The Methacholine Challenge Test for Reversible Airways Disease Assessment: A Practical Guide on How to Interpret New 2017 ERS Guidelines

Jason A. Suggett, Mark W. Nagel, Jolyon P. Mitchell


INTRODUCTION

• Methacholine is frequently used to assess the severity of reversible broncho-constrictive disease, such as asthma
• New ERS Technical Standards were published in 2017 recommending a shift from use of PC20 to PD20 for bronchial challenge testing
• Allows comparable results from different aerosol delivery devices or protocols and allows use of any nebulizer where delivery characteristics are known
• The change from PC20 to PD20 has the potential to confuse how to execute the protocol in a practical manner
• The purpose of the present interpretation is therefore to provide a simplified explanation with a practical, step-wise, example of how the test can be performed to meet the new standard

BRONCHIAL CHALLENGE TESTING — DRUG DELIVERY SYSTEM

• The new standard allows for “any suitable nebulizer or dosimeter” with demonstrated device output and particle size characterization
• This poster will provide the data for the AeroEclipse® 1 Breath Actuated Nebulizer (BAN, Trudell Medical International, London, Canada) using independently reported tidal breathing data used in the new standard
• At least two independent clinical studies have recommended using this breath actuated nebulizer for methacholine challenge testing.

HOW TO PERFORM THE CHALLENGE TEST: EXAMPLE CALCULATION OF PD20

1 Prepare the Methacholine Solutions for Challenge Test
• Dilutions of methacholine can be prepared in the same way as with the previous 1999 guidance
• Table 1 shows an example of a schedule, based on the guidance in the new ERS document

Table 1: Methacholine Concentrate Dilution Schedule in Which the Challenge Agent Concentration is Increased Four-Fold for Each Exposure

<table>
<thead>
<tr>
<th>Label Mass of Concentrate (mg)</th>
<th>Start with</th>
<th>Normal Saline Added to Effect Dilution (mL)</th>
<th>Obtain Diluted Concentration (mg/mL)</th>
<th>Code Letter to Provide Order of Dilution by Lowest Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg</td>
<td>3 mL of A</td>
<td>+9.0</td>
<td>4.0</td>
<td>A</td>
</tr>
<tr>
<td>3 mL of B</td>
<td>+9.0</td>
<td>1.0</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>3 mL of C</td>
<td>+9.0</td>
<td>0.25</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>3 mL of D</td>
<td>+9.0</td>
<td>0.025</td>
<td>E</td>
<td></td>
</tr>
<tr>
<td>3 mL of E</td>
<td>+9.0</td>
<td>0.015625</td>
<td>F</td>
<td></td>
</tr>
</tbody>
</table>

2 Calculate the Delivered Doses at different Methacholine Concentrations

• In order to establish the delivered dose to the lungs (DDMC) during a defined delivery duration, the following need to be known
• Delivery Rate of methacholine
• Fine Droplet Fraction (droplets less than 5 μm aerodynamic diameter)
• Appendix D of the new ERS standard provides the following information for the BAN
• For 20 seconds of tidal breathing, the delivery rate of methacholine (Rmc) at the mouthpiece of the high output device (BAN) is 2.70 mg/min for a solution concentration (Cmc) of 16 mg/ml, when operated from a 50 psi dry gas source
• The Fine Droplet Fraction (FDF), defined as those droplets less than 5 μm aerodynamic diameter, is reported from in vitro measurements of BAN-emitted droplets made by laser diffractionometry as being 0.76
• Hence the DDMC for t=10s can be calculated as:

\[
DDMC = RMC \times FDF \times (t/60)
\]

• In the example provided for 20 seconds with the 16mg/mL concentration, DDMC would therefore be: 2.70 mg/min x 0.76 x 20/60 = 680 μg
• This can further be generalized for any CMC (concentration of methacholine), using 30 seconds tidal breathing with the BAN as:

\[
DDMC = \left[ \frac{CMC}{16 \text{ mg/ml}} \right] \times 680 \text{ μg}
\]

3 Perform the bronchial challenge test

• Once the calculations of DDMC are completed for all the concentrations prepared as part of the test phase in Table 1, the measurement of FEV1 can be conducted at increasing concentrations.
• Table 2 is an example of a bronchial challenge report taken from Appendix F of the new standard
• The PD20 values in this case are based upon a 1 minute tidal breathing test duration as recommended in the standard.

