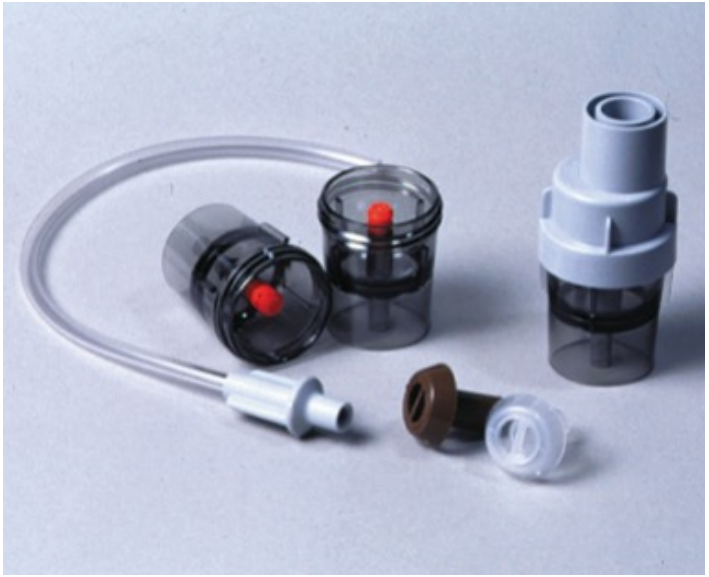


XI. Conference
of functional examinations of the lungs

German guidelines for non-specific challenge testing

Hans-Jürgen Smith, Berlin, Germany

Zlín 19th – 20th May 2023

Methacholine challenge testing is safe and informative

Methacholine challenge tests are most often done to exclude or confirm a suspected diagnosis of asthma.

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

Bronchial challenge testing

Introduction

Bronchial hyperresponsiveness (BHR)

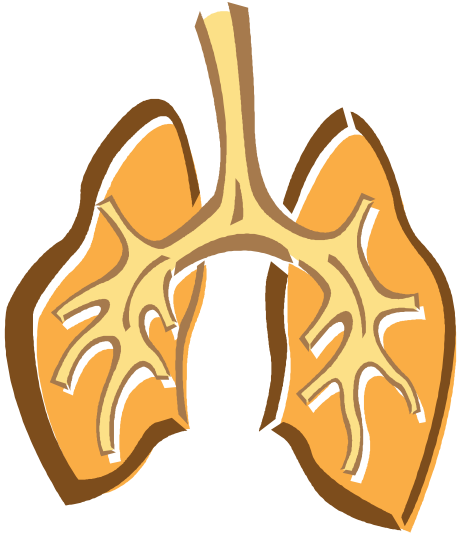
- ⇨ Complex interaction between
  - ⇨ Airway inflammation
  - ⇨ Smooth muscle function
  - ⇨ Mechanics

Measure of BHR

- ⇨ Diagnosis and monitoring of asthma

Bronchial challenge testing

- ⇨ Response in every subject, even healthy ones
- ⇨ Abnormality defined by degree and ease of response



ERS standard on bronchial challenge testing 2017

General considerations and performance of methacholine challenge tests

Nebuliser: Any nebuliser can be used; output, particle size must be known and < 5µm

Inhalation: Tidal breathing – NO maximal manoeuvres; bronchodilatation decreases sensitivity

Provocation protocol:
- ⇨ Diluent step
- ⇨ Start with 1-3 µg methacholine (MCH)
- ⇨ **Concentration oriented**; subsequent doubling or quadruple steps

Contraindications:
- ⇨ Pre-bronchodilator FEV_1 < 60% or < 1.5 L (only adults)
- ⇨ Inability performing reliable spirometry

Spirometry: 30 and 60 s after nebulisation is completed; max 3-4 manoeuvres; report highest FEV1

Provocative dose: **$PD_{-20}FEV_1$** rather than $PC_{-20}FEV_1$ (provocative concentration) for FEV_1 only

Aspects to consider:
- ⇨ Diluent step necessary?
- ⇨ **Dose oriented protocol!**
- ⇨ **Additional observation parameters** from bodyplethysmography or oscillometry

