Editor's key points

- Diagnosis of asthma is often challenging because asthma is associated with variable airflow obstruction. The very low sensitivity of simple spirometry in confirming de novo asthma diagnosis is an important clinical challenge in primary care, as the appearance of normal lung function and the lack of forced expiratory volume in 1 second reversibility might be taken to imply the absence of disease.
- Approximately one-third of patients with respiratory concerns compatible with asthma and normal lung function, including a lack of forced expiratory volume in 1 second reversibility, exhibit airway hyperresponsiveness. To the authors' knowledge, this finding has not been previously reported elsewhere. Individuals with a positive methacholine challenge testing result had significantly greater family history of asthma and presented with significantly reduced baseline and postbronchodilator lung function compared with individuals with a negative methacholine challenge testing result.
- These findings provide important insight into the limitations of simple spirometry for asthma diagnosis and the need for further studies to better clarify the role of methacholine challenge testing in the primary care setting.

Airway hyperresponsiveness in patients with normal spirometry results and symptoms compatible with asthma

Primary care retrospective chart review

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Abstract

Objective To evaluate the proportion of patients with symptoms suggestive of asthma and normal lung function who exhibit airway hyperreactivity with methacholine challenge testing (MCT) in primary care.

Design Retrospective chart review.

Setting Primary care lung clinic in Toronto, Ont.

Participants A total of 69 patients presenting to the lung clinic who had symptoms compatible with asthma, normal spirometry test results, and were referred for MCT.

Main outcome measures Descriptive statistics, frequency counts, independent *t* tests, and χ^2 tests were used to examine differences in the proportion of clinical and demographic variables identified in patients with or without a positive MCT result. Effect size was determined between MCT-positive and MCT-negative patients for both categorical (φ coefficient) and continuous (Hedges *g*) data.

Results Twenty-one patients (30.4%) had positive MCT results, and 48 patients (69.6%) had negative MCT results. Family history of asthma and reduced baseline and postbronchodilator forced expiratory volume in 1 second were associated with a positive MCT result.

Conclusion The findings of this study provide insight into the utility of simple spirometry for asthma diagnosis and the need to further clarify the role of MCT in the primary care setting.

Hyperréactivité des voies aériennes chez les patients ayant des résultats normaux à la spirométrie et des symptômes compatibles avec l'asthme

Revue rétrospective de dossiers en soins primaires

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Résumé

Objectif Évaluer la proportion de patients présentant des symptômes laissant présager l'asthme et une fonction pulmonaire normale qui manifestent une hyperréactivité des voies aériennes à la suite d'un test de provocation à la méthacholine (TPM) en soins primaires.

Type d'étude Une revue rétrospective de dossiers.

Contexte Une clinique de pneumologie en soins primaires à Toronto (Ontario).

Participants Un total de 69 patients qui se sont présentés à la clinique de pneumologie, avaient des symptômes compatibles avec l'asthme, des résultats normaux à la spirométrie et qui ont subi un TPM.

Principaux paramètres à l'étude Des statistiques descriptives, les dénombrements de la fréquence, les tests *t* indépendants et les tests χ^2 ont été utilisés pour examiner les différences dans la proportion de variables cliniques et démographiques cernées chez les patients avec ou sans résultats positifs au TPM. La taille de l'effet a été déterminée entre les patients ayant des résultats positifs au TPM et ceux ayant des tests négatifs au TPM tant pour les données catégorielles (coefficient φ) que pour les données continues (*g* de Hedges).

Résultats Quelque 21 patients (30,4 %) avaient des résultats positifs au TPM et 48 patients (69,6 %) avaient des résultats négatifs au TPM. Des antécédents familiaux d'asthme et un volume expiratoire maximum par seconde au départ et après la bronchodilatation étaient associés à des résultats positifs au TPM.

Conclusion Les constatations de cette étude fournissent des renseignements sur l'utilité de la spirométrie simple pour le diagnostic de l'asthme et la nécessité de mieux préciser le rôle du TPM en milieu de soins primaires.

