



**Karolinska
Institutet**

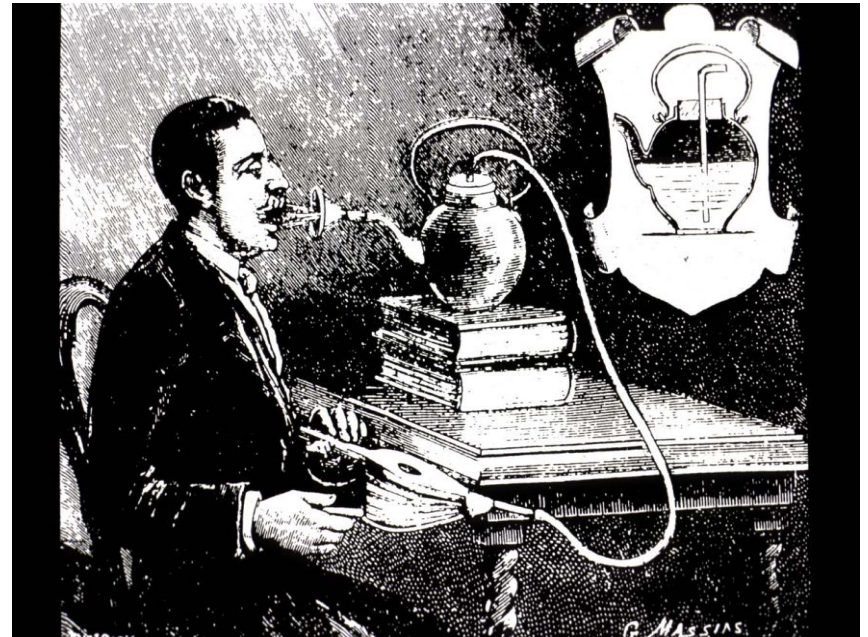
Allergenprovokationer vid astma



Barbro Dahlén
Karolinska Universitetssjukhuset

Allergen provokation

- 1873 Första provokationen
 - Charles Blackley
- 1950-talet FEV1
- 1952 Senreaktionen
 - Herxheimer H
- 1960-70 talet Naturalförlopp
"astma-modell"
 - Orie N et al, Pepys J et al.
- 1969 Barn (kvalster)
 - Van LC, et al.
- 1985 Allergen-inducerad
luftvägsinflammation
påvisad mhja bronkoskopi



