Wheezing on Maximal Forced Exhalation in the Diagnosis of Atypical Asthma

Lack of Sensitivity and Specificity

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Study Objective: To determine whether wheezing on maximal forced exhalation is a predictor of asthma in persons with normal or nearly normal baseline spirometry.

Design: Prospective study of patients referred for methacholine challenge testing.

Setting: Pulmonary function laboratory at a hospital.

Patients: Forty-four patients referred for methacholine challenge testing because of the clinical suspicion of cough variant or otherwise difficult to diagnose asthma, with normal or nearly normal baseline spirometry and without wheezing on routine lung auscultation during quiet breathing.

Interventions: We listened for wheezing on maximal forced exhalation. Wheezing was defined as a continuous sound with a musical quality. Methacholine challenge testing was done. The concentration of methacholine required to produce a 20% fall in baseline FEV_1 (PC_{20}) of less than 8 mg/mL was considered a positive test for asthma.

Measurements and Main Results: Wheezing was present on maximal forced exhalation in 8 of 14 patients with a positive methacholine challenge test (sensitivity = 57%) and absent in 11 of 30 patients with a negative test (specificity = 37%). Furthermore, wheezing on maximal forced exhalation was present in 13 of 27 patients with a PC_{20} greater than 16 mg/mL and absent in 2 of 7 with a PC_{20} less than 4 mg/mL.

Conclusions: Wheezing on maximal forced exhalation is neither sensitive nor specific for airway hyperreactivity.

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Although asthma is a common disease, when symptoms are unusual and when spirometric testing is normal, its diagnosis may be difficult (1). Such persons with "atypical asthma" may only complain of cough and not report wheezing (2). Routine physical examination of the lung fields is often unrevealing (3). Conversely, subjects with such disorders as rhinitis, sinusitis, gastroesophageal reflux, cardiac disease, and psychiatric conditions may have symptoms that mimic asthma (2, 4-7). Because of the difficulties in diagnosis based on history, physical examination, and routine spirometry, nonspecific bronchoprovocation testing such as methacholine challenge testing is considered by many to be the diagnostic test of choice for atypical asthma (7, 8).

The role that auscultation for wheezing on a maximal forced exhalation maneuver may have in diagnosing atypical asthma is unclear. Some authorities have maintained that most asthmatics, even when asymptomatic, have wheezing that is easily audible with a stethoscope on maximal forced exhalation (9, 10). Others, however, have pointed out that many normal persons will wheeze on performing this maneuver (11, 12). In fact, this finding has recently been documented using sophisticated recording techniques (13). Wheezing on maximal forced exhalation that is audible with a stethoscope may therefore be a fairly sensitive, albeit only moderately specific, sign of asthma.

In this study we investigated the sensitivity and specificity of wheezing on maximal forced exhalation in predicting bronchial hyperresponsiveness as assessed by methacholine challenge testing in subjects with symptoms such as cough or dyspnea suggesting asthma but normal or nearly normal baseline spirometry.

Materials and Methods

Subjects and Lung Auscultation

Between 1 April 1987 and 31 March 1988, 46 consecutive patients were recruited after being referred to the pulmonary unit of the Massachusetts General Hospital because of a clinical suspicion of asthma but with normal or nearly normal spirometry. For each patient, before obtaining any knowledge of the patient's history, one of the investigators listened to the chest anteriorly and posteriorly over each lung field and over the trachea (just above the sternal notch). For each position, the patient first breathed with normal tidal volumes and then performed a maximal forced

Table 1. *Symptoms of Patients Referred for Methacholine Challenge Testing**

Symptom	Provocation Concentration of Methacholine for 20% Fall in FEV_1	
	$\leq$ 8 mg/mL (n = 14)	> 8 mg/mL (n = 30)
	n(%)	
Cough	12(86)	19(63)
Dyspnea	9(64)	15(50)
Postnasal drip	5(36)	9(30)
Wheezing	5(36)	8(27)
Stuffy nose	5(36)	8(27)
Chest tightness	3(21)	7(23)
Runny nose	3(21)	6(20)
Sneezing	3(21)	5(17)
Sinus headache	2(14)	6(20)
Itchy, watery eyes	2(14)	4(13)
Hoarse voice	1(7)	2(7)
Other	1(7)	2(7)