Points de repère du rédacteur

- Le diagnostic de l'asthme est souvent difficile, parce que ce problème est associé à une obstruction variable du débit d'air. La sensibilité très faible de la spirométrie simple pour confirmer à nouveau un diagnostic d'asthme est un défi clinique en soins primaires, car l'apparence d'une fonction pulmonaire normale et l'absence de réversibilité du volume expiratoire maximal par seconde pourraient être méprises pour l'exclusion de la maladie.
- Environ le tiers des patients ayant des problèmes respiratoires compatibles avec l'asthme et une fonction pulmonaire normale, y compris l'absence de réversibilité du volume expiratoire maximal par seconde, manifestent une hyperréactivité des voies aériennes. À la connaissance de l'auteur, cette constatation n'a jamais été rapportée antérieurement. Les personnes qui avaient des résultats positifs au test de provocation à la méthacholine avaient significativement plus d'antécédents familiaux d'asthme, et présentaient une fonction pulmonaire significativement réduite au point de départ et après la bronchodilatation en comparaison des personnes dont les résultats au test de provocation à la méthacholine étaient négatifs.
- Ces constatations fournissent des renseignements importants sur les limites d'une spirométrie simple pour le diagnostic de l'asthme et la nécessité d'études additionnelles pour mieux préciser le rôle du test de provocation à la méthacholine en milieu de soins primaires.

Asthma ranks among the most common conditions encountered in primary care and the diagnosis might be difficult to confirm using objective measures because of variable airflow obstruction.[1] Many patients encountered in primary care with mild disease often have normal lung function as indicated by forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) at the time of testing.[2] Currently, no criterion standard for asthma diagnosis exists; however, simple spirometry that includes postbronchodilator challenge testing is recommended as a first-line test in many guidelines around the world[1,3] because of its ease of access, use, and portability. An important challenge with this approach is that documenting FEV_1 reversibility (ie, an improvement of at least 12% and 200 mL after bronchodilator challenge) is difficult among most patients with asthma with normal baseline lung function.[4,5] Aaron et al[6] indicated that asthma diagnosis was confirmed in only 16% of patients with previous physician diagnosis of asthma using postbronchodilator spirometry, and Luks et al[7] found that only 10.8% of similar patients were diagnosed with asthma using simple pre- and postbronchodilator spirometry. Aaron et al[8] reported that only 22.5% of patients with suspected asthma fulfilled FEV_1 reversibility criteria with bronchodilator challenge. These latter studies also reported that methacholine challenge testing (MCT) was useful in excluding a diagnosis of asthma in most patients. Finally, among asthma patients with lower lung function compared with the studies cited above, Macy et al[9] found that 62% of patients with asthma were identified using FEV_1 reversibility. Taken together, these reports might suggest that baseline lung function influences bronchodilator responsiveness. The studies outlined previously[4,5] also highlight that MCT is much more sensitive for confirmation of asthma diagnosis among patients with a previous diagnosis of asthma who have normal lung function.

The very low sensitivity of simple spirometry in confirming asthma diagnosis represents an important clinical challenge in primary care with respect to de novo asthma diagnosis, as the appearance of normal lung function and the lack of FEV_1 reversibility might be taken to imply the absence of disease. In patients with symptoms compatible with asthma who have normal spirometry results, MCT is recommended to clarify clinical suspicion.[1] At the time of publication, there are no studies that describe airway hyperreactivity among patients in primary care who have symptoms compatible with asthma, no previous diagnosis of asthma, normal baseline lung function, and lack of FEV_1 reversibility.

The primary purpose of this study was to evaluate the proportion of patients who have symptoms suggestive of asthma and normal lung function (including a lack of FEV_1 reversibility) who exhibit airway hyperreactivity using MCT in primary care. The secondary objective was to determine whether there are differences in clinical characteristics between patients with positive and negative MCT results.

Methods

Study population

This was a retrospective chart review of 69 patients with symptoms compatible with asthma who attended a primary care lung clinic in Toronto, Ont. Patients were included if they had a clinical history compatible with asthma, had normal spirometry test results (ie, FEV_1-FVC ratio > 0.70 or at the lower limit of normal; both FEV_1 and FVC values greater than 80% of predicted normal; and an improvement in FEV_1 of less than 12% and 200 mL after bronchodilator challenge), and underwent MCT. Data were excluded from this study if chart notes suggested a previous asthma diagnosis.