Allergen provokation

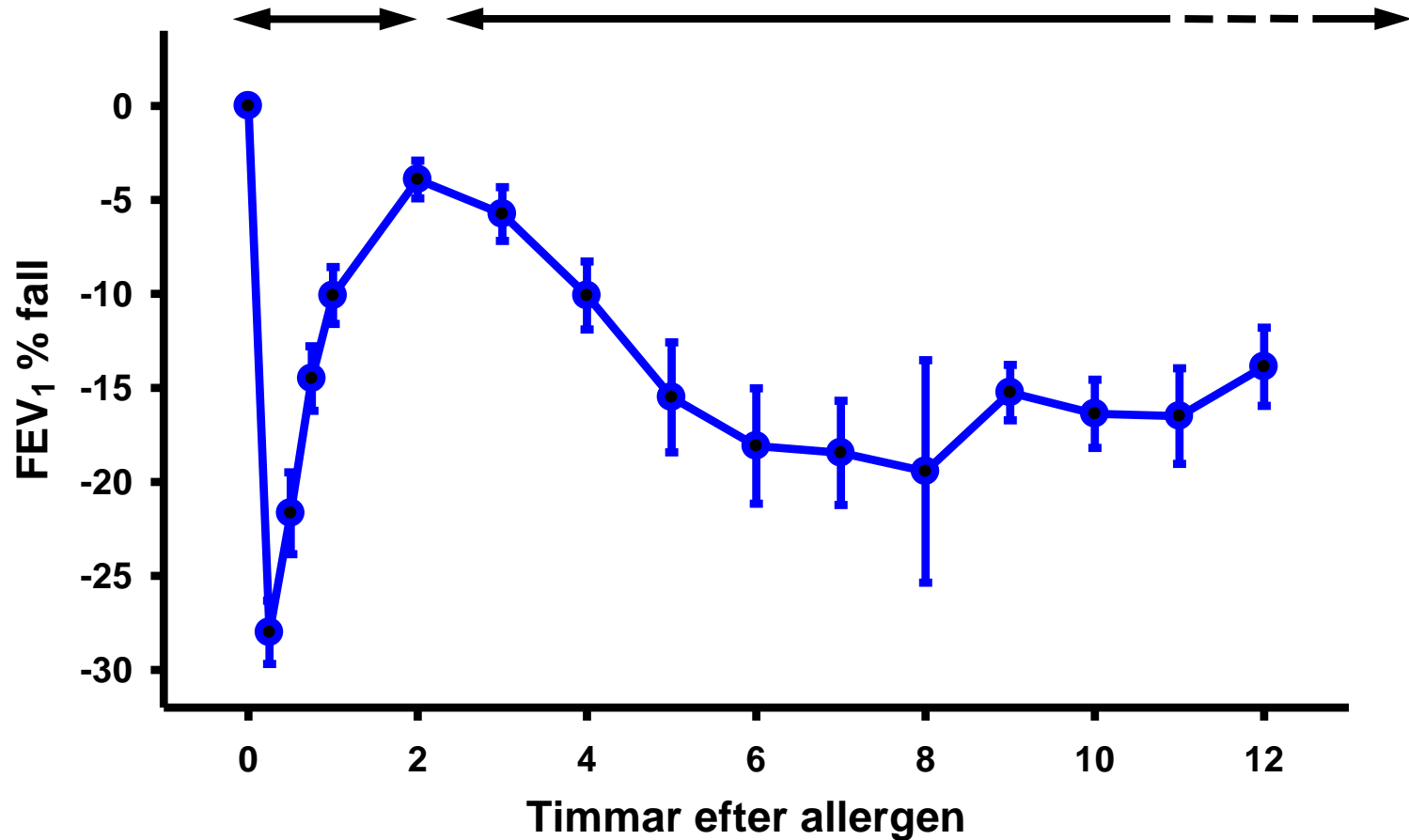
Tidig reaktion: 15-30 min

Senreaktion: 3-(8)-12- timmar

EAR= early asthmatic response

LAR= late asthmatic response

25 - 50%



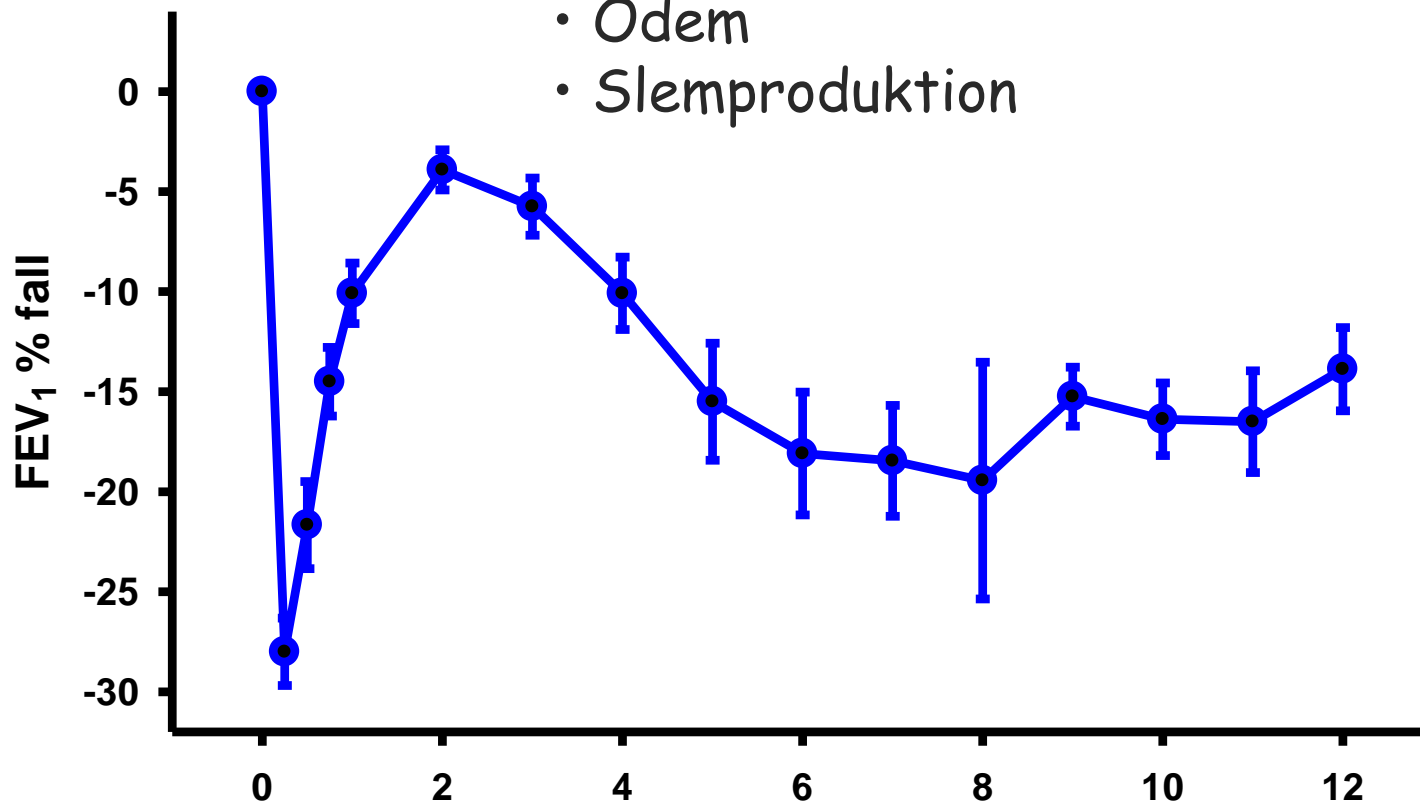
