

Use of Specific Inhalation Challenge in the Evaluation of Workers at Risk for Occupational Asthma*

A Survey of Pulmonary, Allergy, and Occupational Medicine Residency Training Programs in the United States and Canada

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Study objectives: To document the current practice of occupational asthma (OA) diagnosis and use of specific inhalation challenge (SIC).

Design, setting, and participants: A survey evaluating the current practice of SIC was mailed to 259 residency training programs in adult pulmonary diseases, allergy and immunology, and occupational medicine accredited in the United States and Canada during the year 2000.

Results: Forty-six percent (123 of 259 programs) participated. Ninety-two programs reported that patients with OA were seen during the previous year, 15 programs reported that SIC had been performed, and 10 programs reported that patients had been referred to other sites for SIC. A total of 259 patients underwent SIC. No unexpected adverse reactions were reported. Forty-one programs reported that they had been willing to undertake SIC but were unable to do so. The most common barriers cited were lack of availability of SIC within the evaluating institution, inability to locate a site for referral, concerns about reimbursement, and lack of an appropriate diagnostic reagent for use in SIC. Seventy-four programs indicated that SIC was useful, and 34 programs included training in the use of SIC as part of the residency curriculum.

Conclusion: Although SIC is considered the “gold standard” for objective documentation of OA, the test is performed in only a few institutions in the United States and Canada. Many institutions indicate that SIC is not available, even when desired for patient management. Only a minority of participating residency training programs include SIC as a formal part of the training curriculum. (CHEST 2002; 121:1323–1328)

Key words: occupational asthma; specific inhalation challenge; residency training program

Abbreviations: BHR = bronchial hyperreactivity; OA = occupational asthma; SIC = specific inhalation challenge

Work-related asthma has become the most prevalent occupational lung disease in industrialized countries.^{1,2} It has been classified into work-aggravated asthma, characterized by exacerbation of preexisting asthma at work; irritant-induced asthma, also known as reactive airways dysfunction syndrome; and sensitizer-induced occupational asthma (OA).³ OA is generally

associated with a latency period of months to years between first exposure to an agent and development of immunologic sensitization and asthma.

The certainty of the diagnosis of OA depends on how well the physician proves that the worker has asthma, that asthma occurs in relation to workplace exposures, and that a specific sensitizing agent in the workplace has resulted in the development of this illness. Asthma is usually diagnosed by a combination of history, clinical findings during an exacerbation, and demonstration of bronchial hyperreactivity (BHR). BHR can be demonstrated by spirometric response to a bronchodilator, or spirometric response to a constrictor such as methacholine, histamine, or cold air—features typically, but not always, apparent in patients with OA.^{4,5}

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There is a substantial body of work that recognizes that physicians are frequently incorrect in demonstrating the relationship between asthma and the workplace. The clinical diagnosis of OA is difficult. Linkages between asthma and workplace exposures can be objectively assessed in several ways. Immunologic tests can document systemic sensitization to workplace allergens; however, they may also reflect an immune response to an agent unrelated to asthma. Serial ambulatory measurement of peak flow rates over a period of several weeks at work and then away from work can be used to document excessive variability while at work.⁶ Such serial peak flow measurements can assist in diagnosis of OA, yet difficulties in the interpretability and validity of records are frequently encountered.⁷⁻¹⁰

Serial measurements of BHR performed at work and then after at least 2 weeks away from exposure can be used to establish a linkage between workplace exposures and asthma. A significant lessening in BHR after removal from the workplace is supportive of a diagnosis of OA. However, in western red cedar workers, this approach was less helpful than peak flow monitoring.¹¹ Potential problems with use of BHR for diagnosis of OA include sensitivity, as OA can occur without BHR.¹² Specificity is a particularly important problem, as BHR can be caused by a number of processes other than OA, such as asthma unrelated to the workplace, allergic rhinitis, viral upper respiratory tract infections, and COPD.¹³⁻¹⁵ The sensitivity and specificity of BHR is influenced by the cutoff used to define an abnormal test result and the definition of asthma that is used. Nevertheless, the absence of BHR within 24 h of the worker's usual respiratory symptoms with workplace exposure makes the diagnosis of OA exceedingly unlikely, and correlates well with negative peak flow results. Thus, serial BHR measurements at and then away from work may be a useful adjunct to serial peak flow monitoring, but careful clinical correlation is required.