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

Concentration versus dose oriented protocols

Higher patient safety when dose oriented

Concentration protocol

- Defined concentration of an agonist is inhaled
- Concentration is doubled or quadrupled
- *Evaluation* is related to the inhaled concentration in the particular step

Concentration $mg \cdot mL^{-1}$	Dose µg
0.0625	1.425
0.25	5.938
1	23.75
4	95
16	380
2 min tidal breathing	

English Wright nebuliser

- Every step with new MCH concentration
- Protocol time consuming

Effective dose higher than calculated.
MCH of previous step not complete metabolised

Cumulative dose protocol

- Single concentration of an agonist is inhaled in all steps
- The number of breaths and/or duration is increased
- *Evaluation* is related to cumulative dose

Number of breaths	Dose mg	Cumulative dose mg
1	0,015	0,015
2	0,045	0,060
5	0,180	0,240
13	0,720	0,960
Single concentration of 16 $mg \cdot mL^{-1}$		

Philips/Respironics SideStream nebuliser

- Single MCH concentration only
- Protocol is fast

Effective cumulative dose always lower than calculated.
Metabolism decreases dose!

German challenge protocol

Dose oriented 1-concentration short protocol

Without diluent step!

Step	Concen-tration	Nebulisation bolus p. breath	Number of breaths	Dose	Cumulative dose	Substance	Exposure time
B1	-						0
1	1.6%	0,234 s	1	15 µg	15 µg	Methacholine	90 s
2	1.6%	0,352 s	2	45 µg	60 µg	Methacholine	90 s
3	1.6%	0,563 s	5	180 µg	240 µg	Methacholine	90 s
4	1.6%	0,856 s	13	720 µg	960 µg	Methacholine	90 s
D1	-			2 Puffs		Salbutamol	10 min

B1 baseline, 1…4 provocation steps, D1 dilatation

Use of Philips/Respironics SideStream nebuliser calibrated to 240 $\mu L \cdot min^{-1}$
Impulse nebulisation (bolus)

Merget R, et al. Development of a 1-concentration-4-step dosimeter protocol for methacholine testing. Respiratory Medicine 2009; 103: 607-613

Observation parameters

Determination value based on provocation dose (PD)

Stimulus to smooth muscle receptors is provocation dose **PD**.

Use of provocation concentration **PC** no longer recommended.

Method	Target parameter	Determination value	Condition	PD-Determination value
Spirometry	FEV_1	-20%		PD_{-20} FEV_1
Body	sReff	+100%	$sR_{eff} \geq 2$ kPa·s	PD_{+100} sR_{eff}
Body	sGeff	-40%	$sG_{eff} \leq 0{,}5$ $kPa^{-1} \cdot s^{-1}$	PD_{-40} sG_{eff}
IOS	R5	+40%		PD_{+40} R5Hz
IOS	Fres	+35%		PD_{+35} Fres