Allergen provokation

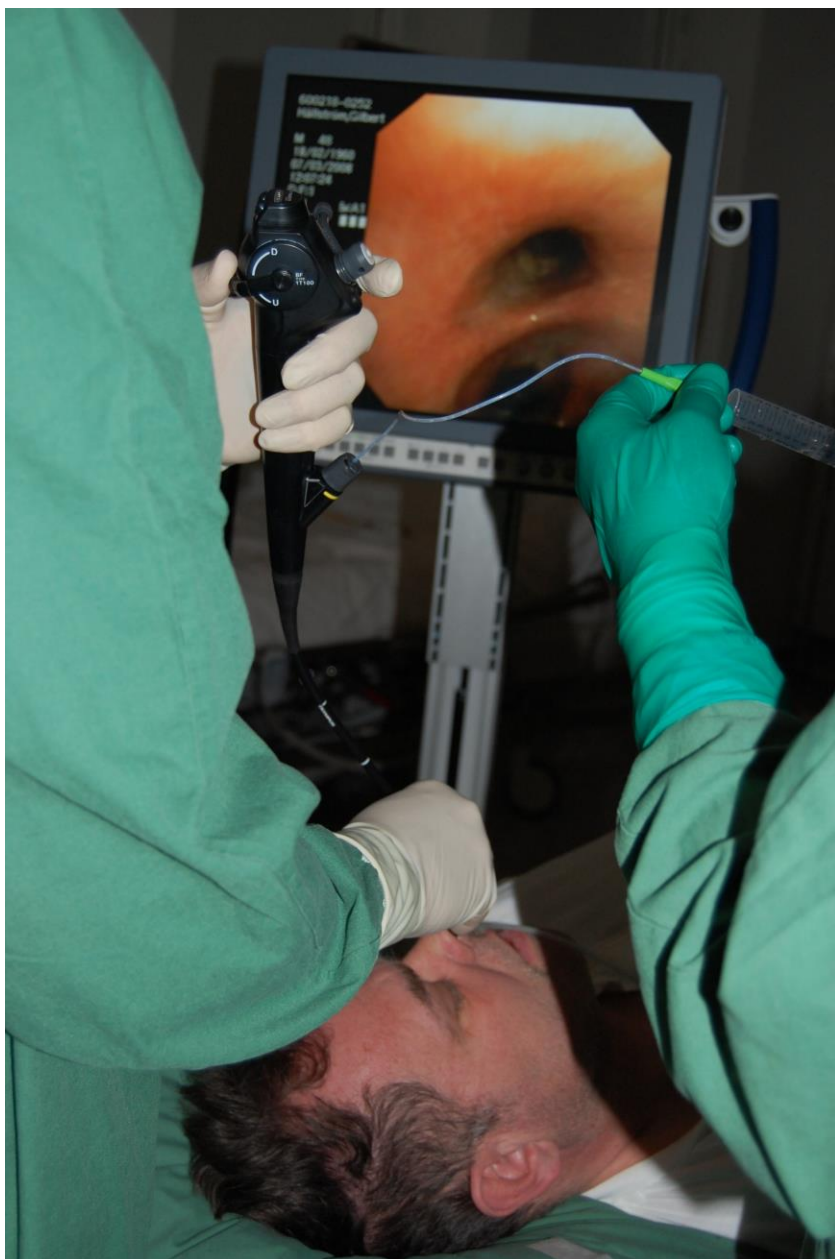
Tidig reaktion

Senreaktion



- Bronkspasm
- Cellinfiltration (eosinofiler, lymfocyter, basofiler: degranulerin/aktivering)
- Ödem
- Slemproduktion