Finally, specific inhalation challenge (SIC) with occupational agents conducted either in a laboratory or in the workplace can establish linkages between workplace exposures and asthma. In fact, SIC has been described as the "gold standard" for diagnosis of OA.¹⁶ In research settings, SIC has been used to investigate performance characteristics of other measures used to diagnose OA. For example, in one series, 63 isocyanate-exposed workers with a physician's diagnosis of OA were referred for SIC.¹⁷ Eighty-eight percent reported work-related respiratory symptoms and 97% noted an improvement in chest complaints when away from the workplace, yet only 33 workers had airway responsiveness following SIC with the offending agent. To make the diagnosis even more difficult, 43% of those who did not

respond to SIC had BHR, confirming the fact that the measurement of nonspecific airway hyperresponsiveness may help in the diagnosis of asthma, but does not diagnose OA. Importantly, the surprisingly low percentage of patients clinically suspected of having OA who have a positive SIC finding to the suspected offending agent in the above-mentioned study (48%) is similar to data reported by others.^{18,19}

It is a common perception that SIC is only performed in a few specialized centers in the United States. In this article, we sought to document usage of SIC in the United States and Canada by conducting a survey of representatives of three different types of academic residency training programs likely to use SIC in patient management: pulmonary and critical care medicine, allergy and clinical immunology, and occupational medicine. Queries focused on current practice and methods used to diagnose OA, perceptions about SIC, usage of SIC, and barriers to using SIC.

MATERIALS AND METHODS

The study sample was program directors or, in some cases, their designees at all adult residency training programs in pulmonary and critical care medicine, allergy and clinical immunology, and occupational medicine accredited by the American College for Graduate Medical Education in the United States and Canada during the year 2000. A total of 259 surveys were mailed to program directors as identified by the American College for Graduate Medical Education in June 2000, followed by a reminder letter in August. Responses were received from 123 programs, and all were received by November 2000. The survey included questions regarding the number of OA cases seen at each institution and the methods used to assess OA in the previous year. We asked whether SIC was performed in the training program or by referral and how many patients had been studied. We asked about specific types of agents used to perform SIC, methods used to generate exposures, potential complications, and indications for referral of patients, such as academic or legal concerns. We also investigated barriers to performing SIC, whether SIC was formally covered in training program curricula, and attitudes about SIC. Descriptive statistics were conducted using computer software (JMPIN, version 3.2; SAS Institute, Cary, NC).

RESULTS

Characteristics of training programs responding to the survey are shown in Table 1. The overall participation rate was 123 of 259 programs (47.5%). Ninety-two of 123 programs (74.8%) reported that OA had been diagnosed. Overall, these programs reported 2,373 cases of OA, 1,330 cases (56%) in the pulmonary and critical care medicine programs, 320 cases (13.5%) in the allergy and clinical immunology programs, and 723 cases (30.5%) in the occupational medicine programs. The geographic distributions of

Table 1—Characteristics of Training Programs Completing the Study*

Type of Program	Contacted	Responded	Seeing OA Patients	Think SIC Useful	Perform SIC	Refer for SIC	SIC Not Available	Training in SIC
Pulmonary	150	71	55	45	6	2	23	11
Allergy	72	30	17	17	6	3	6	10
Occupational medicine	37	22	20	12	3	5	12	13
Total	259	123	92	74	15	10	41	34

*Data are presented as No.

