Absence of Hyperresponsiveness to Methacholine in a Worker with Methylene Diphenyl Diisocyanate (MDI)-Induced Asthma*


A 29-year-old man had a persuasive history of respiratory illness following exposures to methylene diphenyl diisocyanate (MDI). He was evaluated by measuring bronchial reactivity to methacholine, both before and after controlled laboratory exposures to MDI. Despite evidence of progressive declines in FEV, with increasing (but subirritant) doses of MDI on three consecutive days, there was no bronchial hyperresponsiveness to methacholine, before or after MDI challenge. We conclude that the absence of nonspecific bronchial hyperresponsiveness does not exclude the possibility of isocyanate asthma. In the face of a compelling history, a negative result of methacholine challenge should not deter observation or laboratory testing for specific respiratory allergy to these chemicals.

Our current understanding of occupational asthma indicates a link between this illness and nonspecific bronchial hyperresponsiveness (NSBH). Specifically, NSBH is increased after sensitization by agents that cause occupational asthma. In patients with occupational asthma, NSBH does not depend on the presence of atopy or FEV, % predicted; and after cessation of exposure to the sensitizing agent and abatement of asthma, NSBH declines toward normal values.\(^1\) NSBH is so often found in asthma, occupational or otherwise, that its absence in a patient is taken as evidence that the illness is, in fact, not asthma.\(^2\)

Over 200 substances have been implicated as causative agents of occupational asthma.\(^3\) One group, the isocyanates, are used in the production of polyurethane foams, coatings and elastomers. Of these, toluene diisocyanate (TDI) has been most frequently studied. Other isocyanates, including methylene diphenyl diisocyanate (MDI), possess airway sensitizing characteristics.\(^4\) The current Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for MDI is 20 ppb vapor, equivalent to 204 \(\mu g/m^3\) aerosol.\(^5\)

The present report is about a worker with symptoms of occupational asthma. Hypersensitivity to MDI was proven by progressively larger falls in FEV, during challenges with increasing (but subirritant) doses of MDI on three consecutive days. Bronchial hyperresponsiveness to methacholine could not be demonstrated before or after the MDI challenge.

**Case Report**

The patient is a 29-year-old white man with no personal or family history of atopy and no recent respiratory infection. He has smoked two packages of cigarettes daily from the age of 15 to the present. Approximately five years prior to this evaluation, on the second day spent unloading a railroad tank car containing MDI, he developed complaints of generalized itching, swelling around the eyes, and nasal congestion and discharge. That evening he experienced cough, chest tightness and wheeze, all of which subsided after an injection of corticosteroids at a local hospital's emergency room.

Following this initial reaction, he has had about a dozen further MDI exposures in the course of his work as technical representative of a chemical company. Each exposure resulted in symptoms similar in kind and timing to those described above. With continued intermittent exposures, these symptoms would persist for several days. Throughout this time he has taken only short courses of over-the-counter antihistamines, and he has required no further emergency room visits. Between exposures he has no allergic or other respiratory complaints. His most recent exposure was two months prior to this evaluation.

His occupational history comprised three years as an infantryman; one year as gas station attendant, waiter, and brewery worker; two years as a salesman of stove heating elements; and the past five and one-half years working for the chemical company. His medical history included pulmonary embolus after a leg fracture.

The physical examination and chest radiographic findings were unremarkable. The hemoglobin concentration was normal, and the white blood cell count was 8,800/cu mm, with 5 percent eosinophils. Results of skin prick testing with ten common inhalant allergens was negative. A radioallergosorbent test (RAST) with MDI conjugated to human serum albumin (MDI-HSA) to detect MDI-specific IgE antibodies was performed using a standard procedure developed in our laboratory.\(^6\) The RAST ratio with MDI-HSA was less than 2 and was therefore considered negative.

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Provocative Challenge Protocol

A challenge protocol was designed to assess bronchial responsiveness to methacholine and MDI. The patient was hospitalized in order to monitor for late reactions. Complete lung function studies were done on days 1 and 6. Exhaled volumes and expiratory flow rates were measured with a dry rolling seal spirometer (Cardio-Pulmonary Instruments series 5000 Pulmolab, Cardio-Pulmonary Instruments, Houston, Texas). At least three satisfactory forced vital capacity maneuvers were recorded during both testing periods. The forced vital capacity (FVC) in the two best curves at each testing differed by less than 5 percent. FVC and forced expiratory volume in one second (FEV₁) were chosen from the largest curve. The FEF₅₋₇₅ was the highest recorded value during each testing session. Test results were compared with predicted values from Knudson and coworkers.⁹ Single breath carbon monoxide diffusing capacity was measured by the method of Arcangel et al.,⁸ and nitrogen washout lung volumes were measured by the method of Boren et al.⁸

Methacholine inhalation challenge tests were performed on days 1 and 6 in a fashion similar to that described by Chai et al.⁶ using the dosimeter devised by Rosenthal and French at Johns Hopkins University, a DeVilbiss No. 646 nebulizer and a bellows spirometer (Jones Pulmonaire, Jones Medical Instruments, Oak Brook, Illinois). After baseline lung function was measured, the maximal FEV₁ was taken from three expiratory maneuvers immediately following and five minutes after each incremental dose of methacholine. The initial methacholine dose was 0.3 cumulative methacholine inhalation units (five breaths of .06 mg/ml solution), with doubling doses to a maximum of 640 cumulative methacholine inhalation units.