Provtagning i luftvägarna

Bronkoskopi

- vävnad
- lungsköljvätska

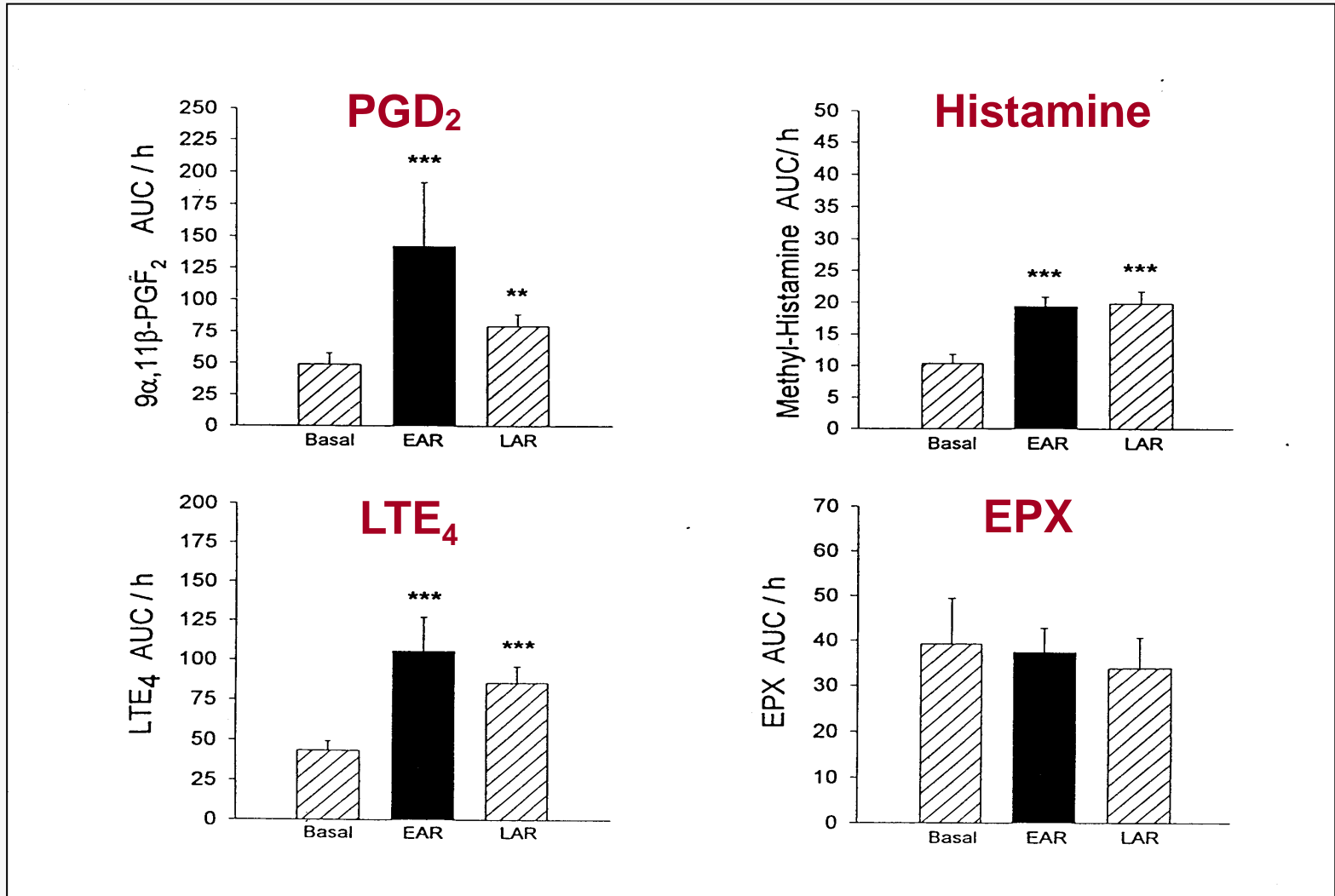
Inducerat sputum

eller

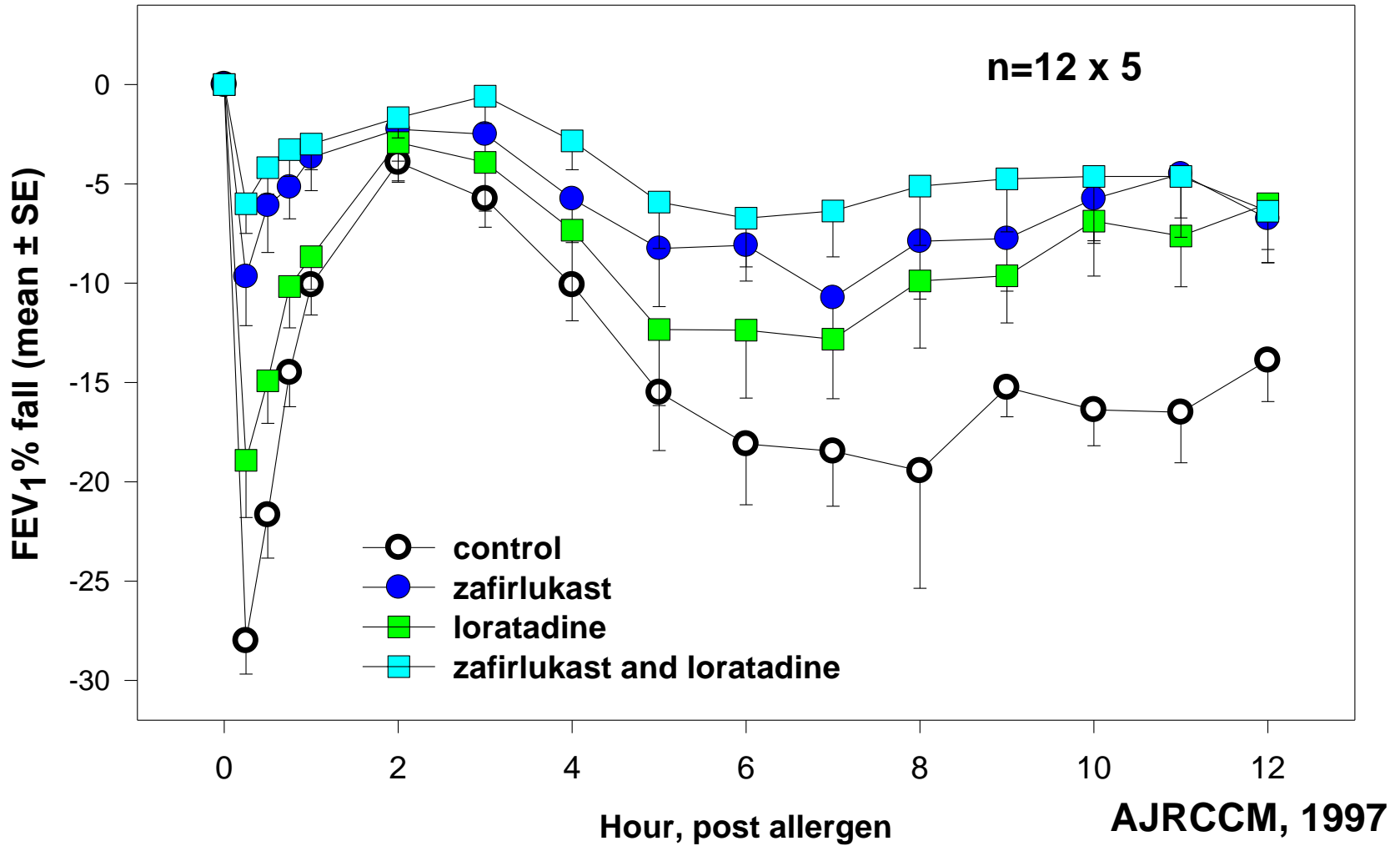
Surrogat markörer i:

- urin**
- blod**
- saliv**
- utandningsluft**

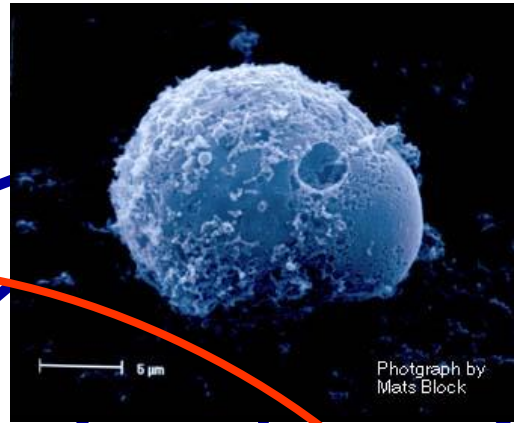
Urin-mediatorer



Allergen challenge



Mast celler



Heparin

Enzymer:

Tryptas
MMP-9

PGD₂

Histamin

Leukotriener

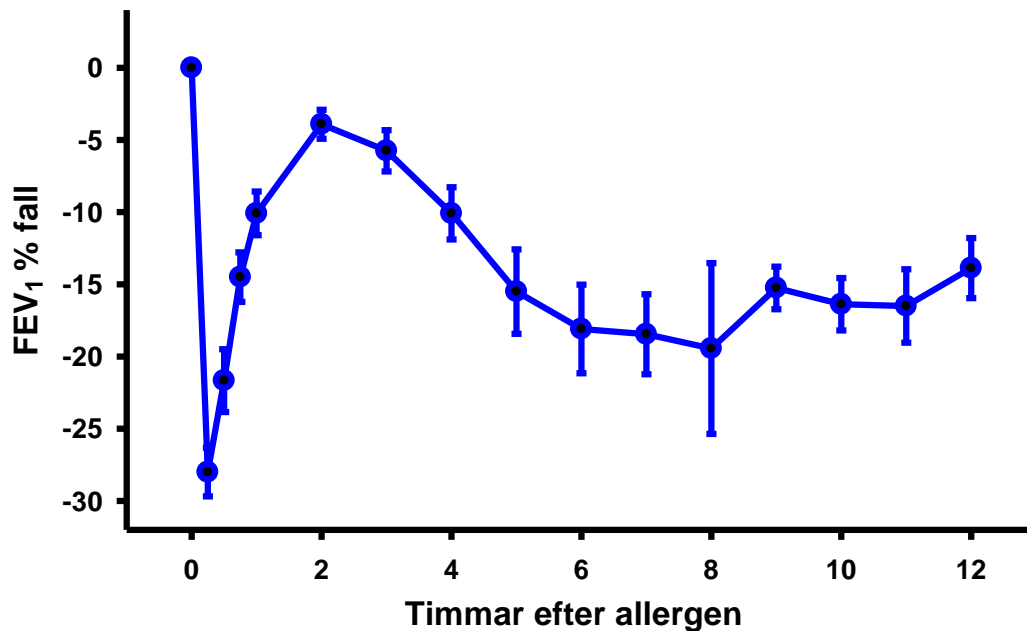
Cytokiner & Growth
Factors: TNF α , IL-4,
IL-5, IL-13, GM-CSF
ca 30!

