

## ORIGINAL ARTICLE

# Determining Chronic Cough Using the Methacholine Bronchial Provocation Test

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## ABSTRACT

**Introduction:** Chronic cough is a common symptom in pulmonology outpatient clinics, often associated with lung conditions, though extrapulmonary causes can also be responsible. This study aimed to detect bronchial hyperreactivity (BHR) and cough-variant asthma using a methacholine bronchial provocation test (BPT) in patients with chronic cough for whom standard diagnostic procedures could not identify a cause.

**Methods:** This prospective study evaluated patients admitted to the clinic who presented with chronic coughs over one year. A BPT was performed on patients for whom standard diagnostic procedures failed to identify a cause, and this selected group was included in this study.

**Results:** This study included a total of 40 patients who were examined for chronic cough symptoms without an identifiable etiology. The BPT was negative (PD20 >16 mg/mL) in 30 patients (75%) and positive in 10 patients (25%). Among the patients with negative BPT results, 13 (43.3%) had no identifiable cause for their cough.

**Conclusion:** This study differs from others by focusing on a selected group of patients with chronic coughs for whom the etiology could not be determined through standard diagnostic procedures. The BPT was performed alongside typical diagnostic tests, and no diagnoses were made in the included patients. Tests identified BHR and cough-variant asthma in 25% of these patients, suggesting that BPT is a valuable tool in diagnosing chronic cough when conventional methods fail.

## INTRODUCTION

Cough is a common symptom experienced by many individuals at some point in their lives. It serves as a defense mechanism preventing the entry of foreign substances into the lower respiratory tract and facilitating the clearance of bronchial and lung secretions. Cough receptors are primarily located in the larynx, trachea, and large airway bifurcations. The afferent pathway involves the vagus nerve, while the efferent pathway includes a complex and coordinated musculoskeletal response.<sup>1</sup> In healthy individuals, mucociliary clearance is important in maintaining airway patency. Cough is considered effective when it achieves its intended purpose. However, chronic and

recurrent cough can lead to numerous complications and significantly impair quality of life. Chronic cough is a challenging symptom to manage regarding diagnosis and treatment and represents a significant medical and economic burden. This has increased the focus on developing diagnostic tests and algorithms to facilitate accurate diagnosis and effective treatment.

Over the past 30 years, research has improved the understanding of the mechanisms underlying cough. When a systematic diagnostic approach is applied to patients with chronic cough, the underlying cause can be identified in 88–100% of cases, with 84–98% of these patients responding to appropriate treatment. When investigating the etiological diagnosis, it is important to determine the duration of the cough. Traditionally, a

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cough lasting less than 3 weeks is classified as acute, while a cough persisting for more than 3 weeks is classified as chronic. However, recent literature defines chronic cough as lasting longer than 8 weeks.<sup>2</sup>

Given the high prevalence of cough as a reason for medical consultation, it has become an important research focus. The most common causes of chronic cough include asthma, gastroesophageal reflux disease (GERD), allergic rhinitis, sinusitis, chronic bronchitis, eosinophilic bronchitis, postnasal drip syndrome (PNDS), tuberculosis, and idiopathic causes.<sup>3-5</sup> Sometimes, diagnostic procedures fail to identify the cause, highlighting the need for additional diagnostic tools, such as bronchial provocation tests (BPT). After excluding other common causes of chronic cough, BPT can be performed to determine airway hypersensitivity in patients with chronic cough and symptoms suggestive of asthma, such as cough, wheezing, and shortness of breath, where pulmonary function tests (PFT) do not reveal airway obstruction.

Various studies have explored the etiology of chronic cough. Unlike other studies, this study focused on patients with chronic cough, where common causes could not be identified through standard diagnostic procedures or empirical treatments. These patients underwent methacholine BPT to detect bronchial hyperreactivity (BHR) and diagnose asthma-related cough. This study aimed to determine the prevalence of BHR in patients with unexplained chronic cough and emphasize the utility of BPT in diagnosing cough-variant asthma before airway remodeling occurs in patients.

## METHODS

### Study Design

This single-center prospective study included patients with chronic cough. The patients were examined for the etiology of their chronic cough. Demographic data such as age, sex, place of residence, occupation, and smoking habits were recorded. A detailed patient history, including family history and medication use, was obtained, followed by a systemic physical examination. Routine laboratory tests, including complete blood count, liver and kidney function tests, and erythrocyte sedimentation rate, were performed for all patients. A sputum examination was performed for *Mycobacterium tuberculosis* and other pathogens. Additional biochemical tests were conducted as clinically indicated.