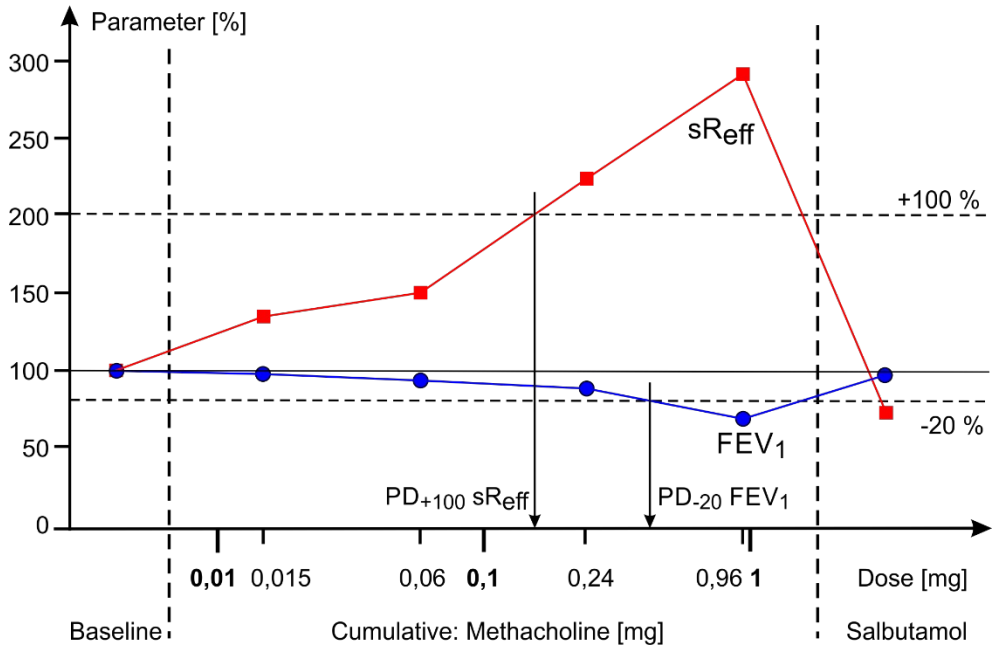
- **Spirometry:** Single forced manoeuvre.
- **Bodyplethysmography:** Tidal breathing body loop without shutter manoeuvre (without volume measurement).
- **IOS:** Tidal breathing analysis.

Dose response curve

Presentation of observation parameters sR_{eff} and FEV_1

Determination of threshold dose (PD) utilizing the dose response graph

- Separately for every parameter
- Depending on nebulizer characteristics
  - Concentration of MCH in solution
  - Output rate – calibrated nebuliser power (calibrated by weight loss)
  - Particle size and distribution
- Inhalation protocol
  - Tidal breathing
  - Bolus application in inspiratory phase
- Testing methods
  - Effective specific resistance, sReff
  - Flow-volume-curve, FEV1, (FVC)
  - Baseline & dilatation – complete body with lung volumes



Dose response graph

- **Cumulative** dose on log scale
- Percentage change linear

Classification of reaction

Specific and depending on challenge protocol

Cumulative provocation dose PD (in mg methacholine)	Degree of hyperresponsiveness
< 0.06	severe
0.06 ≤ PD < 0.240	moderate
0.240 ≤ PD < 0.960	mild
0.960 ≤ PD	normal

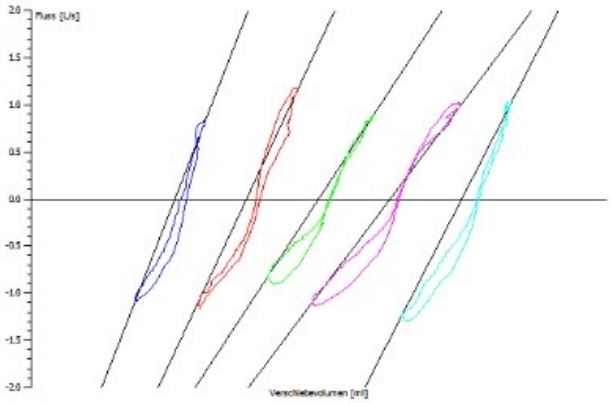
Special case: observation parameter passes threshold in first step (0.015 mg).
PD can't be calculated – severe degree of hyperresponsiveness has to be classified.

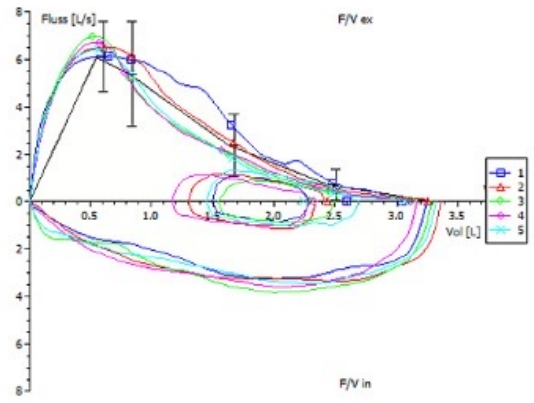
Merget R, et al. Development of a 1-concentration-4-step dosimeter protocol for methacholine testing. Respiratory Medicine 2009; 103: 607-613