Mediatorer av bronkspasm

Allergen provokation

En in vivo, human modell:

- explorera astmans patofysiologi
- undersöka behandlingseffekter



Genom att mäta:

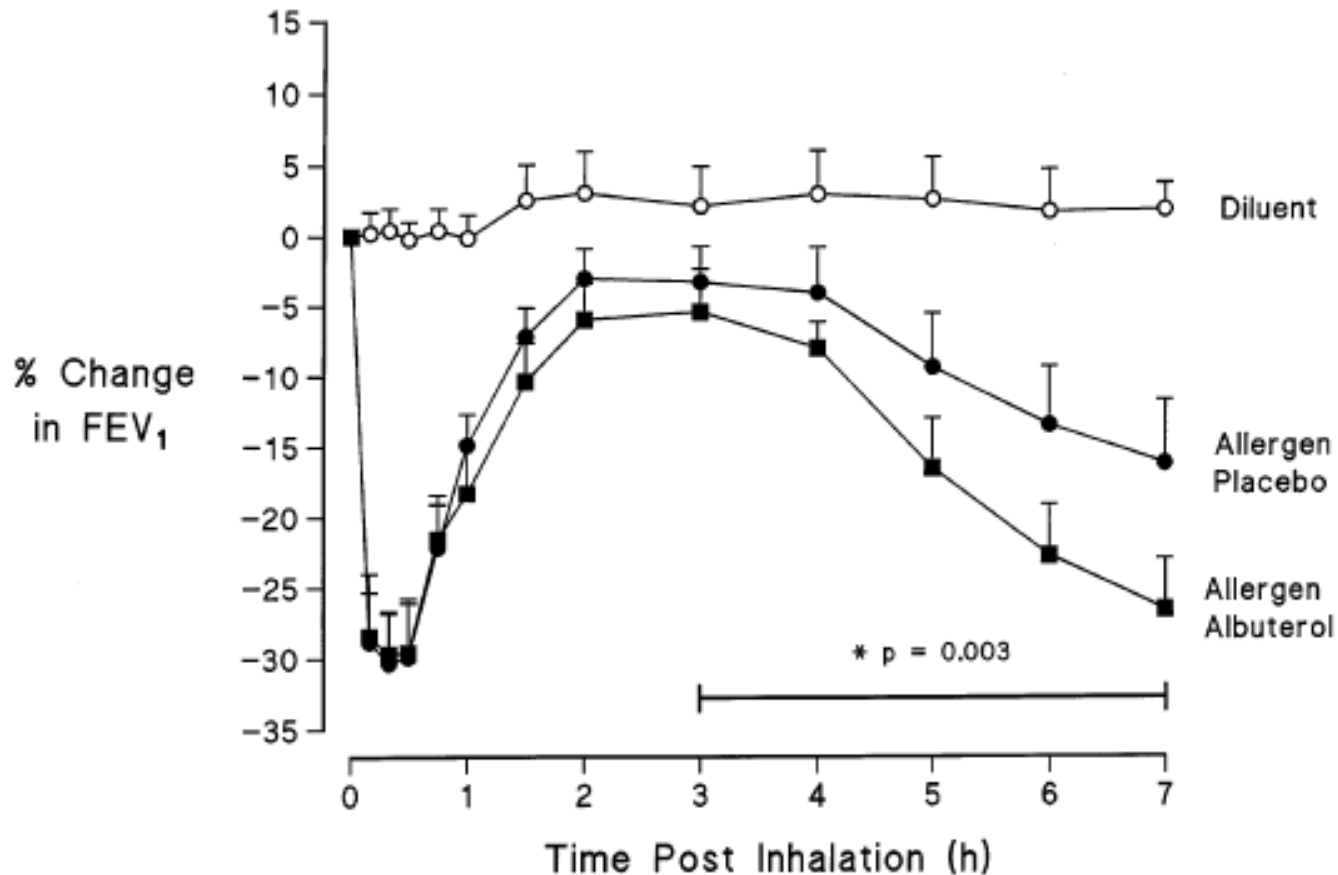
Lungfunktion

