[Original Research]

CHEST

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Methacholine Challenge Testing

A Novel Method for Measuring PD_{20}

Q19 Q2 Q3 Beth E. Davis, PhD; Samuel K. Simonson, BSc; Christianne M. Blais, BSc; and Donald W. Cockcroft, MD

BACKGROUND: New guidelines for methacholine challenge testing recommend reporting the test outcome as dose rather than concentration. Jet nebulizers have historically been used for methacholine challenge testing, but much of the weight loss, often (incorrectly) referred to as aerosol output, is actually evaporation. The Wright nebulizer is well characterized and still widely used, but its availability is unclear, and it is nondisposable. We developed a novel method using a vibrating mesh nebulizer (Solo). This method was compared with the standard 2-min tidal breathing method using the Wright nebulizer. Repeatability within and between nebulizers was also tested.

METHODS: Fifteen patients with mild asthma completed four methacholine challenges (two with the Solo vibrating mesh nebulizer and two with the Wright jet nebulizer). Challenges with the same nebulizer were 24 h apart, and challenges between nebulizers were separated by 1 week. Standard 2-min tidal breathing methods were used with the Wright nebulizer. For the Solo nebulizer, the tidal breathing method was modified by nebulizing to completion 0.5 mL of doubling concentrations of methacholine at 5-min intervals.

RESULTS: Geometric mean methacholine doses required to cause a 20% fall in FEV_1 were similar (96 vs 110 μg; $P > .05$); methacholine concentrations that caused a 20% fall in FEV_1 were significantly lower with the vibrating mesh nebulizer (0.48 vs 4.4 mg/mL; $P < .001$). Repeatability of methacholine doses required to cause a 20% fall in FEV_1 within and between nebulizers was excellent (intraclass correlation coefficient > 0.92).

CONCLUSIONS: We have developed a novel, simple, repeatable method for conducting methacholine challenges using new nebulizer technology. Importantly, the method meets recommendations set out in the new guidelines.

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ABBREVIATIONS: ICC = intraclass correlation coefficient; PC_{20} = concentration of methacholine that caused a 20% fall in FEV_1; PD_{20} = dose of methacholine that caused a 20% fall in FEV_1; MCT = methacholine challenge test; Ti/Ttot = quotient of time of inspiration and sum of time of inspiration and expiration (duty cycle)

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Bronchoprovocation with direct-acting stimuli has been used for decades to assess airway responsiveness. In the clinical setting, the high sensitivity and high negative predictive value of the methacholine challenge test (MCT) function best to exclude a diagnosis of asthma when the test result is negative, provided that symptoms are clinically current and deep inhalations are not used.[1] In the research setting, MCT serves to identify appropriate clinical trial participants and determine the efficacy of respiratory therapeutics.[2]

Test standardization is key for MCT outcome comparisons within and between different laboratories and/or protocols, and consensus guidelines are important resources for achieving this goal.[3] Updated guidelines (European Respiratory Society 2017[4]) recommend that airway responsiveness be reported as the dose of methacholine required to cause a 20% fall in FEV_1 (PD_{20}) and not the concentration (PC_{20}). The literature supports this recommendation.[5,6] However, reporting the PD_{20} is problematic with currently used jet nebulizers (eg, Wright; Roxon Medi-Tech) because the amount of aerosol delivered, measured as weight loss, significantly overestimates the dose. This overestimation is due to evaporative loss inherent to jet nebulizers and to tidal breathing from a continuous outputting nebulizer. Both factors must be accounted for when determining dose; the former has shown to be as much as 75%,[7] and the latter is controlled for by factoring in the time spent inhaling using the duty cycle (defined as the ratio of duration of inspiration to duration of inspiration plus duration of expiration [Ti/Ttot]).[8]

In addition, commonly used jet nebulizers such as the Wright and the Bennett-Twin (Puritan-Bennett Corporation) are becoming increasingly difficult to obtain. Evaporative loss with vibrating mesh nebulizers such as the Solo (Aerogen Ltd) is not a concern, and these types of nebulizers should be readily available. The goal of the present study was to investigate the Solo nebulizer with a modified tidal breathing protocol. PC_{20} and PD_{20} outcomes were compared vs those obtained with the highly characterized Wright jet nebulizer and the highly standardized 2-min tidal breathing protocol. Test repeatability for both nebulizers was also assessed.