OA cases and SIC procedures are shown in Figure 1. Three hundred eight cases of OA (13%) were diagnosed in Canada, while 2,065 cases of OA (87%) were diagnosed in the United States. In contrast, 129 of 308 cases of OA (42%) evaluated in Canada involved SIC, while only 130 of 2,065 cases of OA (6%) in the United States involved SIC.

A variety of methods were used to diagnose OA. Thirty-seven percent (34 of 92 programs) indicated a willingness to diagnose OA based on clinical history alone, 73% (67 of 92 programs) based on clinical history and spirometry, 66% (61 of 92 programs) based on clinical history and serial peak flow rate measurements, and 78% (72 of 92 programs) based on clinical history and nonspecific BHR. Sixteen percent (15 of 92 programs) reported that SIC was performed in the training program, while 11% (10 of 92 programs) reported that SIC was obtained on a referral basis outside the training program. Other methods less frequently used to diagnose OA were workplace challenge (three programs), skin or radioallergosorbent testing (three programs), and induced sputum (one program).

In the programs in which serial peak flow measurements were used to diagnose OA, the mean length of peak flow monitoring was 14 days. Monitoring periods ranged from 2 to 60 days. Among those programs in which BHR was used to assist in

diagnosis of OA, methacholine was the most commonly used nonspecific inhalation challenge test agent (67 of 92 programs; 73%). Histamine was used by 5% (5 of 92 programs), cold air by 2% (2 of 92 programs), exercise by 2% (2 of 92 programs), and carbachol by 1% (1 of 92 programs).

Representatives from 74 training programs expressed the opinion that SIC was useful, and 25 training programs reported that patients were studied by SIC or by referring them for the procedure (Table 1). Indications for SIC reported by programs included identification of agents triggering respiratory symptoms (22 programs), compensation or legal reasons (14 programs), or academic reasons such as research or a case report (13 programs). Fifteen programs reported a total of 259 SIC procedures during the previous 12 months. Table 2 lists the specific location and contact of 12 of these programs; 3 programs asked that their locations not be disclosed. Of the 15 programs in which SIC was conducted, 154 procedures were performed in 6 pulmonary programs, 75 procedures were performed in 6 allergy programs, and 30 procedures were performed in 3 occupational medicine programs. With regard to generation of exposures to workplace agents, 87% (13 of 15 programs) of those in which SIC was performed used controlled laboratory exposures, 67% (10 of 15 programs) simulated workplace activity in the laboratory, and 7% (1 of 15 programs) used workplace challenge. Workplace agents reported to have been used in exposures are detailed in Table 3. No serious adverse reactions to SIC were reported over the last 12 months by any of the respondents.

Among all training programs that contributed to the survey, 60% (74 of 123) had the opinion that SIC was a clinically useful procedure. Among those feeling that SIC was useful, 55% (41 of 74) had wanted to do the test but been unable to obtain it (Table 1). Barriers to obtaining the test were reported to be an inability to perform the test within the institution sponsoring the program ($n = 37$); lack of a specific agent for use in challenge studies ($n = 20$); lack of reimbursement by insurance ($n = 16$); inability to find a referral site ($n = 15$); concern about legal or

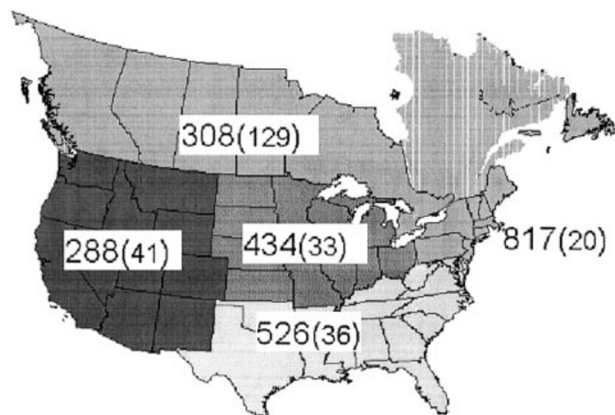


FIGURE 1. The number of OA cases and, in parenthesis, the number of SICs in the last 12 months by region.

