
Role and application of provocation in the diagnosis of occupational latex allergy

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INTRODUCTION

Allergic sensitivity to the plant protein constituents of natural rubber latex has become a major occupational hazard for health care workers and for certain patients with repetitive latex exposures.^{1,2} Epidemiologic studies from Europe indicate that between 2.2% and 10.7% of health care workers and between 1% and 2% of laboratory personnel are latex allergic.³⁻⁵ More recently, Brown et al studied a group of anesthesiologists and found the prevalence of latex allergy with clinical symptoms to be 2.4% and the prevalence of asymptomatic latex sensitization to be 10.1%.⁶ The prevalence of latex sensitization in children with spina bifida approaches 45%, possibly due to prolonged or repeated latex allergen exposure due to multiple surgical procedures and/or chronic indwelling catheters.⁷⁻⁹

Contact urticaria is the most common manifestation of latex allergy. The clinical sequelae of latex allergy also include other rashes, rhinoconjunctivitis, asthma, and systemic anaphylaxis.² These allergic reactions are elicited in sensitized individuals by exposure to a group of allergenic latex proteins. Some allergen attaches to cornstarch particles and becomes airborne when powdered latex gloves are used.¹⁰ Latex proteins can also be absorbed through repeated contact with

the skin (especially after abrasion) or mucosal surfaces.

The diagnosis of latex allergy depends primarily on a clinical history in which latex exposure is associated with clinical allergy symptoms. Confirmatory skin tests and serologic tests that have been developed to measure specific anti-latex IgE often have reduced sensitivity and specificity.¹¹⁻¹³ When the clinical history and anti-latex IgE tests are discordant, natural provocation procedures are useful to adjudicate the patients' true latex sensitivity status.

CHALLENGES USING LATEX EXTRACTS

The most basic latex allergen challenge method involves the monitoring of patient symptoms and peak expiratory flow rates (PEFRs) in and out of a latex allergen-containing environment. Unfortunately, this approach often yields unsatisfactory results because it is rarely possible to quantify the amount of latex allergen exposure. Other methods have been developed to mimic natural latex inhalation exposure in a controlled environment. Marcos et al challenged a single latex-allergic patient and two latex nonallergic asthmatic controls using serial inhalations of an aqueous surgical glove extract. Pulmonary function as measured by spirometry declined in the latex allergic subject but not in the controls.¹⁴ Pisati et al challenged four latex-allergic subjects with serial dilutions of aqueous extracts from powdered surgical gloves, unpowdered surgical gloves, and cornstarch powder nebulized into a small challenge room. Pulmonary function as measured by spirometry declined in all subjects after exposure to powdered latex surgical glove extract and in two

subjects after exposure to the nonpowdered latex surgical glove extract, but not after exposure to the cornstarch powder extract.¹⁵ Unfortunately, bronchial inhalation challenges using latex glove extracts do not simulate natural exposures, especially since the contribution of glove powder is not accounted for in the test system.

GLOVE USE TESTS

Other investigators have employed glove use tests as a model of natural exposure to latex gloves.¹⁶⁻²³ Latex gloves are donned and the patient is observed for 15 to 60 minutes for the development of skin pruritis, erythema, and rash and for nasal and bronchial symptoms. Non-latex gloves are used as controls.

Glove use tests have significant limitations. Subjective symptoms frequently dominate subject responses. Masking is difficult or impossible. The latex exposure occurs mainly through intact skin, which is inefficient because the integument is a formidable barrier. Because of this, sensitivity increases when active hand dermatitis is present at the time of the challenge. In addition, the allergen content of latex gloves is highly variable even between lots from a single manufacturer; thus, there is some risk for the development of a systemic allergic reaction because the challenge dose absorbed is not controllable.

MODIFIED GLOVE PROVOCATIONAL PROTOCOL

We have developed a modified glove provocation protocol to address some of these limitations. First, goggles and a silicone (non-latex) half-mask respirator equipped with activated charcoal filter cartridges (3M Company) are donned to minimize respiratory expo-

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sure. Next, the subject's hands are washed but not dried. A bifurcated needle is then used to puncture the skin through saline drops in three places on the volar aspect of both hands. A Dermaphor glove liner is applied to the control hand. High allergen content latex gloves are then placed on both hands. Following this, circular pressure is applied over the puncture sites 50 times. The subject is then observed for 15 to 30 minutes for skin and respiratory symptoms and signs.