- tidig reaktion
- senreaktion

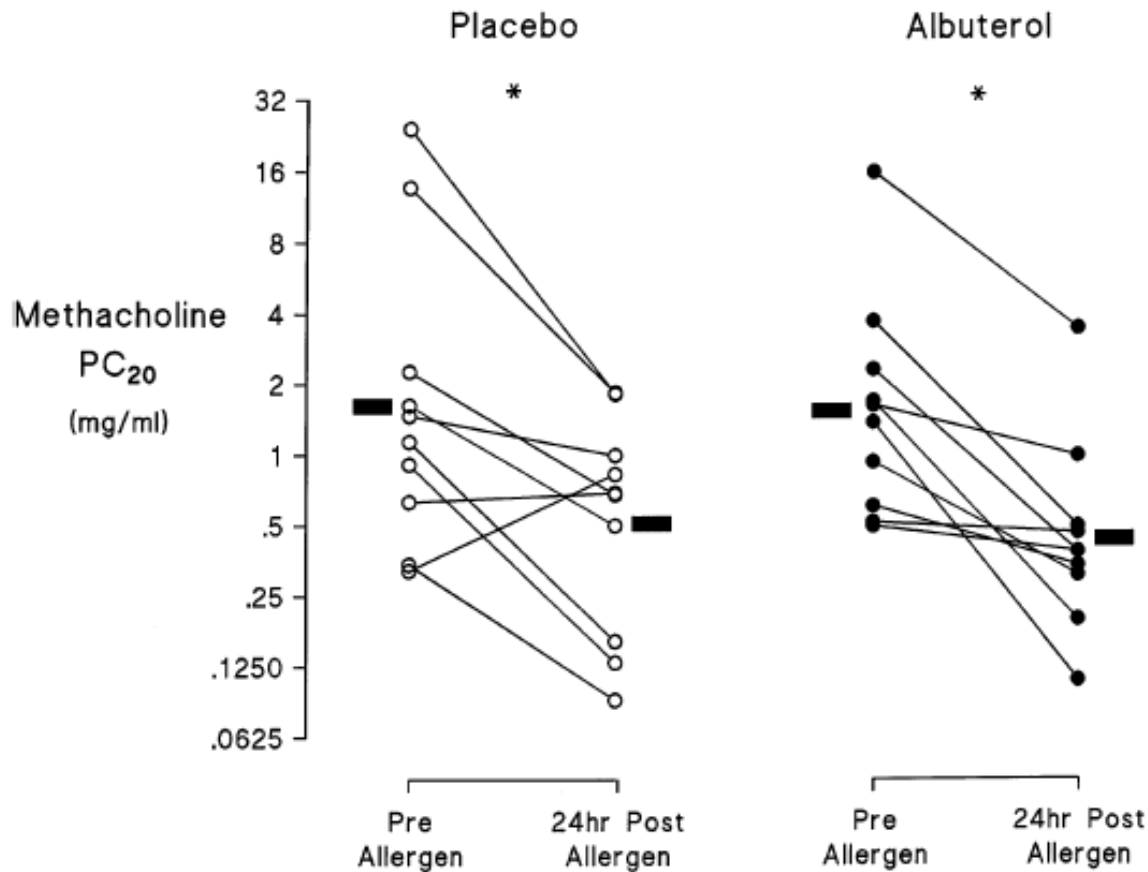
Inflammation

- tex eosinofiler
- Hyperreaktivitet

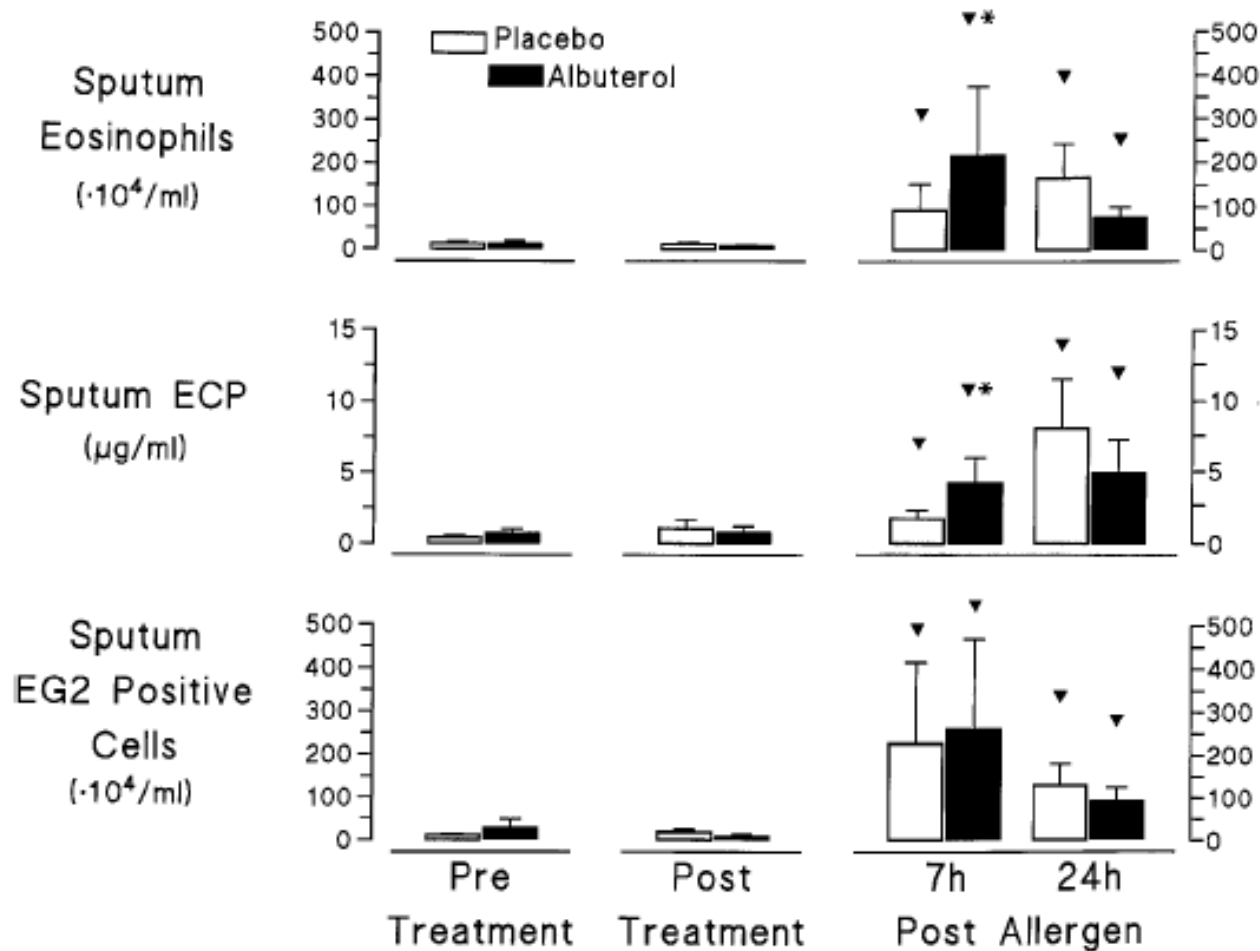
Effekt av 7 dagar salbutamol 800µg/day - på sen-reaktion