Symptomatic participants with normal lung function who did not exhibit reversible airflow obstruction with simple spirometry were referred to a local respiratory specialty clinic for MCT only; a formal consultation with a specialist was not requested. All the MCT was performed at the same facility using a technique and standard following the American Thoracic Society (ATS)[4]: provocative concentration (PC_{20}) of methacholine. A 20% reduction in FEV_1 (PC_{20} less than 8 mg/mL) was considered consistent with asthma.[4]

Clinical and demographic variables

Sex, age, body mass index, family history of asthma, history of cigarette smoking, nasal allergy symptoms, allergy skin test results, spirometry results, and MCT results were collected. In order to reflect a real-world approach to asthma diagnosis, we did not gather data related to sputum samples or blood eosinophil counts. *Cigarette smoking* was defined as active smoking during the period of respiratory and chest concerns. Patients with a smoking history of more than 10 years were excluded to reduce the likelihood of including individuals with chronic obstructive pulmonary disease. Nasal allergy symptoms included rhinorrhea, rhinitis, nasal congestion, and sneezing. For many patients, atopic status was confirmed using the skin-prick method. Symptoms compatible with asthma included cough, wheeze, shortness of breath, and chest tightness. A positive MCT result was defined as PC_{20} less than 8 mg/mL.[10] Pre- and postbronchodilator spirometry was performed on each patient according to ATS standards.[11] None of the patients were taking inhaled or oral medications that could influence spirometry results at the time of initial testing.

The best of 3 technically satisfactory FVC and FEV_1 values were reported. Patient spirometry findings were compared to predicted values based on sex, race, age, and height. Reversibility criteria included an improvement in FEV_1 of at least 12% and 200 mL above baseline after bronchodilator challenge.[1]

Statistical analysis

Descriptive statistics, frequency counts, independent *t* tests, and χ^2 tests were conducted to examine differences in the proportion of clinical and demographic variables identified in patients with positive or negative MCT results. Effect size was determined between patients with positive and negative MCT results for both categorical (φ coefficient) and continuous (Hedges *g*) data.

Results

Of the 69 patients whose charts were reviewed, all had a clinical history compatible with asthma and all had spirometry results that did not fulfil the ATS reversibility criteria. Twenty-one patients (30.4%) had positive MCT results, and 48 patients (69.6%) had negative MCT results.

As shown in **Table 1**, most patients were middle-aged women (65.2%). Few patients smoked (5.8%) and the remainder gave a history of never smoking. Cough was the predominant respiratory complaint (76.8%). Patients who had a family history of asthma were more likely to have positive results on MCT ($P=.016$) than negative MCT results. Patients with positive MCT results had lower absolute baseline and postbronchodilator FEV_1 compared to those with negative MCT results ($P=.040$ and $P=.046$, respectively). No significant differences

Table 1. Baseline demographic and clinical characteristics of all study participants