MDI has a low vapor pressure at room temperature, and it must be dispersed as an aerosol to generate controlled atmospheres of greater than 7 ppb. A solution of 5 grams MDI per 100 ml acetone was used to produce the concentrations required for challenge testing. As a control, the patient was challenged with acetone alone on day 2 (OSHA PEL for acetone = 1,000 ppm; approximate odor threshold = 20 ppm).

The eventual protocol, revised after day 3 on a day-to-day basis in light of the preceding response, was:

Day 1: Complete lung function testing and methacholine inhalation challenge.

Day 2: Challenge to 6 ppm acetone for 30 minutes.

Day 3: Challenge to 8 ppm acetone and 118 μg/m³ (11.5 ppb) MDI for 30 minutes.

Day 4: Challenge to 13 ppm acetone and 317 μg/m³ (31 ppb) MDI for 60 minutes.

Day 5: Challenge to 9 ppm acetone and 348 μg/m³ (34 ppb) MDI for 60 minutes.

Day 6: Repeat complete lung function testing and methacholine inhalation challenge.

The challenge was initiated by placing the patient in the stainless steel laminar flow inhalation exposure chamber (dimensions: 4 feet wide, 6.2 feet high, 7.2 feet long). A window allowed observation of the subject throughout the procedure. The chamber was constantly flushed with air at flow rates up to 180 cubic feet per minute (cfm). Air entering the chamber passed through high efficiency particulate and activated carbon filters. MDI was then introduced by metering a constant flow of MDI/acetone solution into a heated flash evaporator, entraining the resultant vapor in heated nitrogen, and injecting the mixture into the filtered air stream. The maximum nitrogen flow used was 0.25 cfm. MDI and acetone levels were continuously monitored in the chamber using an MDA scientific model 7000 isocyanate monitor and a Miran model 1A infrared monitor.

Forced expiratory maneuvers were performed pre-exposure, every ten minutes for 80 minutes after initiation of exposure, and hourly for approximately six hours, using a Jones Pulmonaire spirometer and supervised by the pulmonary function technician. In the evening, a Jones Pulmonaire spirometer was placed in the hospital room and forced expiratory maneuvers performed hourly until bedtime and whenever the participant awoke during the night hours. The subject was trained in the use of this spirometer and performed several supervised forced expiratory maneuvers nightly to confirm proper technique.

Results

Initial lung function testing results were within normal limits (Table 1). Comparing the maximal initial (day 1) and final (day 6) lung function results, declines in FEV₁ of 540 ml (11 percent), FVC of 350 ml (6 percent), and FEF₅₋₇₅ of 1.58 L/sec (28 percent) were seen. The total lung capacity and diffusing capacity remained unchanged, while the residual volume increased 167 ml (16 percent). These changes indicated diminishing airway conductance, probably accompanied by slight air trapping.

Measured bronchial responsiveness to methacholine showed a maximal FEV₁ decline of 2 percent on day 1 (at 320 cumulative methacholine breath units) and 15 percent (at 640 units) on day 6 (Fig 1).

The results of daily challenges to increasing concentrations of MDI are shown in Figure 2. This graph depicts daily baseline and post-challenge values of FEV₁ in relation to dosage. By day 5, the baseline

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21509/ on 06/26/2017)
FEV₁ was 80 percent of the first day's baseline. The maximal decline in response to MDI inhalation also occurred on day 5, when the FEV₁ was 69 percent of that day's baseline at three hours and 15 minutes after starting exposure. A late reaction occurred on the final two days of MDI challenge. Maximal decline of FEV₁ in a late reaction occurred 14 hours after initiating exposure on day 4, a fall to 70 percent of that day's baseline. Despite these declines, there was no complaint of chest tightness or cough and no finding of wheeze at any time in the entire evaluation. However, periorbital edema, rhinitis and generalized itching occurred soon after the initial exposure to MDI (day 3) and persisted throughout the remainder of the evaluation.

**DISCUSSION**

Provocative inhalation challenge confirmed that this patient has occupational asthma caused by MDI. He became symptomatic after receiving presumably high exposures while unloading a railroad tank car. Repeat workplace MDI exposures have resulted in recurrent, reproducible episodes of rhinitis, periorbital edema and generalized itching. We provoked those manifestations in the laboratory, and also showed a progressive FEV₁ decline with increasing MDI exposure. The maximal MDI exposure during testing approximated one and one-half times the PEL, a subirritant dose (ie, one not productive of symptoms or acute lung function declines in nonallergic persons).