* There were no differences between the proportion of patients reporting any of the symptoms among patients with a PC_{20} less than 8 mg/mL and those with a PC_{20} greater than 8 mg/mL ($P > 0.05$).

exhalation. For the maximal forced exhalation, the patient was instructed to inhale fully and then exhale through a wide open mouth as forcefully and quickly as possible. A wheeze was defined as a continuous sound with a musical quality. "Monophonic" wheezing denoted a single note or several notes starting and ending at different times. "Polyphonic" wheezing contained several notes starting and ending simultaneously, like a dissonant musical chord (12). The wheeze was considered "prolonged" if it was judged to last at least two-thirds of the expiratory cycle. The characteristics of the wheeze were noted, as well as whether the wheeze was heard more loudly somewhere over the lung fields or the trachea. To evaluate intraobserver variability, one of the investigators examined all of the subjects, and one of four second physicians, also unaware of the patients' histories and first observer's findings, examined the last 31 patients in similar fashion. In addition, each patient completed a brief questionnaire designed to assess symptoms, allergy history, and both previous and recent treatment. Each patient then underwent methacholine challenge testing.

Spirometry and Methacholine Challenge Testing

Baseline spirometry, including flow-volume loops, was obtained using a P.K. Morgan (North Andover, Massachusetts) rolling seal spirometer. Forced expiratory volume in one second (FEV_1) was determined by a computer using the back extrapolation technique. FEV_1, forced vital capacity (FVC), and peak expiratory flow rate were determined using BTPS (body temperature, ambient pressure, saturated with water vapor) corrected values. Prediction equations for FEV_1, FVC, and FEV_1/FVC (14) and peak expiratory flow rate (15) were used to calculate percent predicted values. Only subjects whose FEV_1 and FEV_1/FVC were 78% predicted or greater were included in the study. No patient had used a beta-agonist inhaler during the 12 hours before the test, nor had any patient used theophylline compounds or antihistamines within the preceding 24 hours. Methacholine challenge testing was done using a method modified from that described by Juniper and colleagues (16). The test aerosols were generated continuously by disposable Hudson nebulizers set at flow rates of 8 L/min which delivered a nebulizer output of 0.30 $\pm$ 0.04 mL/min (mean $\pm$ SD). The test solutions were nebulized for 2 minutes with the mask held loosely over the face while the patient breathed normal tidal volumes through the mouth. Methacholine solutions were prepared using an isotonic, pH-buffered aqueous solution as the diluent, prepared from 0.5% sodium chloride, 0.275% sodium bicarbonate, and 0.4% phenol. Solutions of 0, 0.1, 0.5, 1, 2, 5, 10, and 25 mg methacholine/mL diluent were available for each methacholine challenge test.

After patients inhaled the diluent alone, they were administered progressively increasing concentrations of methacholine solutions at approximately 5-minute intervals. The starting concentration of methacholine solution ranged from 0.1 to 1.0 mg/mL depending on baseline spirometry, clinical history, and the recent treatment required to control symptoms (17). Response to each nebulization was measured by the FEV_1 from spirometry done at 1, 2, and 3 minutes after the end of the nebulization. The best of the three efforts was compared to the similarly obtained best effort after the postdiluent nebulization, and the percent fall in FEV_1 recorded. The test was stopped when a fall in FEV_1 of greater than 20% had occurred or after nebulization of the highest concentration of methacholine. The test was considered technically acceptable if the best postdiluent FEV_1 was at least 90% of the best baseline FEV_1 (17).

The methacholine challenge test data were analyzed by linear regression analysis of the log dose-response curve using only those consecutive points representing a fall in FEV_1 of more than 2.5% from the postdiluent value. From the linear regression line, the log dose corresponding to a 20% fall in FEV_1 was calculated. A positive methacholine challenge test was defined as a test with a PC_{20} less than 8 mg/mL.

Statistical Analysis

Ninety-five percent confidence intervals (CI) for proportions were calculated from the corresponding normal distribution approximation (18). Proportions were compared by Fisher exact test. Values are expressed as mean $\pm$ standard deviation unless otherwise indicated.

