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

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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 PC_{20} to PD_{20} 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 PC_{20} to PD_{20} 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**** II 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[1,2]

HOW TO PERFORM THE CHALLENGE TEST: EXAMPLE CALCULATION OF PD_{20}

1 Prepare the Methacholine Solutions for Challenge Test

- Dilutions of methacholine concentrate 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[3]

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

Label Mass of Concentrate (mg)	Start with	Normal Saline Added to Effect Dilution (mL)	Obtain Diluted Concentration (C_{MC}) (mg/mL)	Code Letter to Provide Order of Dilution (see second column)
100	100 mg	+6.25	16.0	A
	3 mL of A	+9.0	4.0	B
	3 mL of B	+9.0	1.0	C
	3 mL of C	+9.0	0.25	D
	3 mL of D	+9.0	0.0625	E
	3 mL of E	+9.0	0.015625	F

2 Calculate the Delivered Doses at different Methacholine Concentrations

- In order to establish the delivered dose to the lungs (DD_{MC}) 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[3] provides the following information for the BAN
  - For 20 seconds of tidal breathing, the delivery rate of methacholine (R_{MC}) at the mouthpiece of the high output device (BAN) is 2.70 mg/min for a solution concentration (C_{MC}) 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 diffractometry as being 0.76[3]
- Hence the DD_{MC} for t(s) can be calculated as:

$$DD_{MC} = R_{MC} \times FDF \times (t/60)$$

- In the example provided for 20 seconds with the 16mg/mL concentration, DD_{MC} would therefore be: 2.70 mg/min X 0.76 X 20/60 = 680 µg
- This can further be generalized for any C_{MC} (concentration of methacholine), using 20 seconds tidal breathing with the BAN as:

$$DD_{MC} = \left[C_{MC} / 16\ mg/ml\right] \times 680\ \mu g$$

3 Perform the bronchial challenge test

- Once the calculations of DD_{MC} are completed for all the concentrations prepared as part of the test phase in Table 1, the measurement of FEV_1 can be conducted at increasing concentrations.
- Table 2 is an example of a bronchial challenge report taken from Appendix F of the new standard[3]. The DD_{MC} 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

In this particular example, the test was terminated after exposure to **127 µg (D2)** and the dose at the second to last exposure **D1 is 31.8 µg**.

Time of exposure	Test Phase	DD_{MC} (µg) (1 min tidal breathing)	FEV_1 (L)	FEV_1 (% of reference)	Change in FEV_1 (% pre-challenge value)
T_0	Pre-challenge	N/A	3.10	N/A	N/A
T_0 + 10 min	Post diluent (reference condition)	N/A	3.00	100	N/A
T_0 + 15 min	0.015625 mg/mL	1.9	3.05	102	-2
T_0 + 20 min	0.0625 mg/mL	7.65	2.94	98	2
T_0 + 25 min	0.25 mg/mL	31.8	2.62	87	13
T_0 + 30 min	1.0 mg/mL	127	2.16	72	28
T_0 + 45 min	After bronchodilator administration	N/A	3.20	107	-7

4 Determination of PD_{20}

- The PD_{20} calculation below illustrates use of the example data from Table 2 where R_1 and R_2 are the percentage decreases in FEV_1 for D_1 and D_2, respectively

$$PD_{20} = antilog \left\{ log\ D_1 + \frac{(log\ D_2 - log\ D_1)\ (20 - R_1)}{(R_2 - R_1)} \right\}$$

$$PD_{20} = antilog \left\{ 3.46 + \frac{(4.84 - 3.46)\ (20 - 13)}{(28 - 13)} \right\}$$

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

5 Assessment of Airway Hyper-Responsiveness (AHR)

- The PD_{20} value can then be used to interpret the degree of AHR using values from the ERS document[3] represented in Table 3

Table 3: Categorization of AHR to PD_{20} of Methacholine

PD_{20} (µg)	Interpretation
>400	Normal
100–400	Borderline AHR
25–100	Mild AHR
6–25	Moderate AHR
<6	Marked AHR

- 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 PD_{20} 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 Dole SD, Bola SS, Foty RG, Marshall LC, Nelligan KA, Coates AL. *Provocative dose of methacholine causing a 20% drop in FEV_1 should be used to interpret methacholine challenge tests with modern nebulizers.* Ann Am Thorac Soc. 2015; 12(3):357–363.

2 El-Gammal AI, Killian KJ, Scime TX, Beaudin S, Schlatman A, Cockcroft DW, Gauvreau GM. *Comparison of the provocative concentration of methacholine causing a 20% fall in FEV_1 between the **AeroEclipse* II** breath-actuated nebulizer and the Wright nebulizer in adult subjects with asthma.* Ann Am Thorac Soc. 2015; 12(7): 1039–1043.

3 Coates AL, *et al*. *ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests.* Eur Respir J 2017;49:1601526.

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