Asthmatic symptoms occurred after natural exposure, but not following laboratory exposure. These complaints might have developed in association with a further decline in FEV₁, had we continued MDI exposures or increased their concentration. Periorbital edema, pruritis and rhinitis preceded symptoms of asthma that developed in the workplace, and accompanied the declines in FEV₁ measured in the laboratory. These systemic features represent a vigorous mediator response and clinically mimic seasonal allergy, an IgE mediated phenomenon. No atopy was found, and RAST to MDI-HSA was negative.

Our inability to obtain a positive RAST to MDI-HSA was not unexpected. Positive RAST has been demonstrated in only 15-20 percent of serum samples from individuals proven reactive to TDI by provocative inhalation challenge.¹⁴ There are a number of possible reasons for these findings. Isocyanates are highly reactive chemicals whose usefulness lies in their ability to form polymers. This reactivity makes it difficult to prepare well-characterized antigens for the RAST and to be certain that the antigens are appropriate. Recent findings suggest that the RAST reactivity may reflect in vivo reactions of isocyanates with respiratory proteins to form neoantigens for which IgE antibodies have specificity.¹⁵ Finally, it is possible that type 1, IgE-
mediated hypersensitivity may not be the mechanism of action in all individuals, but that other mechanisms such as altered adrenergic receptor function may be involved.14

Lack of bronchial hyperresponsiveness to methacholine before and after asthma attacks provoked by exposure to another isocyanate, TDI, has been the subject of two reports.15,16 Ours is the first report of such an occurrence in an individual with proven MDI asthma. Reports of absent NSBH in an asthmatic patient are still so rare as to raise concern about the adequacy of the protocols used to define NSBH. We are aware that airway obstruction lessens in some asthmatic patients following a deep inspiration. We also recognize that NSBH determined by methacholine inhalation may not be equivalent to NSBH measured by inhalation of other bronchoconstrictive agents (eg, histamine). Most spirometric testing is done, however, after full rather than partial inspiration. Methacholine is widely used, and it gives about the same overall results as testing with other agents.

Our methacholine protocol provides a cumulative dose of 640 units if no FEV1, decline of 20 percent of baseline occurs.17 This is in contrast to the protocol put forth by Chai et al,10 where methacholine inhalation was discontinued at 225 cumulative units if no FEV1 decline of ≥20 percent occurred. If we had used that protocol, the day 6 maximal FEV1, decline from baseline would have approximated 7 percent at 225 cumulative methacholine units. The actual maximal FEV1, decline on day 6 was 15 percent at 640 cumulative units. While this is not considered a positive response, it does suggest a trend toward increasing responsiveness that would not have been evident if testing had been stopped at the lower dose.

NSBH varies with asthma activity.12,13 When asthma is quiescent, previously measured NSBH can abate. In this report, the absence of active asthma and the two-month hiatus from workplace MDI exposure might explain the absence of NSBH apparent at the start of testing. It is quite rare, however, for NSBH to remain absent following recrudescence of occupational asthma.

Smith et al13 described a woman exposed to TDI-containing paints who developed throat irritation and dry cough, followed soon after by difficulty breathing. Her complaints were worse on the first day back at work and improved as the work week progressed. Lung function tests were normal away from exposure; immunologic tests (specific IgE antibody to p-tolyl isocyanate, lymphocyte inhibition factor to TDI antigen) were negative; and NSBH (to methacholine) was absent when maximal symptoms were present, and also before and after TDI inhalation six months later. On exposure to TDI, she wheezed and had a significant dose-related immediate FEV1, decline. The worsening of symptoms on Monday with improvement later in the work week suggests a byssinosis-like airway response, and implies even further variation in the symptomatology of isocyanate asthma.

Hargreave et al18 reported a 37-year-old man who developed TDI asthma in the production of polyurethane foam. The timing of his symptoms indicated a delayed response, and he had mild increase in NSBH and mild air flow obstruction. After discontinuing work, his symptoms resolved and his bronchial responsiveness and lung function returned to normal. Following return to work after a two-month lay-off, initial episodes of asthma occurred when bronchial responsiveness to methacholine was still in the nonasthmatic range. With continuing episodes of asthma, NSBH developed, only to resolve after ceasing workplace exposure to TDI.

The two cited cases and our case have several features in common. First, all had normal baseline lung function; second, variable air flow obstruction was diagnosed after a relatively short duration of symptoms, or with intermittent symptoms following infrequent exposures; and third, asthma symptoms occurred only in association with exposure to the specific offending agent, and not in association with cold air, exercise or irritant exposures. These features imply that occupational asthma in these three cases was diagnosed relatively early in its course. At that stage there is a good prognosis, assuming no further occupational exposure.80

In conclusion, this is the first reported case of MDI asthma where bronchial hyperresponsiveness to methacholine was absent immediately before and after a positive challenge with the sensitizing agent. Laboratory exposures to MDI resulted in significant acute declines in FEV1, and also produced ocular, nasal and systemic symptoms. We caution investigators that normal bronchial responsiveness is not always equivalent to the absence of isocyanate asthma. In the occasional patient with isocyanate exposure and a compelling history of workplace-related chest symptoms, but lacking nonspecific bronchial hyperresponsiveness, a specific isocyanate challenge may be necessary to exclude or establish the diagnosis of occupational asthma.

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