Challenge report

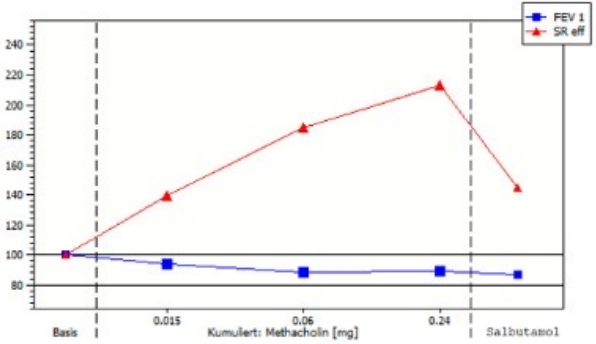
Observation parameters sR_{eff} and FEV_1

Moderate degree of hyperresponsiveness, measured with bodyplethysmography only.





	Predict.	Baseline	% Predict.	Provo 1	Provo 2	Provo 3	Dilatation
Substance				MCH	MCH	MCH	Salbutamol
Dose				0.015 mg	0.045 mg	0.18 mg	2 Puffs
Cumulative				0.015 mg	0.06 mg	0.24 mg	2 Puffs
sR_{eff}	0.96	0.99	103	1.38	1.84	2.12	1.44
FEV_1	2.57	2.59	101	2.43	2.29	2.32	2.24



Threshold dose

PD_{+100} sR_{eff} : 0.1261 mg cumulative

PD_{-20} FEV_1: Couldn't be calculated !

! Spirometry missed confirmation of hyperresponsiveness.

Summary

German guideline for non-specific challenge testing

- ➪ Dosimetry applying Philips/Respironics SideStream nebuliser
- ➪ Challenge protocol
  - ➪ Without diluent step
  - ➪ 1 concentration, 4 steps short protocol
  - ➪ Low dose in 1st step for patient safety
- ➪ Inhalation
  - ➪ Tidal breathing with inspiratory methacholine bolus
- ➪ Observation – bodyplethysmography recommended!
  - ➪ Body loops; single forced manoeuvre

PD_{-20} FEV_1 in comparison to PD_{-40} sG_{eff}

➪ Identical in 32.9 % of asthmatics

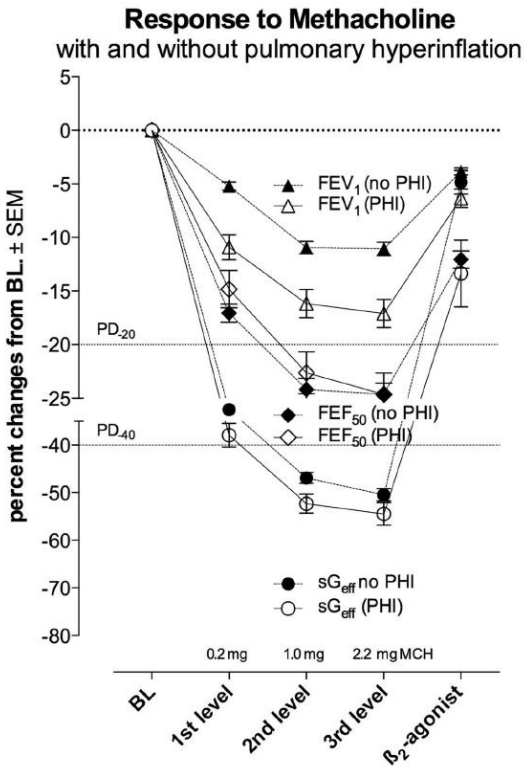
➪ In disagreement 67.1 % of asthmatics

FEV_1 ➪ One level later in 24.9%

➪ Two levels later in 21.9 %

➪ Three levels later in 6 %

➪ Not reached in 13.5 %



Kraemer R, Smith HJ et al. Diagnostic accuracy of methacholine challenge tests assessing airway hyperreactivity in asthmatic patients – a multifunctional approach. Respiratory Research 2016; 17:154