Seventeen latex skin test and radioallergosorbent test (RAST) positive subjects have undergone this modified glove provocation protocol. All of the subjects experienced local pruritis with measurable wheals and erythema responses at the puncture sites on the latex exposed hand. None of the subjects developed reactions on the opposite control hand.¹⁸

The modified glove protocol addresses the limited sensitivity of the glove use test by abrading the skin with a bifurcated needle, but significant limitations remain. Masking remains difficult or impossible and the amount of latex exposure is still not easy to quantitate and reproduce. Also, the protocol does not assess conjunctival and respiratory responses, which occur in many latex-allergic patients. Finally, it can be argued that this method is nothing more than a modified skin test and thus does not add diagnostic value.

TWO STAGE LATEX PROVOCATION TEST

A 2-stage latex provocation test has been developed to allow the assessment of respiratory as well as cutaneous reactions. During stage 1, the skin is punctured with a bifurcated needle in three places on the volar aspect of the hand and whole latex glove application proceeds as in the modified glove provocation protocol. Goggles and a facemask are employed during the entire first stage to minimize respiratory exposure. A synthetic glove is applied in parallel on the control hand. Symptoms and skin responses are recorded over 30 minutes after the exposure.

The second stage proceeds if the first stage does not convincingly demonstrate latex allergy. The mask and goggles are removed and the subject is asked to blow up a new powdered latex glove and expel it slowly in the face. Subjects are observed for one hour. Symptoms and PEFs are recorded as responses. A positive challenge result to latex was defined as a PEF drop of 20% or greater or a clinically significant increase in respiratory symptoms (Fig 1). To prevent environmental contamination, the procedure should be undertaken in an environmentally controlled chamber, or a high volume high efficiency particulate arresting (HEPA) filtration device can be used to purify the room air.

The two stage latex challenge was used in a multi-center latex skin test study to adjudicate discordant latex allergy histories and skin test results.²⁴ Twenty-five of 158 latex allergy history probable subjects had negative latex skin tests. Twenty-four of these subjects had negative 2-stage challenges. One of these twenty-five had a positive pulmonary response at stage 2 of the challenge. Five of 180 subjects had a negative history of latex allergy but a positive latex skin test. All five of these individuals had negative 2-stage provocation tests. In this study, there were 56 subjects with a latex allergy history confined to contact dermatitis. Two of these individuals had positive

latex allergy skin tests but neither of these had a positive reaction to the 2-stage latex allergen challenge procedure. These results suggest that this method may be usefully employed in studies of the diagnostic performance of anti-latex IgE tests. Unfortunately, the inability to mask patients and to quantify latex allergen exposure remain as limitations.

GLOVE USE PROTOCOL EMPLOYING A LAMINAR FLOW HELMET AND INHALATION CHAMBER

In this protocol, invented by Laoprasert et al, subjects undergo seven sequential challenges by donning and discarding vinyl gloves, low latex allergen powder-free gloves, and five sets of high latex allergen powdered gloves. With each exposure, the subject's spirometry and symptom scores are monitored for up to 60 minutes inside of a challenge chamber. The subjects wear a laminar flow helmet during all challenges but its HEPA filter was only in place during the first two challenges with the high latex allergen powdered gloves. Spirometry (FEV₁) and symptom scores were the outcome variables. Latex aeroallergen levels were measured outside of the helmet using area samplers and inside of the helmet using personal breathing zone samplers.

Eleven latex-allergic subjects were challenged using this method. Pulmo-



Figure 1. Stage two of the 2-stage latex provocation test.

nary function, symptom scores, and exterior aeroallergen levels were not significantly different when the vinyl glove challenges were compared with the powder-free latex glove challenges. Exterior aeroallergen levels were significantly higher when the powdered latex gloves were used compared with when vinyl or powder-free latex gloves were used. The decline in FEV₁ and increase in symptom scores was greater during the third and fourth challenge with powdered latex gloves when no HEPA filter was in place than during the first two powdered glove challenges with the HEPA filter in place. Also, reproducible declines in FEV₁ could be shown in four subjects who were rechallenged. Measurement of latex aeroallergen inside and outside of the helmet with the HEPA filter in place demonstrated the efficacy of the HEPA filter system. The allergic and asthma symptoms that resulted from these challenges were easily managed by the administration of inhaled bronchodilators, ipratropium nasal spray, and oral antihistamines.²⁵

This protocol allows for safe and controlled exposure to latex gloves and yields semiquantitative data. It also has the advantage of quantitating the aeroallergen levels both in and outside of the helmet. One limitation of this technique is that it is difficult to mask. Another drawback is the requirement

for environmental containment during the procedure.