Materials and Methods

Study Design

This randomized crossover study was performed in individual participants who completed four methacholine challenges (two with the Solo and two with the Wright). Challenges with the same nebulizer were conducted 24 h apart.[9] Challenges between nebulizers were separated by 1 week. Screening challenges were performed with the Wright as required (ie, never or no recent MCT data).

Participants

Subjects were ≥ 18 years of age with a diagnosis of asthma, an FEV_1 ≥ 65% predicted,[10] and a methacholine PC_{20} ≤ 16 mg/mL. Four weeks without a respiratory infection and/or relevant allergen exposure was required. Treatment with any agent known to alter the response to methacholine was withheld for the appropriate duration prior to testing.[4] Signed informed consent (University of Saskatchewan Biomedical Research Ethics Board, Bio-REB #16-256) was obtained.

Methacholine Challenges

Methacholine: Doubling concentrations of methacholine from 0.03 to 32 mg/mL were prepared from dry powder stock (1,600 mg; Provocholine, Methapharm Inc), stored between 2°C and 8°C and warmed to room temperature before use.

Nebulizers: A Solo vibrating mesh nebulizer with Pro-X Controller (Aerogen Ltd), fitted with a t-piece, mouthpiece, and filter, were used. Also used was the Wright jet nebulizer (with fitted Hans Rudolph two-way nonrebreathing valve [Hans Rudolph]) and filter. Wright nebulizers were calibrated to deliver 0.13 g/min weight loss prior to study start. The identical Solo nebulizer and the identical Wright nebulizer were used within an individual for both methacholine challenges.

Standard 2-Minute Tidal Breathing Method

The standard 2-min tidal breathing method with a volume of 1.5 mL of methacholine was used for challenges with the Wright nebulizer.[11] Spirometry was measured in triplicate followed by inhalation of 0.9% normal saline via a mouthpiece and with nose clips in place. FEV_1 was captured 30 and 90 s postinhalation. Any nontechnically acceptable FEV_1 was immediately repeated. Ninety seconds later (ie, 5 min from the start of the diluent inhalation), the first methacholine concentration was inhaled for 2 min via tidal breathing, followed by FEV_1 measurements at 30 and 90 s. Inhalation of doubling concentrations of methacholine ensued at 5-min intervals until the lowest FEV_1 postmethacholine inhalation fell at least 17% compared with the lowest postdiluent inhalation. The same methacholine starting concentration was used for both tests within an individual.

Volumetric Method

The volumetric method was used for challenges with the Solo nebulizer. Challenges began with baseline spirometry, again in triplicate, followed by diluent inhalation. As precisely as possible, 0.5 mL was drawn up with a 1-mL syringe and loaded into the nebulizer. The nebulizer was run on continuous mode until the production of visible aerosol ceased; this process required 91 to 166 s. Participants inhaled via tidal breathing and with nose clips in place. FEV_1 was measured at 30 and 90 s after completion of the inhalation. Five minutes after the start of the diluent inhalation, 0.5 mL of the initial methacholine concentration was loaded, aerosolized, and inhaled until aerosol was no longer visible. FEV_1 was measured at 30 and 90 s. Doubling concentrations of 0.5 mL of methacholine were loaded at 5-min intervals (start of one inhalation to the start of the next inhalation) and aerosolized completely until the lowest postmethacholine FEV_1 decreased at least 17% relative to the lowest postdiluent FEV_1. The starting

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