Table 2—Residency Training Programs Conducting SIC in the United States and Canada

Training Program Director	Program	Address
Mark R. Cullen, MD	Occupational medicine	Yale University School of Medicine, 135 College Street, 3rd Floor, New Haven, CT 06510
Theodore M. Freeman, MD	Allergy and clinical immunology	Wilford Hall Medical Center, WHMC/PSMA, 2200 Berquist Drive, Suite 1, Lackland AFB, TX 78236-5300 Theodore.Freeman@59mdw.whmc.af.mil
Alain Desjardins, MD, FRCPC	Pulmonary and critical care	Sacre-Coeur Hospital, 5400 Gouin Quest, Montreal, PQ, Canada H4J 1C5 alin.desjardins@videotron.ca
Gregory Downey, MD	Pulmonary and critical care	University of Toronto, 1 King's College, Medical Sciences Bldg., RM 6265 Toronto, ON, Canada M5S 1A8 gregory.downey@utoronto.ca
Stuart F. Quan, MD	Pulmonary and critical care	University of Arizona, 1501 N. Campbell Avenue, PO Box 245030, Tucson, AZ 85724-5030 squan@resp-sci.arizona.edu
Jim Cheng, MD (Tom Noseworthy, MD current director)	Occupational medicine	University of Alberta, 13-103 Clinical Science Bldg., Edmonton, AB, Canada T6G 2G3 tom.noseworthy@ualberta.ca
David Stubbing, MB, BS, FRCPC	Pulmonary and critical care	Hamilton Health Sciences Corporation, PO Box 2000, Hamilton, ON, Canada L8N 3Z5 stubbing@hhsc.ca
Robert G. Townley, MD	Allergy and clinical immunology	Creighton University Center for Allergy, Asthma, Immunology, 2500 California Street, Omaha, NE 68178 diva@creighton.edu
James R. Baker, MD	Allergy and clinical immunology	The University of Michigan Medical Center, 1500 E. Medical Center Drive/3918 Taubman Center, Ann Arbor, MI 48109-0666 johari@umich.edu
Zuhair K. Ballas, MD	Allergy and clinical immunology	The University of Iowa Hospitals and Clinics, Department of Internal Medicine, 200 Hawkins Drive, Iowa City, IA 52242 ballasz@uiowa.edu
David Bernstein, MD	Allergy and clinical immunology	University of Cincinnati College of Medicine, Division of Immunology, 231 Bethesda Avenue, ML 563, Cincinnati, OH 45267 bernstdd@email.uc.edu
Lanny J. Rosenwasser, MD	Allergy and clinical immunology	National Jewish Center for Immunology and Respiratory Medicine, 1400 Jackson Street, Denver, CO 80206 rosenwasserl@njc.org

liability issues (n = 8); inability to obtain institutional review board or safety division approval (n = 4); and refusal by patient (n = 1). Training on indications, performance, and interpretation of SIC testing as part of the curriculum of the residency training program was reported by 11 pulmonary programs, 10 allergy programs, and 13 occupational medicine programs (Table 1).

DISCUSSION

Responses to our survey have important implications both for current practice of OA diagnosis

in general and current utilization of SIC in particular. With regard to diagnosis of OA, results suggest that suboptimal approaches may often be used to diagnose OA. For example, 37% of programs in which patients with OA were observed reported a willingness to diagnose OA based on clinical history alone. However, a number of studies^{16,20} suggest that clinical history has poor specificity for establishing linkages between workplace exposures and asthma. Thus, use of clinical history alone would be expected to result in substantial overdiagnosis of OA.

