baseline FEV1%pred, and

FEV1/FVC%pred as risk factors for positive BPT. HU Yiqing et al. [20] recommended pulmonary function testing for people aged 40 years and above, and that patients with low baseline FEV1%pred and FEV1/FVC%pred accompanied by symptoms such as cough, chest tightness, and wheezing should be considered for possible AHR and timely provocation testing to rule out asthma. The risk of positive provocation in high BMI individuals was 1.114 times that of normal BMI individuals. MICHALOVICH et al. [21] demonstrated that obese asthmatic and obese non-asthmatic patients were more likely to have airway inflammation compared to non-obese asthmatic patients and healthy subjects, with obese asthmatic patients showing more significant airway inflammation. SUNADOME et al. [22] included 4,650 residents in their study and found a positive correlation between eosinophil count and BMI, suggesting that high BMI may increase airway sensitivity by increasing the probability of airway inflammation. Furthermore, this study showed that in adult patients with positive provocation, the lower the baseline FEV1, FEV1%pred, FEV1/FVC, and FEV1/FVC%pred, the more pronounced the AHR. Therefore, our team recommends that during BPT procedures, for patients with low baseline FEV1 and FEV1/FVC, especially females, individuals over 40 years old, and those with high BMI, the dose of provocative agent should be increased slowly with close observation for potential adverse reactions. Additionally, during treatment, known allergen stimulation should be minimized.

This study found that BPT has been widely implemented in clinical practice with high safety. YU Xinxin et al. [23] included 28 asthma patients, 23 post-infectious cough patients, and 21 healthy subjects in their BPT study, with some patients experiencing adverse reactions such as cough, dry throat, and throat itching, all of which resolved after treatment. LI et al. [24] also reported only mild adverse reactions in some children after completing BPT, which resolved after salbutamol inhalation. Similarly, this study showed that not a single patient experienced severe adverse reactions from provocation testing. Nevertheless, the induction of airway spasm by provocative agents inherently carries certain risks, and vigilance for adverse events is still required during the procedure, with corresponding emergency equipment readily available.

Due to the single-center retrospective nature of this study, certain limitations exist; however, the large sample size and strict adherence to standard operating procedures and interpretation criteria ensure good representativeness. We look forward to future multi-center real-world studies with larger sample sizes to provide more references for improving clinical practice.

In conclusion, BPT remains the gold standard for rapid clinical diagnosis of AHR and offers significant clinical guidance value. In addition to its common use in respiratory departments, other internal medicine and surgical departments also show relatively high positive detection rates in patients suspected of having AHR, highlighting the need for increased attention to BPT. For patients with low baseline FEV1 and FEV1/FVC, particularly females, individuals over 40 years old, and those with high BMI, the possibility of AHR should be considered.

While BPT demonstrates high overall safety, close monitoring of FEV1 changes and adverse reactions during provocation testing remains essential.

Author Contributions: LIU Shuyi, GAO Yi, and ZHENG Jinping conceived the study. LIU Shuyi, LI Yun, YE Peitao, and TAN Lunfang collected, acquired, and cleaned the data. LIU Shuyi, LI Yun, and XIE Yanqing performed statistical analysis and created figures and tables. LIU Shuyi drafted the manuscript. LIU Shuyi, LI Yun, YE Peitao, TAN Lunfang, XIE Yanqing, GAO Yi, and ZHENG Jinping revised the final version and take responsibility for the paper.

Conflicts of Interest: None declared.

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(Received: October 15, 2024; Revised: February 23, 2025) (Editor: CUI Sha)

Note: Figure translations are in progress. See original paper for figures.