HOODED EXPOSURE CHAMBER

Glove use challenges are helpful in demonstrating clinical latex allergy, but do not assess the relative degree of clinical latex sensitivity. They also are complicated by difficulty with masking and the risk of a systemic allergic reaction since glove allergen potency is highly variable. The hooded exposure chamber (HEC) was developed to address these limitations.

The HEC is a latex allergen exposure device that allows graded latex aeroallergen exposure to the conjunctiva, upper airway, and lower airway. Latex-associated cornstarch (LAC) is obtained from powdered latex gloves and assayed to determine the relative amount of latex allergen on the cornstarch particles. Native cornstarch not associated with latex allergen (CS) is used to make serial 2-fold dilutions of the LAC. A cloud of respirable LAC particles (1 to 10 microns in diameter) is reliably produced using an impinger device and then introduced into a hood that fits over the head using an air pump (Fig 2). The challenge begins with air alone and CS and then proceeds to LAC in sequentially more potent 2-fold LAC dilutions in 18-minute

iterations. Peak expiratory flow rates and previously validated chest and rhinoconjunctival symptom scores are recorded.²⁶ Operational criteria for a positive response were developed during a pilot study. These are (1) PEFR drop of 15% or greater (Fig 3A, dashed line); or (2) PEFR drop of at least 10% and a symptom score of 3 or greater (Fig 3A, B, and C dotted line); or (3) symptom score of 6 or more (Fig B and C dashed line). A laser particle counter is used to monitor particle counts within the HEC. The challenge apparatus is kept in an externally ventilated chemical fume hood and an industrial HEPA filtration device is run in the challenge lab to prevent environmental contamination with latex aeroallergen.²⁷⁻²⁹

Eight latex skin test-positive and RAST-positive subjects have undergone the HEC procedure. All eight subjects individually reached one of the three criteria for a positive challenge response. No subject responded to air alone or CS that were administered as control challenges before the LAC. The responses were confined to symptoms and signs of mild allergic rhinoconjunctivitis and/or asthma that either resolved spontaneously or with inhaled albuterol (Fig 3). No systemic reactions were observed and no late phase reactions were reported.

These preliminary data indicate that the HEC challenge method provides a safe and sensitive method for the semiquantitative detection of clinical latex sensitivity. One advantage of the HEC system is that masked challenges can be carried out. In addition, the relative amount of latex exposure can be controlled in a crude but quantitative fashion, which should lead to good reproducibility. The advantages and disadvantages of the HEC procedure for latex aeroallergen challenge are now under study:

Advantages

- Safe
- Sensitive
- Allows semi-quantitative allergen exposure
- Yields quantitative data
- Masking possible



Figure 2. The HEC challenge apparatus in an externally ventilated fume hood.