Results

Of the 46 subjects undergoing methacholine challenge testing, the 44 (19 men and 25 women) who had technically acceptable methacholine challenge tests constituted the study group. The mean age was 44 $\pm$ 16 years. FEV_1, FVC, and peak expiratory flow rate expressed as a percent of predicted values were 96% $\pm$ 12%, 97% $\pm$ 12%, and 110% $\pm$ 17%, respectively. No patient had an FEV_1, FVC, or peak expiratory flow rate less than 78% of predicted. Cough was a "most bothersome symptom" in 30 patients, dyspnea in 16, and other symptoms such as wheezing, chest tightness, and throat clearing in 4. Although there was a tendency for cough and dyspnea to be reported more frequently in subjects with a PC_{20} less than 8mg/mL, no symptom was commoner in this group than in those with PC_{20} greater than 8mg/mL ($P > 0.05$) (Table 1).

Of the 31 patients evaluated by two physicians, there was complete agreement that wheezing was absent on routine auscultation in all subjects and agreement as to the presence or absence of a wheeze on maximal forced exhalation in 28 of 31 patients. Of the 17 patients who were felt to wheeze by both physicians, there was agreement as to whether or not the wheeze was heard more loudly over the trachea when compared with the lung fields in 15. Since there was excellent agreement between physicians on the physical examination, the physical examination findings of the investigator were considered further with respect to all 44 subjects.

The relationships between wheezing and methacholine challenge test results are summarized in Table 2 and Figure 1. Wheezing on maximal forced exhalation was heard in 8 of 14 patients with a positive methacholine challenge test and was absent in 11 of 30 patients with a negative methacholine challenge test. The sensitivity of wheezing on maximal forced exhalation in predicting a positive methacholine challenge test was 57% (CI, 31% to 88%) and the specificity was 37% (CI, 20% to 54%). When the definition of a positive methacholine challenge test was liberalized to include all those tests with a PC_{20} less than 16 mg/mL, or restricted to only those tests with a PC_{20} less than 4 mg/mL, neither the sensitivity nor specificity was changed ($P > 0.05$). Regardless of which of the above cut-off values was used to define a positive methacholine challenge test, wheezing on maximal forced exhalation was just as common in those with a negative as in those with a positive test ($P \geq 0.05$). The positive predictive value of wheezing was quite low, with only 8 of 27 of patients who wheezed having a PC_{20} below 8 mg/mL. All 5 patients with a PC_{20} less than 3 mg/mL, however, had wheezing on maximal forced exhalation.

Wheezing on maximal forced exhalation which was heard more loudly over some part of the lung fields than over the trachea was quite specific for a positive methacholine challenge test; only 4 of 30 patients with a PC_{20} greater than 8 mg/mL had this finding (specificity = 87%). Its sensitivity, however, was very poor, with only 3 of 14 patients with a PC_{20} less than 8 mg/mL having wheezing on maximal forced exhalation louder over the lung fields.

Five patients were felt to have both prolonged and polyphonic wheezing. Two had PC_{20} values greater than 25 mg/mL and the others had PC_{20} values of 6, 3, and 0.5 mg/mL, respectively. A sixth patient was found to have prolonged but monophonic wheezing; his PC_{20} was greater than 25 mg/mL.

Discussion

The patients in this study should be representative of those suspected of having atypical asthma on the basis

Table 2. *Wheezing on Maximal Forced Exhalation and Methacholine Challenge Test Result**

Cut-off Value for a Positive Methacholine Challenge	Methacholine Challenge	
	Positive	Negative
	n/n(%)	
PC_{20}		
< 16 mg/mL	9/16(56)	18/28(64)
< 8 mg/mL	8/14(57)	19/30(63)
< 4 mg/mL	5/7(71)	22/37(59)

* The PC_{20} is the concentration of methacholine required to produce a 20% fall in FEV_1. For each cut-off value for a positive methacholine challenge test, there is no difference ($P > 0.05$) between the percent of those who wheeze on maximal forced exhalation with a positive methacholine challenge test and those who wheeze with a negative methacholine challenge test. Neither the sensitivity (% wheezing with a positive methacholine challenge test) nor specificity (100% minus % wheezing with a negative methacholine challenge test) differs between the cut-off values ($P > 0.05$).