Table 3—Most Common Workplace Agents Used in SIC

Agents
Isocyanates
Latex
Flour
Wood particles
Ragweed pollen
Plicatic acid
Wall board
Epoxy resins
Rodent litter
Cat
Dog
Bird
Mites
Formaldehyde
Glutaraldehyde
Red cedar
Perfume
Cement
Asphalt ingredients
Cleaning solutions
Photocopy material
Laquer
Amines
Welding fumes

Another potential problem in diagnosis of OA suggested by this survey is performance of ambulatory serial peak flow monitoring. A 1995 consensus statement⁶ suggested that to reliably establish a linkage between peak flow variability and work exposures, monitoring should be conducted for a minimum of 2 weeks at work and 2 weeks away from work. In contrast, the mean duration of peak flow monitoring reported by programs in response to this survey was 14 days, with one program reporting having used as little as 2 days. Monitoring of such short durations might result in substantial misclassification of patients as having OA. As a general rule, the duration of monitoring is dependent on severity of the disease, medications requirement, duration, compliance, and exposure situation. Serial peak flow measurements for such a short term may be insufficient to improve work-related peak flow variability, or the improvement, if any, following removal from work.

With regard to SIC, it is apparent that relatively few centers in the United States and Canada use this approach to linkage of workplace exposures and asthma. Furthermore, it is clear that SIC is used far more frequently in Canada than in the United States. Although SIC has been described by some authorities to be the “gold standard” test for objective confirmation of associations between workplace exposures and asthma, it is by no means perfect. A negative test result

may not exclude the diagnosis of OA if the relevant exposure causing asthma at work is not reproduced. Either exposure to the wrong agent or wrong levels of an agent can lead to such false-negative reactions.²¹ False-negative reactions can also occur if workers have been removed from workplace exposures for a sufficient period of time to decrease reactivity to SIC.²² False-positive reactions can also occur to agents provided at “irritant” level.²³ The imperfect performance characteristics of SIC, coupled with technical demands for generation of controlled exposures, test expense, and time required to perform tests, all likely contributed to the relatively small number of training programs in which the procedure was done. The markedly more frequent rate of use of SIC to diagnose OA in Canada than in the United States is likely related to differences in the legal and worker’s compensation systems of the two countries. However, our data suggest that demand does exist for increased access to SIC for diagnosis of OA.

There are several concerns regarding this work. One of the limitations of this survey is the low participation rate (47.5%). It is possible that the listing of the training programs conducting SIC is incomplete (Table 2). Some programs in which SIC was conducted may not have responded to the survey. Despite of our efforts to increase the response rate, 53% of the pulmonary programs, 58% of the allergy programs, and 41% of the occupational medicine programs did not respond. Additionally, questions were limited to the “last 12 months” at the time of the survey; therefore, it is likely that SIC is no longer conducted in some programs.

In conclusion, our data suggest that suboptimal approaches are often used to establish the diagnosis of OA. Furthermore, even though some authorities have described SIC as the “gold standard” test for objective confirmation of associations between workplace exposures and asthma, the procedure is performed in only a small number of training programs. SIC is much more likely to be used to diagnose OA in Canada than in the United States, suggesting that issues related to the differing medical, legal, and compensation systems of the two countries impact on test usage. Finally, our data suggest that demand does exist for increased access to SIC for diagnosis of OA.

REFERENCES

- 1 Provencher S, Labrenche FP, De Guire L. Physician based surveillance system for occupational respiratory diseases: the experience of PROPULSE, Quebec, Canada. *Occup Environ Med* 1997; 54:272–276
- 2 Gannon PF, Burge PS. The SHIELD scheme in the West Midlands Region, United Kingdom: Midland Thoracic Society Research Group. *Br J Ind Med* 1993; 50:791–796
- 3 Friedman-Jimenez G, Beckett WS, Szeinuk J, et al. Clinical

