REPLACING THE ENGLISH WRIGHT AND THE DEVILBISS 646 NEBULIZERS FOR METHACHOLINE CHALLENGE TESTS (MCT)
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Rationale
In the 2000 ATS standard for performing MCT two delivery systems were proposed: the English Wright™ (EW) for two-minutes of tidal breathing and the DeVilbiss 646™ (DeV) for the 5 breath dosimeter method. The former is obsolete and hard to acquire, and the latter has variable output and an elaborate calibration scheme is necessary for both. Hence, many other delivery systems have come into use without standardization. This study evaluated other potential delivery systems for the MCT.

Methods
Devices compared were the breath actuated disposable AeroEclipse II BAN™ (AER) and the Viasys Aerosol Provocation System™ which uses the SideStream Medicaid Pro nebulizer to simulate the EW system. The AER only produces aerosol during inspiration which significantly limits environmental contamination. The protocol for the Viasys device suggests that 19 breaths would be equivalent to the 2-minutes EW tidal breathing method. Rates of output for the EW and AER were measured using a breathing simulator (modified Harvard Animal Ventilator, Hollistan MA) (tidal volume 750 mL, respiratory rate 15 and inspiratory time 1.6 seconds) and particle size distribution was measured by laser diffraction allowing the calculation of estimated pulmonary deposition of methacholine during in vivo two minute tidal breathing MCT. For the dosimeter method, an inhalation was simulated with a tidal volume of 3L over a 2-second duration, using a spirometry calibration syringe. A pulse of 0.6 seconds activated the DeV. In all cases, methacholine was eluted from filters at the “mouth” and assayed by high performance liquid chromatography (HPLC). The amount of methacholine captured at the “mouth” multiplied by the fraction of the mass of the aerosol carried in particles ≤ 5µm was the estimated pulmonary deposition.

Results
For a concentration of 16 mg/mL the rates of deposition for the EW and AER were 0.19±0.07 vs. 2.05±0.16 mg/min, indicating that 12 seconds of inhalation from the AER would be equivalent to two minutes with EW. The recommended 19 breaths for the Viasys deposited 0.80±0.06 mg or 0.04 mg/breath. The estimated pulmonary deposition was 0.17±0.02 mg for 5 breaths dosimeter method or 0.03 mg/breath.

Conclusions
It is clear that the EW has a very low rate of output compared to modern nebulizers. In order to change from one delivery system to another, adjustments of inhalation duration will be necessary. From these data it will be possible to design an in vivo study comparing modern aerosol delivery systems for MCT.

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PROVOCATIVE DOSE 20, NOT PROVOCATIVE CONCENTRATION 20, DETERMINES BRONCHIAL HYPERRESPONSIVENESS IN CHILDREN WITH ASTHMA
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Rationale
International standards for methacholine challenge testing (MCT) to diagnose asthma recommend a 2 minute tidal breathing protocol with the English-Wright nebulizer (EW), the EW is now obsolete. Currently, the provocative concentration of methacholine causing a 20% drop in FEV1 (PC20) is recommended to determine the level of bronchial hyperresponsiveness, not the provocative dose (PD20). The objectives were to (1) determine if cumulative dose or concentration was the determinant for airway hyperresponsiveness and (2) validate an MCT using a modern, faster and environmentally safer delivery system, the breath actuated AeroEclipse™ II nebulizer (Aero).

Methods
Subjects aged 10 to 18 years, with physician diagnosed asthma, participated in multiple randomized, controlled crossover experiments comparing four different MCT protocols using standard methacholine concentrations and spirometry measurements but varying: (1) nebulizer used (EW versus Aero) (2) methacholine inhalation time (assumed to be directly related to dose delivered), and (3) methacholine starting concentration (to test for a cumulative effect). Total dose was based on total number of breaths and the in vitro performance characteristics of the nebulizer. Experiment A: 16 subjects EW protocol versus Aero with a 30 second inhalation time (Aero 30) Experiment B: 30 subjects EW protocol versus Aero with a 20 second inhalation time (Aero20) Experiment C: 13 subjects EW protocol versus Aero 30 protocol using the final methacholine concentration inhaled during experiment A as the starting concentration. Paired student T tests, intraclass correlation coefficients (ICC), and Bland Altman graphs were used to compare PC20 and PD20 obtained with EW versus Aero in each experiment.

Results
33 children (17 male), aged 14.8 +/- 6.8 SD years, with median PC20 1.36 mg/ml (0.143- 32 mg/ml) participated. Comparison of PC20 between EW and Aero in experiments A, B and C demonstrated a statistically significant difference between the two nebulizers (Figures 1 and 2). Comparison of PD20 between EW and Aero in experiments A, B and C demonstrated no statistically significant difference (Figures 1 and 2). ICC for Experiment A PC20 and PD20 were 0.54 (0.11 – 0.80) and 0.64 (0.25 – 0.85) respectively and for Experiment B PC20 and PD20 were 0.62 (0.31 – 0.81) and 0.73 (0.48 – 0.87) respectively.

Conclusions
These results demonstrate that dose, not concentration, is the important determinant for bronchial responsiveness in MCT as dose of delivered methacholine accumulates and PD20 more accurately accounts for this cumulative effect. Our results also validate the use of the Aero for MCT.

See figures on next page...
Figure One

Comparison of Concentration (PC\textsubscript{20}) and Dose (PD\textsubscript{20}) for English-Wright and Aero-30

n = 16
p = 0.001

Figure 2

Comparison of Concentration (PC\textsubscript{20}) and Dose (PD\textsubscript{20}) for English-Wright and Aero20

n = 30
p = 0.0038\

*Used conservative estimate of PC\textsubscript{20}=32 for negative tests

n = 30
p = 0.0647*