CHARACTERISTIC	ALL (N = 69)	POSITIVE MCT RESULT (n = 21)	NEGATIVE MCT RESULT (n = 48)	*P* VALUE	EFFECT SIZE (φ OR *g*)
Female sex, n (%)	45 (65.2)	14 (66.7)	31 (64.6)	.867	0.02
Mean (SD) age, y	41.14 (16.03)	38.52 (19.04)	42.29 (14.59)	.373	0.18
Mean (SD) BMI, kg/m^2	26.60 (5.01)	26.07 (5.45)	26.81 (4.86)	.590	0.14
Smoker, n (%)	4 (5.8)	1 (4.8)	3 (6.3)	> .99	-0.03
Family history, n (%)	22 (31.9)	11 (52.4)	11 (22.9)	.016	0.29
Nasal allergy symptoms, n (%)	29 (42.0)	9 (42.9)	20 (41.7)	.927	0.01
Allergy history, n (%)	42 (60.9)	14 (66.7)	28 (58.3)	.514	0.08
Baseline symptoms, n (%)					
• Cough	53 (76.8)	16 (76.2)	37 (77.1)	> .99	-0.01
• Wheeze	32 (46.4)	11 (52.4)	21 (43.8)	.508	0.08
• Shortness of breath	36 (52.2)	13 (61.9)	23 (47.9)	.284	0.13
• Chest tightness	31 (44.9)	10 (47.6)	21 (43.8)	.766	0.04
Spirometry results, mean (SD)					
• Pre FVC, L	3.60 (1.08)	3.24 (0.89)	3.77 (1.13)	.065	0.49
• Post FVC, L	3.62 (1.11)	3.24 (0.93)	3.79 (1.15)	.059	0.50
• Pre FVC, %*	96.32 (14.71)	93.23 (13.16)	97.67 (15.27)	.251	0.30
• Post FVC, %*	96.77 (15.21)	92.90 (12.07)	98.46 (16.22)	.165	0.37
• Pre FEV_1, L	2.99 (0.84)	2.68 (0.66)	3.13 (0.88)	.040	0.54
• Post FEV_1, L	3.09 (0.87)	2.77 (0.73)	3.22 (0.90)	.046	0.52
• Pre FEV_1, %*	96.59 (15.02)	92.02 (14.15)	98.59 (15.09)	.095	0.44
• Post FEV_1, %*	99.76 (15.69)	95.08 (14.35)	101.80 (15.95)	.102	0.43
• ΔFEV_1, L†	0.10 (0.12)	0.10 (0.13)	0.10 (0.12)	.970	0.00
• ΔFEV_1, %†	3.22 (4.16)	3.33 (4.14)	3.18 (4.21)	.892	0.04
• Pre FEV_1-FVC	0.84 (0.07)	0.84 (0.07)	0.85 (0.07)	.638	0.14
• Post FEV_1-FVC	0.87 (0.07)	0.87 (0.08)	0.86 (0.06)	.905	0.15
• Pre FEF_{25-75}, L/s	3.28 (1.09)	2.88 (0.96)	3.45 (1.11)	.053	0.53
• Post FEF_{25-75}, L/s	3.62 (1.07)	3.24 (1.08)	3.78 (1.04)	.058	0.51

BMI—body mass index, FEF_{25-75}—forced expiratory flow at 25% to 75% of the pulmonary volume, FEV_1—forced expiratory volume in 1 s, FVC—forced vital capacity, MCT—methacholine challenge testing, post—postbronchodilation, pre—prebronchodilation.
*Pre- and postbronchodilator percentages are compared to predicted values before and after bronchodilation.
†Change in volume or percentage before and after bronchodilation.

were identified in pre- and post-FVC or in pre- and post–forced expiratory flow at 25% to 75% of the pulmonary volume (FEF_{25-75}) between patients with positive and negative MCT results; however, trending group differences and moderate effect sizes were observed. The mean (SD) PC_{20} for all patients with positive MCT results was 4.39 (2.89) mg/mL. Body mass index, FEF_{25-75}, and MCT referral date data were not retrievable for 3, 3, and 5 patients, respectively, and were therefore not included in the analysis. The mean (SD) time from initial clinic spirometry testing to MCT was 32.73 (48.03) days, with a range of 0 to 237 days.

Discussion

Our findings suggest that approximately one-third of patients in primary care with symptoms compatible with asthma and normal lung function exhibit airway hyperresponsiveness to methacholine. This is higher than the prevalence of positive MCT results in studies of bronchial hyperreactivity in the general population, which ranged from 10% to 20%.[12] In the present study, individuals with a positive MCT result were more likely to report a family history of asthma and demonstrated lower lung function before and after bronchodilator challenge testing compared with individuals with a negative MCT result.

To our knowledge, no studies conducted in primary care, or elsewhere, have reported that patients with symptoms compatible with asthma and normal lung function (ie, who do not meet FEV_1 reversibility criteria) underwent MCT for further diagnostic clarification. This approach is consistent with recommendations in various asthma management guidelines where spirometry is suggested as a first-line diagnostic test.[1,3] Within a tertiary care setting, Hedman et al[13] demonstrated that in the absence of details about reversibility testing, approximately 34% of patients with unexplained cough, wheeze, and dyspnea had a positive MCT result. An additional study conducted in a specialty care setting reported that MCT results were positive in 30.4% of patients with mild, nonspecific respiratory symptoms and normal lung function (using the FEV_1-FVC ratio), although no discussion about FEV_1 reversibility is provided.[14] Taken together, these studies indicate that simple spirometry in the absence of MCT might not identify a group of patients with symptoms compatible with asthma and normal lung function, yet who exhibit airway hyperresponsiveness consistent with a diagnosis of asthma. This finding is of particular clinical relevance, as most individuals with a positive MCT result typically go on to receive guideline-recommended treatment for asthma.[13]