All patients underwent posteroanterior chest X-rays, sinus X-rays (Water's view), and spirometry examination with reversibility testing. In patients with lung parenchymal disease or bronchiectasis, high-

resolution tomography of the lungs (HRCT) was performed on direct radiographs. Bronchoscopy was performed on patients when indicated. Patients with GERD were referred to the gastroenterology department according to their clinical complaints, and the recommended diagnostic tests, including gastroscopy and gastroesophageal reflux scintigraphy, were performed. Empirical antireflux treatment was administered when appropriate. An echocardiographic examination and cardiology consultation were conducted to exclude cardiac causes. Patients whose chronic cough etiology could not be determined after these examinations were included in this study. Exclusion criteria included patients who smoked, those with a respiratory tract infection in the last 3 weeks, and those who failed to respond to empirical treatments.

Bronchial hyperreactivity was investigated by performing a BPT with methacholine in the patient group. Methacholine (16 mg/mL) was prepared by dissolving dry salt methacholine in 0.9% NaCl, and BPT was applied using a 5-breath dosimetry method.<sup>6</sup> A positive test was defined as a  $\geq 20\%$  decrease in baseline FEV1 value. Results were classified as follows: Provocative dose (PD20)  $< 1$  mg/mL was defined as severe BHR; PD20 1–4 mg/mL as moderate BHR; PD20 4–16 mg/mL as mild BHR; and PD20  $> 16$  mg/mL as borderline BHR (considered negative).

The patients were monitored for a one-hour post-test and re-examined for any changes in lung sounds. Low-dose, inhaled corticosteroids were given to patients who were BPT-positive. Bronchial provocation test-negative cases were followed for three months with monthly assessments. In patients whose cough complaints did not improve during the follow-up, further investigations were conducted.

### Ethics Statement

This study was approved by the Scientific Ethics Committee of Ondokuz Mayıs University. Written informed consent was obtained from all participants before they participated in this study.

## RESULTS

Chronic cough causes such as gastroesophageal reflux, sinusitis, asthma, chronic obstructive pulmonary disease (COPD), parenchymal lung diseases, heart failure, active upper respiratory tract infection, pneumonia, lung malignancy, and the use of angiotensin-converting enzyme (ACE) inhibitors were excluded, and no etiology of chronic cough was determined. Spirometry examination, chest X-rays, sinus X-rays, and computed tomography (CT) results were normal in all patients included in this study. Patients

were evaluated at least three weeks after any upper respiratory tract infection. A total of 40 patients with no identifiable etiology for chronic cough were enrolled in

this study, comprising 10 males (25%) and 30 females (75%), with a mean age of 37.9 years (range 18–76 years). General patient data are summarized in [Table 1](#).

**Table 1.** General data about the study

Characteristics	Frequency (N = 40)	Percentage (%)
Gender Distribution		
Male	10	25
Female	30	75
Mean Age	37.9 years old	
Methacholine Bronchial Provocation Test (BPT) Results		
Positive	10	25
Negative	30	75
Cough Duration		
BPT positive	14.8±5.192 weeks	
BPT negative	13.07±5.192 weeks	
Causes of Negative BPT		
Environmental exposure	4	13.3
Postinfectious cough	8	26.6
Rhinitis	5	16.6
No cause identified	13	43.3
Bronchial Hyperreactivity (BHR) Severity		
Severe BHR (0.25 mg/ml)	2	5
Moderate BHR (1 mg/ml)	1	2.5
Mild BHR (4-16 mg/ml)	7	70

All patients underwent methacholine BPT. Of these, 10 patients (25%) had positive BPT results, while 30 patients (75%) had negative results (PD20 >16 mg/mL). The mean cough duration was 14.8±5.192 weeks in BPT-positive cases and 13.07±5.192 weeks in BPT-negative cases. Among the 30 patients with negative BPT results, 4 (13.3%) had environmental exposures, 8 (26.6%) had a post-infective cough, and 5 (16.6%) had rhinitis. Environmental exposures included a hairdresser exposed to hair dye, an animal breeder, and two students exposed to dormitory blanket dust. In 13 patients (43.3%), no cause of cough could be determined. These 13 patients were followed for three months with monthly assessments, and all experienced spontaneous resolution of cough without treatment.