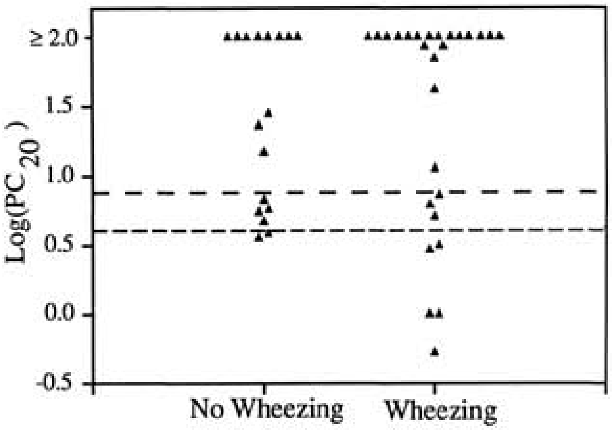

Figure 1. Methacholine challenge test results and wheezing. The PC_{20} is the concentration of methacholine required to produce a 20% fall in FEV_1 (forced expiratory volume in one second). The top dashed line represents a PC_{20} of 8 mg/mL and the lower dashed line represents a PC_{20} of 4 mg/mL.

of symptoms of cough or dyspnea, with normal or nearly normal spirometry. It is unlikely that physicians based their referral decisions for methacholine challenge testing on whether or not they heard wheezing restricted to maximal forced exhalation. In this group of patients, wheezing on maximal forced exhalation lacked both sensitivity and specificity in predicting the results of methacholine challenge testing.

Methacholine challenge testing has been shown to have excellent sensitivity in diagnosing asthma (7, 19-21). Using histamine, which has a similar dose-response relationship as methacholine (16, 17), Cockcroft (22) found that 69% of asymptomatic asthmatics and 100% of mildly symptomatic asthmatics had PC_{20} values less than 8 mg/mL. Only 3% of normal subjects have PC_{20} values less than 8 mg/mL (23). The specificity in clinical practice, however, may be less impressive. Chronic and allergic rhinitis have been sources of confusion regarding the specificity of methacholine challenge testing. Most investigators have found that roughly 25% to 50% of patients with allergic rhinitis have increased nonspecific bronchial responsiveness (21, 22, 24, 25). Since many persons with rhinitis who have positive methacholine challenge tests, have other subtle objective evidence of asthma (26) or later develop overt asthma (24), it is unclear whether these persons have methacholine challenge tests that are truly false positive or have subclinical asthma. The increased bronchial responsiveness found in most persons with allergic rhinitis, however, is generally mild (20, 22) and greater than 4 mg/mL (26). Hence, by lowering the cutoff PC_{20} value used to diagnose asthma to 4 mg/mL, methacholine challenge testing should be very specific for asthma.

We found that wheezing on maximal forced exhalation was not successful in separating individuals with a positive methacholine challenge test from those with a negative test regardless of whether the cutoff PC_{20} was 16, 8, or 4 mg/mL. In fact, neither the specificity nor sensitivity of wheezing on maximal forced exhalation was changed by these manipulations, with the true positive rate and false positive rate remaining unchanged. Using a cutoff PC_{20} of 8 mg/mL, only 8 of