Our finding that a positive MCT result was related to family history of asthma aligns with known risk factors for asthma.[1] Furthermore, our findings related to airway hyperresponsiveness among symptomatic patients are consistent with previous reports.[13,14] We extend these findings by showing that symptomatic patients with a positive MCT result have prebronchodilator lung function that would be considered within the normal range (mean [SD] pre-FEV_1 absolute value = 2.68 [0.66] L compared to predicted values), but is significantly lower compared to individuals with negative pre- and post-FEV_1 MCT absolute values (**Table 1**). Furthermore, while it is not significant, it is worth noting that pre- and post-FVC and FEF_{25-75} demonstrated moderate effect sizes and trended toward being significantly lower in individuals with positive MCT results. Together, these observations are consistent with an increase in airway tone against a background of heightened airway hyperresponsiveness.

Reports[8] suggest that asthma overdiagnosis might be as high as 30% when objective tests are used for diagnostic confirmation. For example, Aaron et al[8] demonstrated that when patients diagnosed with asthma were subjected to objective tests for diagnostic confirmation, 30% did not meet criteria for asthma. While simple spirometry is currently recommended as a first-line test for objective confirmation of asthma, our findings raise awareness about the limitations of this approach for suspected asthma in primary care. Unlike simple spirometry, MCT is less available and requires specific skills for testing and interpretation. In the present study, the average time from initial clinic spirometry to MCT was about 32 days in a large urban setting, a finding that could be different in smaller and more remote areas. It is also relevant to note that in our study, referral to a specialty centre was only for MCT, eliminating the cost of a formal consultation from a respiratory specialist, an approach that requires further study in terms of possible cost savings and strategic care planning at the community level. It is relevant to note that airway challenge testing has undergone changes in the past decade that include current recommendations to base the test result on a methacholine dose (ie, provocative dose) instead of a methacholine concentration (ie, PC_{20}) that causes a 20% fall in FEV_1.[15] This change has facilitated comparisons of results from different devices and protocols; however, it would not affect the findings of the present study as methacholine testing took place at the same centre using a single protocol.

Taken together, our findings highlight the importance of reminding family physicians of the limitations of simple spirometry for asthma diagnosis and the need for further research relating to the feasibility of having rapid access to MCT in the community setting, including the development of management approaches that take into consideration the potential lag time from initial presentation to MCT in some communities. It is also important to consider that the ability to apply our findings will relate to the availability of MCT to family physicians in regions across Canada.

Limitations

Important limitations of this work warrant consideration. Within this study, patients with respiratory concerns and abnormalities in lung function that would be consistent with asthma were excluded, as these patients typically would not be candidates for MCT. These data might provide a pragmatic perspective on the utility of simple spirometry in this broader population. Furthermore, as we did not consider seasonal variations in symptoms, it is possible that testing out of season might result in false-negative MCT results, which tend to underestimate the proportion of patients exhibiting a positive MCT result. However, it is noteworthy that MCT has very high specificity in general.[16] The data in the present study were gathered within a quality improvement framework from a single clinic; this approach might limit the generalizability of our results. Finally, differences in the number of patients identified as having either positive or negative MCT results (ie, n=21 vs n=48, respectively) might have influenced our power to detect significant differences between these groups.

Conclusion

We report for the first time that approximately one-third of patients in primary care with respiratory symptoms compatible with asthma and normal lung function, including a lack of FEV_1 reversibility, exhibit airway hyperresponsiveness. Individuals with a positive MCT result had significantly greater family history of asthma and presented with significantly reduced baseline and postbronchodilator lung function compared with individuals with a negative MCT result. These findings provide important insight into the limitations of simple spirometry for asthma diagnosis and the need for further studies to better clarify the role of MCT in the primary care setting.

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Contributors

All authors contributed to the concept and design of this study; data gathering, analysis, and interpretation; and preparing the manuscript for submission.

Competing interests

None declared

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