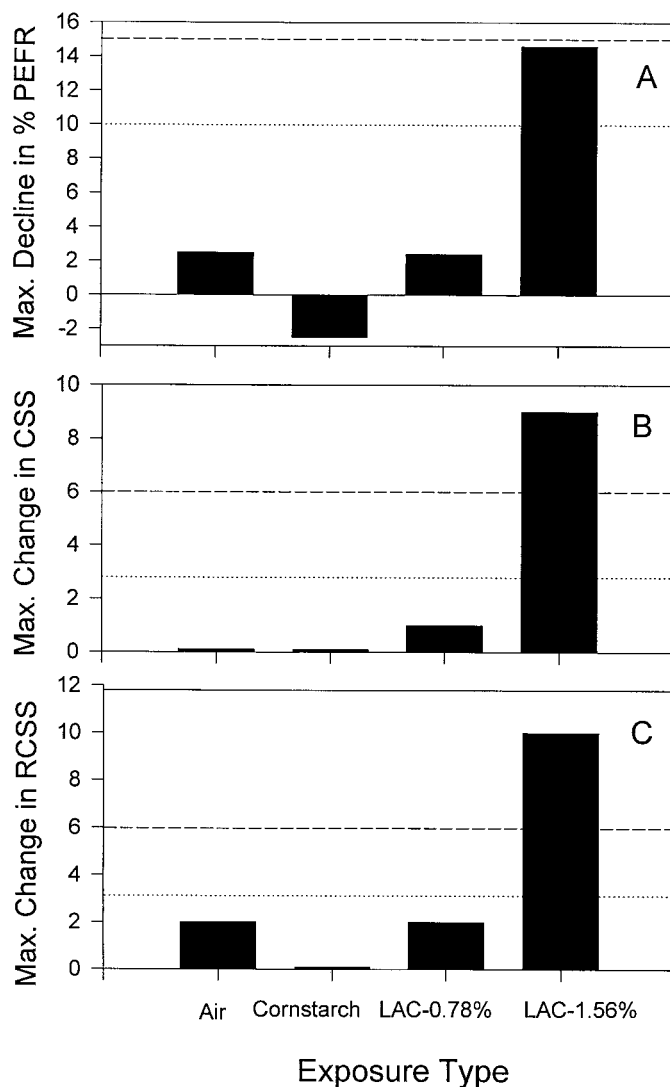


Figure 3. Data from a representative subject. (A) Maximum decline in PEFR. The negative value corresponds to a small increase in PEFR from baseline. (B) Maximum change in chest symptom score (CSS) from baseline. (C) Maximum change in rhinoconjunctival symptom score (RCSS) from baseline. The dashed and dotted lines correspond to threshold criteria for a positive challenge (see text). This subject met the criteria for a positive challenge at the 1.56% LAC concentration level (dilution factor 1:64).

Disadvantages

- Variation in LAC potency from different sources and within sources
- Acquisition of LAC is time consuming and labor intensive
- Requirement for specialized and expensive equipment and lab space
- Individual challenge series are time consuming

A disadvantage of the HEC system is the requirement for large batches of high-potency LAC. Latex-associated cornstarch must be washed out of powdered latex gloves in a very labor-intensive manner. Also, the allergen potency varies widely between latex glove manufactures and even between lots from a single manufacturer. This

can be addressed by using an in vitro assay to quantitate the amount of latex allergen on the cornstarch particles derived from gloves from the different manufacturers or lots. To get around this, efforts are currently underway to manufacture LAC using non-ammoniated latex allergen extract and cornstarch particles. Another disadvantage of the HEC system is that it requires specialized and expensive equipment and lab space. It is also rather time consuming with an individual challenge series taking as long as four hours.

UTILITY OF LATEX PROVOCATIONAL CHALLENGES

A variety of techniques have been developed for latex allergen challenge (Table 1). These methods have several useful applications. The provocation tests can help clarify discordant clinical histories and latex skin test or serologic data. This is particularly true of the HEC method, which allows for masked challenges. When the clinical history suggests latex allergy but the presence of anti-latex IgE cannot be demonstrated, provocation methods can improve latex allergy diagnostic sensitivity or identify non-IgE mechanisms of latex sensitivity. When the clinical history is unconvincing but the presence of anti-latex IgE has been demonstrated, provocation methods can uncover asymptomatic latex sensitized individuals. In addition, when patients have become convinced of their latex sensitivity despite negative tests for anti-latex IgE and a questionable clinical history, a blinded challenge protocol which includes control exposures may help to unveil anticipatory reactions. We have used the HEC challenge procedure successfully in several cases of unconvincing occupational disability claims for latex sensitivity. An additional potential use for these methods is to quantify clinical latex sensitivity in research studies of latex allergy natural history and interventions (eg, allergen avoidance or immu-

Table 1. Summary of Provocational Latex Challenge Studies

Challenge Method	Reference
Challenges with latex extract	Marcos et al, 1991; Pisat et al, 1994
Glove use tests	Baur et al, 1990; Brughami et al, 1995; Hamilton et al, 1997; Jagaer et al, 1992; Kelly et al, 1994; Turjahmaa et al, 1998; Vandenplas et al, 1995
Modified glove provocative protocol	Hamilton et al, 1997
Two-stage latex provocation test	Hamilton et al, 1998
Glove use with laminar flow helmet and inhalation chamber	Laoprasert et al, 1998
Hooded exposure chamber	Kurtz et al, 1999

notherapy). Finally, these techniques can be used as a gold standard in the determination of the diagnostic sensitivity of tests for the presence of anti-latex IgE (ie, skin tests and in vitro immunoassays). The 2-stage provocative protocol has already been used in this capacity during a multicenter latex skin test study.

CONCLUSION

The diagnosis of latex allergy continues to rely on clinical history. Confirmatory serologic tests are now widely available. A well standardized skin test reagent will become available in the United States in the near future as an additional confirmatory test. Despite the availability of these tests, certain clinical scenarios call for challenge tests. A number of safe latex allergen challenge models have been developed. Efforts are now underway to refine semi-quantitative latex challenge models and to document their reproducibility, so that they can be used in clinical studies of latex allergy natural history and interventions.

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