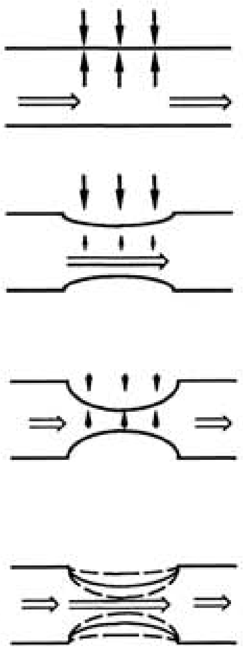

Figure 2. Postulated wheeze mechanism. The stability of the airway wall depends on a balance between internal air pressure and external forces, and on the mechanical characteristics of the airway itself. When a narrowing of the lumen occurs, the air velocity must increase through the constricted region to maintain a constant mass flow rate. According to the Bernoulli principle, the increased air velocity leads to a decrease in air pressure, thus allowing external forces to further collapse the airway. When the lumen has been reduced so much that the flow decreases, the process begins to reverse itself as the pressure inside the airway begins to increase and reopen the lumen. When conditions are right, the airway wall flutters between nearly occluded and occluded positions and produces wheezing. Short open arrows indicate slower flow; long open arrows indicate faster flow. Large closed arrows indicate higher pressure; small closed arrows indicate lower pressure. Modified from Murphy and Holford (32); reproduced with permission.

14 patients with a positive methacholine challenge test had wheezing, and of those who wheezed, only 8 of 27 had a positive methacholine challenge test. However, all 5 persons who had PC_{20} values of less than 3 mg/mL wheezed on maximal forced exhalation, suggesting that those with very reactive airways will have wheezing on maximal forced exhalation.

We found no relation between the type of wheezing (louder over the lung than trachea, or prolonged and polyphonic) and the methacholine challenge test results. Because transmission of lung sounds is better through the airways than lung parenchyma, wheezing that is loudest over the trachea may originate further down the bronchial tree (27).

Wheezing is felt to occur due to rapid oscillations of bronchial walls between an occluded and nearly occluded position (13, 28) (Figure 2). Due to the Bernoulli principle, for a given wall mass, fluid mass, and wall stiffness, oscillations will occur when a critical velocity of flow is exceeded (12, 29). When an airway is already narrowed by inflammation or bronchospasm, the velocity of flow across the narrowing will be greater for any given driving pressure. Because the total cross-sectional area of higher order bronchi is much greater than that of the central airways, the velocity of flow in these small airways is much slower. Therefore, if the narrowing is confined to peripheral bronchi, the velocity of flow may never exceed the critical velocity necessary to produce a wheeze (28). In asthmatics with normal or nearly normal baseline FEV_1, FVC, and FEV_1/FVC, one would expect that airway narrowing is either absent or confined to the peripheral airways. This theory could explain the lack of sensitivity of wheezing on maximal forced exhalation in detecting these asthmatics. We found that 6 of 14 subjects with a positive methacholine challenge test ($PC_{20} < 8$ mg/mL) did not wheeze.

Wheezing on maximal forced exhalation in normal persons is probably due to the velocity of airflow in large, central airways exceeding the critical velocity. The sudden positive intrathoracic pressure at the start of a forceful exhalation can result in flattening of large airways just as flow is beginning. Using recording equipment, Charbonneau and colleagues (13) found wheezing in 53 of 83 maximal forced exhalations of 32 normal persons. We found wheezing on maximal forced exhalation in 19 of 30 persons who had a negative methacholine challenge test ($PC_{20} > 8$ mg/mL).

Aside from this normal physiologic cause of wheezing, there are other possible mechanisms of wheezing. Irwin and colleagues (30) found flow-volume loop evidence of variable upper airway obstruction in patients with postnasal drip that disappeared after successful treatment. Factitious asthma with loud tracheal wheezing can occur due to exhalation against vocal cords held in apposition either consciously or unconsciously (3, 31).

Care must be taken not to extend the results of this study to auscultatory observations made during a submaximal forceful exhalation. Normal persons are considered not to wheeze except on a maximal expiratory effort (11, 12). The asthmatic with airflow obstruction, on the other hand, may progress from single monophonic, to bitonal, and finally polyphonic wheezing as the expiratory effort is progressively increased (12). The only patient in our study who had wheezing on submaximal exhalations had a PC_{20} of 0.5 mg/mL, and had prolonged, polyphonic wheezing on maximal forced exhalation.

In patients with symptoms of cough or dyspnea and normal or nearly normal baseline spirometry, short, monophonic wheezing heard only on maximal forced exhalation is just as likely to occur among those with positive as those with negative methacholine challenge tests. This finding remains true over a wide range of provocation concentrations used to define a positive test. Wheezing on maximal forced exhalation in these subjects lacks sensitivity and specificity in diagnosing asthma.

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