- evaluation, management and prevention of work-related asthma. *Am J Ind Med* 2000; 37:121–141
- 4 Hargreave FE, Ramsdale EH, Pugsley SO. Occupational asthma without bronchial hyperresponsiveness. *Am Rev Respir Dis* 1984; 130:513–515
 - 5 Banks DE, Barkman HW Jr., Butcher BT, et al. Absence of hyper-responsiveness to methacholine in a worker with methylene diphenyl diisocyanate (MDI) asthma. *Chest* 1986; 89:389–393
 - 6 Moscato G, Godnic-Cvar J, Maestrelli P, et al. Statement on self-monitoring peak expiratory flows in the investigation of occupational asthma; Subcommittee on Occupational Allergy of European Academy of Allergy and Clinical Immunology. *J Allergy Clin Immunol* 1995; 96:295–301
 - 7 Burge PS, O'Brien IM, Harries MG. Peak flow records in the diagnosis of occupational asthma due to isocyanates. *Thorax* 1979; 34:317–323
 - 8 Liss GM, Tarlo SM. Peak expiratory flow rates in possible occupational asthma. *Chest* 1991; 100:63–69
 - 9 Cote J, Kennedy S, Chan-Yeung M. Sensitivity and specificity of PC₂₀ and peak expiratory flow rates in cedar asthma. *J Allergy Clin Immunol* 1990; 85:592–598
 - 10 Hankinson JL. Beyond the peak flow meter: newer technologies for determining and documenting changes in lung function in the workplace. *Occup Med* 2000; 15:411–420
 - 11 Cote J, Kennedy S, Chan-Yeung M, et al. Sensitivity and specificity of PC₂₀ and peak expiratory flow rates in cedar asthma. *J Allergy Clin Immunol* 1990; 85:592–598
 - 12 Lemiere C, Cartier A, Malo JL, et al. Persistent specific bronchial reactivity to occupational agents in workers with normal nonspecific bronchial reactivity. *Am J Respir Crit Care Med* 2000; 162:976–980
 - 13 Empey DW, Laitinen LA, Jacobs L, et al. Mechanism of bronchial hyperreactivity in normal subjects after upper respiratory tract infection. *Am Rev Respir Dis* 1976; 113:131–139
 - 14 Paggiaro PL, Vagaggini B, Drate FL, et al. Bronchial hyperresponsiveness and toluene diisocyanate: long-term change in sensitized asthmatic subjects. *Chest* 1993; 103:423–428
 - 15 Yan K, Salome CM, Woolcock AJ. Prevalence and nature of bronchial hyperresponsiveness in subjects with chronic obstructive pulmonary diseases. *Am Rev Respir Dis* 1985; 132:25–29
 - 16 Cartier A, Malo JL. Occupational challenge test. In: Bernstein IL, Chan-Yeung M, Malo J-L, et al, eds. *Asthma in the workplace*. New York, NY: Marcel Dekker, 1999; 211–233
 - 17 Banks DE, Sastre J, Butcher BT, et al. Role of inhalation challenge testing in the diagnosis of isocyanate-induced asthma. *Chest* 1989; 95:414–423
 - 18 Karol MH, Tollerud DJ, Campbell TR, et al. Predictive value of airways hyperresponsiveness and circulating IgE for identifying types of responses to toluene diisocyanate inhalation challenge. *Am J Respir Crit Care Med* 1994; 149:611–615
 - 19 Moller DR, Brooks SM, McKay RT, et al. Chronic asthma due to toluene diisocyanate. *Chest* 1986; 90:494–499
 - 20 Malo JL, Ghezzi H, L'Archeveque J, et al. Is the clinical history a satisfactory means of diagnosing occupational asthma? *Am Rev Respir Dis* 1991; 143:528–532
 - 21 Carroll KB, Secombe CJP, Pepys J. Asthma due to non-occupational asthma to toluene (tolylene) diisocyanate. *Clin Allergy* 1976; 6:99–104
 - 22 Banks DE, Rando RJ. Recurrent asthma induced by toluene diisocyanate. *Thorax* 1988; 43:660–662
 - 23 Malo JL, Cartier A, L'Archevêque J, et al. Kinetics on the recovery from bronchial obstruction due to hyperventilation of cold air in asthmatic subjects. *Eur Respir J* 1988; 1:384–388