Bronchial hyperreactivity was detected in 2 patients (5%) at a dose of 0.25 mg/mL (severe BHR), 1 patient (2.5%) at 1 mg/mL (moderate BHR), and 7 patients (70%) at doses of 4–16 mg/mL (mild BHR). The most common symptom apart from cough was sensitivity to dust odors, reported by 28 patients (70%). A relationship between cough duration and chronic cough diagnoses was observed, with idiopathic cough patients experiencing longer symptoms (mean 16.3 weeks). All patients with positive BPT results were treated with low-dose inhaled corticosteroids (budesonide 200 mcg/day), and cough symptoms improved within the first week of treatment.

## DISCUSSION

Cough is a physiological reflex that protects against aspiration in healthy individuals. However, in

some cases, the cough reflex can persist abnormally, causing discomfort. Cough is classified by duration as acute (<3 weeks), subacute (3–8 weeks), or chronic (>8 weeks).<sup>2</sup> Asthma is known to have phenotypes where cough is the predominant symptom, making it important to investigate the underlying etiology of chronic cough.<sup>7</sup>

This study conducted a series of diagnostic procedures after taking detailed histories and performing physical examinations on patients with chronic coughs. A BPT was conducted on patients with unexplained cough-variant asthma to identify ‘cough-variant asthma.’ This study found that 25% of patients with chronic cough of unknown origin had cough-variant asthma.

A previous study involving 43 chronic cough patients had a sample size similar to this study.<sup>8</sup> Using impulse oscillometry, the previous study investigated the bronchodilator effect of deep inspiration in individuals with classic asthma, cough-variant asthma, and healthy controls.<sup>8</sup> However, unlike in this study, patients already diagnosed with asthma and cough-variant asthma were also included in their study design. This study suggested that a chronic cough of unknown cause might represent a clinical phenotype distinct from healthy individuals and those with asthma. In the previous study, 7 patients exhibited cough as the sole symptom.<sup>8</sup> Similarly, in this study, 13 patients had a negative BPT, and no cause for their cough could be determined.

Recent studies have described a subgroup of chronic cough patients suspected of having cough-variant asthma and who coughed during high-dose methacholine challenge but exhibited normal airway sensitivity.<sup>9,10</sup> In this study, patients who coughed but had negative BPT results showed similar characteristics

to this group. Most studies focus on the relationship between BHR and asthma, but few address BHR in patients with COPD. In a study by Rosyid, *et al.* (2017), BPT was performed on healthy smokers and smokers with COPD.<sup>11</sup> The study found that smokers with BHR were more likely to have COPD, highlighting the diagnostic potential of BPT in detecting early airway changes before bronchial mucosa remodeling occurs.

The key distinction of this study lies in the highly selective nature of the patient cohort, in which causes such as postnasal drip, gastroesophageal reflux, and ACE inhibitor use were excluded. This allowed this study to diagnose cough-variant asthma in isolation. Other studies on chronic cough have generally investigated only cough symptoms without such strict exclusion criteria.<sup>10,12–14</sup>

Bronchial provocation test proved useful in diagnosing chronic cough. Treatment with inhaled corticosteroids can be effective.<sup>15</sup> Additionally, biological agents play an important role in controlling inflammation, and early intervention may prevent airway remodeling due to local inflammation, thereby delaying the onset of future obstructive findings.<sup>16,17</sup> This approach has been increasingly integrated into clinical guidelines.<sup>18–20</sup>

## CONCLUSION

In conclusion, this study differs from others by focusing on a highly selected group of patients whose etiology of chronic cough could not be determined. This study highlighted the importance of considering asthma with BHR, specifically cough-variant asthma, in such cases. Further research is needed to determine whether chronic cough represents a distinct disease state or a “pre-pathological” phenotype at risk of progressing to cough-variant asthma or more severe forms of asthma over time.

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## Conflict of Interest

The authors declared there is no conflict of interest.

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## Authors' Contributions

Study conception and design: EAA, OU. Material preparation, data collection, and analysis: EAA, OU. Writing the first draft manuscript: EAA. All authors

contributed and approved the final version of the manuscript.

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