Table 2: Example Bronchial Challenge Report

<table>
<thead>
<tr>
<th>Time of exposure</th>
<th>Test Phase</th>
<th>DDMC (μg)</th>
<th>FEV1 (%)</th>
<th>FEV1 (%) of reference</th>
<th>Change in FEV1 (% pre-challenge level)</th>
</tr>
</thead>
<tbody>
<tr>
<td>t0</td>
<td>Pre-challenge</td>
<td>N/A</td>
<td>100</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>t0 + 10 min</td>
<td>Post diluent administration</td>
<td>N/A</td>
<td>900</td>
<td>100</td>
<td>N/A</td>
</tr>
<tr>
<td>t0 + 15 min</td>
<td>0.10 (65 mg), 1.9</td>
<td>1.9</td>
<td>0.05</td>
<td>100</td>
<td>-7</td>
</tr>
<tr>
<td>t0 + 20 min</td>
<td>0.65 mg/mL, 7.65</td>
<td>7.65</td>
<td>0.94</td>
<td>99</td>
<td>3</td>
</tr>
<tr>
<td>t0 + 25 min</td>
<td>0.65 mg/mL, 31.6</td>
<td>31.6</td>
<td>2.65</td>
<td>87</td>
<td>13</td>
</tr>
<tr>
<td>t0 + 30 min</td>
<td>1.0 mg/mL, 127</td>
<td>127</td>
<td>0.18</td>
<td>70</td>
<td>-8</td>
</tr>
<tr>
<td>t0 + 65 min</td>
<td>Post diluent administration</td>
<td>N/A</td>
<td>3.20</td>
<td>100</td>
<td>-7</td>
</tr>
</tbody>
</table>

4 Determination of PD20

• The PD20 calculation below illustrates use of the example data from Table 2 where R1 and R2 are the percentage decreases in FEV1 for D1 and D2, respectively

\[
PD20 = \text{antilog} \left\{ \frac{\log D_1 - \log D_2 (20 \cdot R_1)}{\log (R_2 - R_1)} \right\}
\]

• Consequently, from this particular example above, the bronchial responsiveness (PD20) is determined as 61 μg

5 Assessment of Airway Hyper-Responsiveness (AHR)

• The PD20 value can then be used to interpret the degree of AHR using values from the ERS document represented in Table 3

Table 3: Categorization of AHR to PD20 of Methacholine

<table>
<thead>
<tr>
<th>PD20 (μg)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 400</td>
<td>Normal</td>
</tr>
<tr>
<td>100–400</td>
<td>Borderline AHR</td>
</tr>
<tr>
<td>25–100</td>
<td>Mild AHR</td>
</tr>
<tr>
<td>6–25</td>
<td>Moderate AHR</td>
</tr>
<tr>
<td>&lt; 6</td>
<td>Marked AHR</td>
</tr>
</tbody>
</table>

• Based on the given example, the patient would be considered to have Mild AHR

CONCLUSIONS

• The new ERS standard allows the use of a more appropriate PD20 endpoint to assess airway hyper-responsiveness
• The methacholine challenge test procedure, calculation and interpretation have been described in an attempt to provide a meaningful practical demonstration of how the new guideline could be put into practice clinically

REFERENCES

1. El-Gammal AI, Bola SS, Foty RG, Marshall LC, Nelligan KA, Coates AL, Dole SD. Determination of PD20 for bronchial challenge testing — a practical, step-wise, example of how the test can be performed to meet the new standard. Eur Respir J 2017;49:1601526.

2. Scime TX, Beaudin S, Schlatman A, Cockcroft DW, Gauvreau GM. New 2017 ERS Guidelines for bronchial challenge testing — a practical, step-wise, example of how the test can be performed to meet the new standard. Eur Respir J 2017;49:1601526.

3. Dole SD, Bola SS, Foty RG, Marshall LC, Nelligan KA, Coates AL. Tidal breathing with the BAN as:

\[
3 \text{ mL of E}
\]

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Drug Delivery to the Lungs 28
December 6 – 8, 2017
Edinburgh, Scotland

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