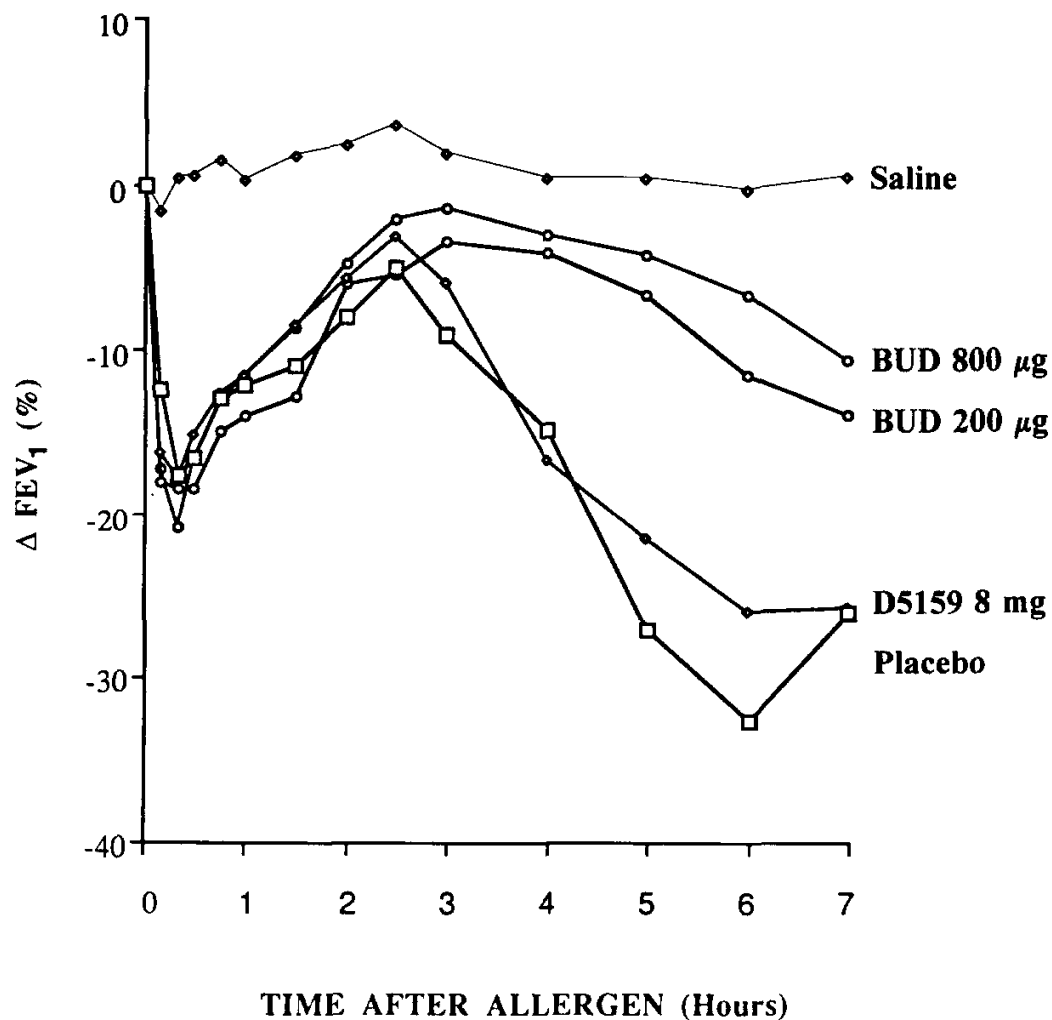
Effekt av 7 dagar salbutamol 800µg/day - på bronkiell hyperreaktivitet



Effekt av 7 dagar salbutamol 800 μ g/day - på sputum-eosinofiler



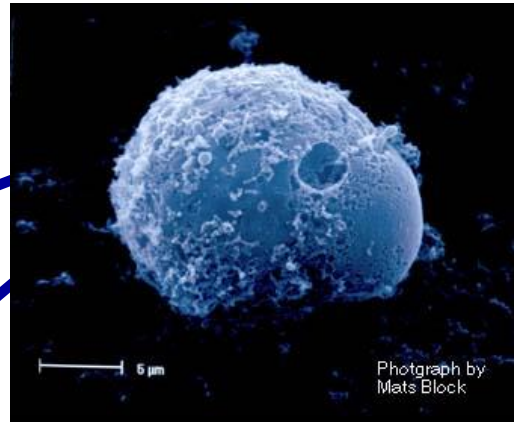
Effekt av en single-dos inhalationskortison - på allergen-inducerad luftvägsobstruktion



**Budesonid
vs
icke aktiv
inhalationssteroid**

**Hämmar:
Senreaktion
BHR
Sputum-
eosinofiler**

Mast celler



Heparin

Enzymer:

Tryptas
MMP-9

PGD₂

Histamin

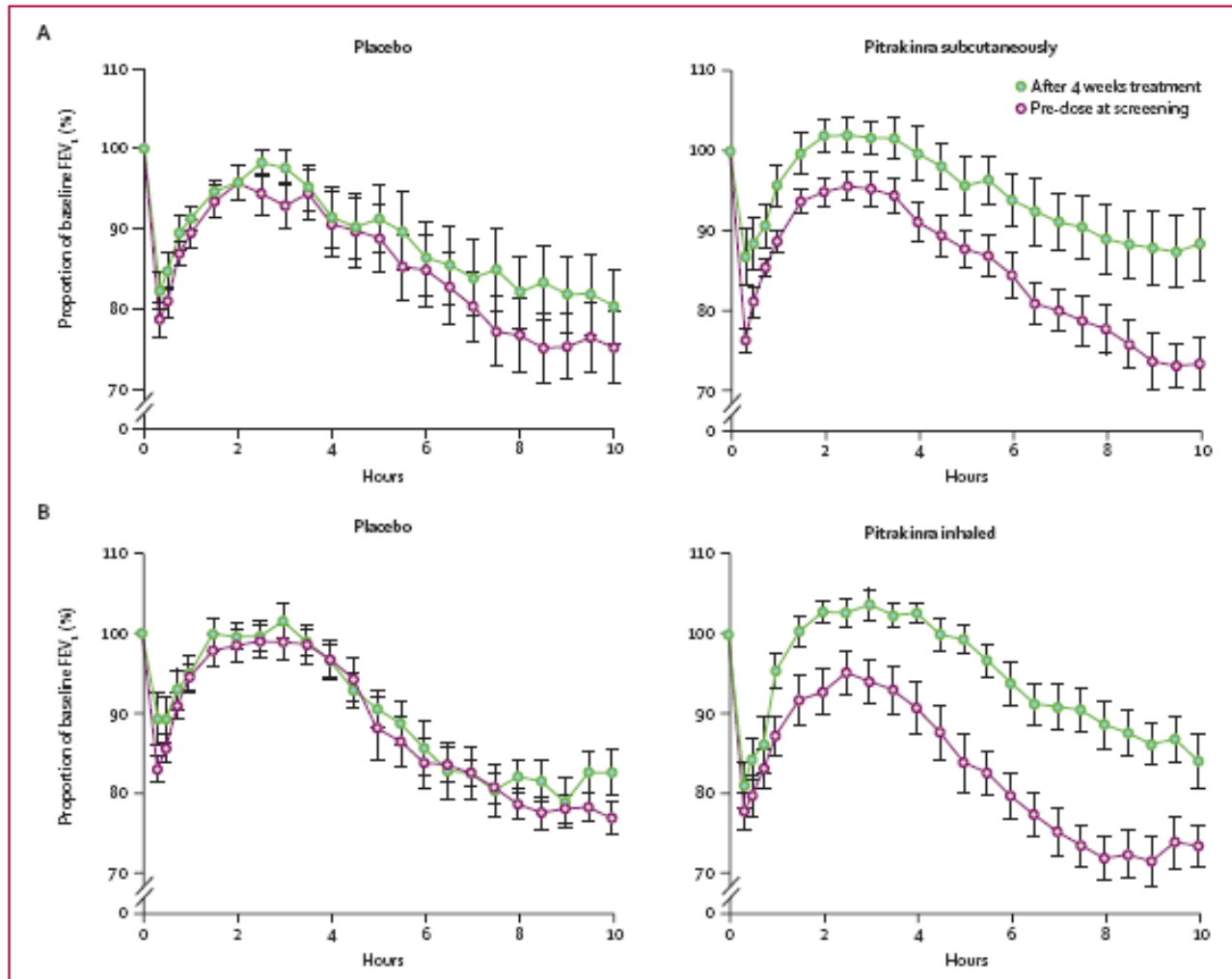


Leukotriener

Cytokiner & Growth
Factors: TNF α , IL-4,
IL-5, IL-13, GM-CSF
ca 30!

Mediatorer av bronkspasm

Hämning av IL-4 och IL-13 (pitrakinra) - effekt på senreaktion

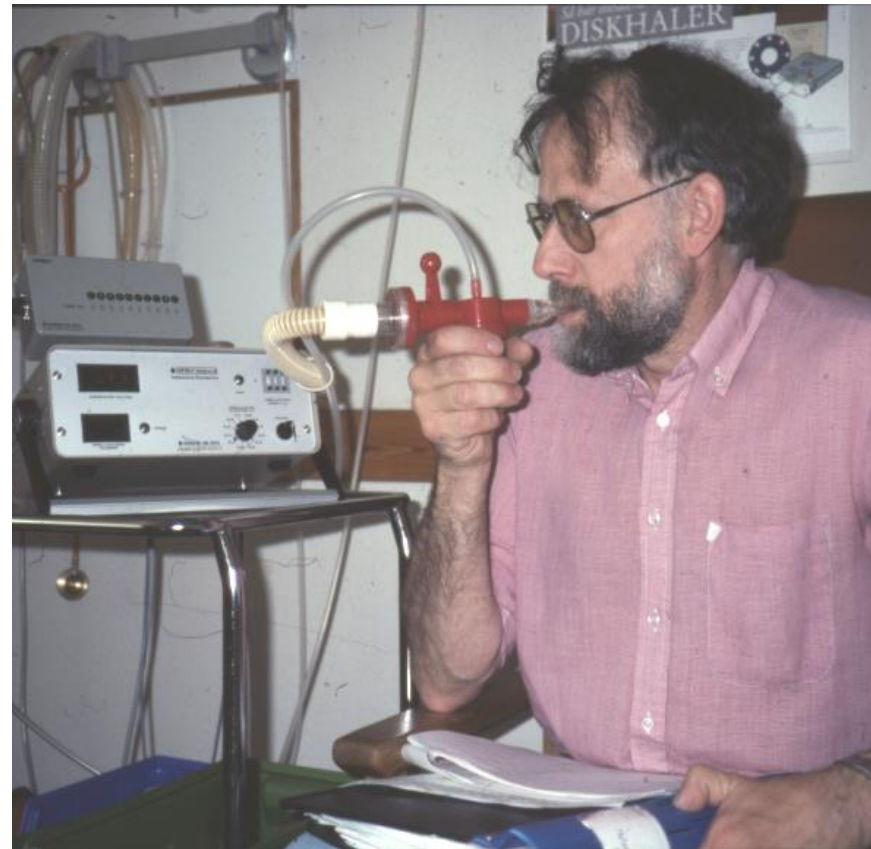


Allergen provokation

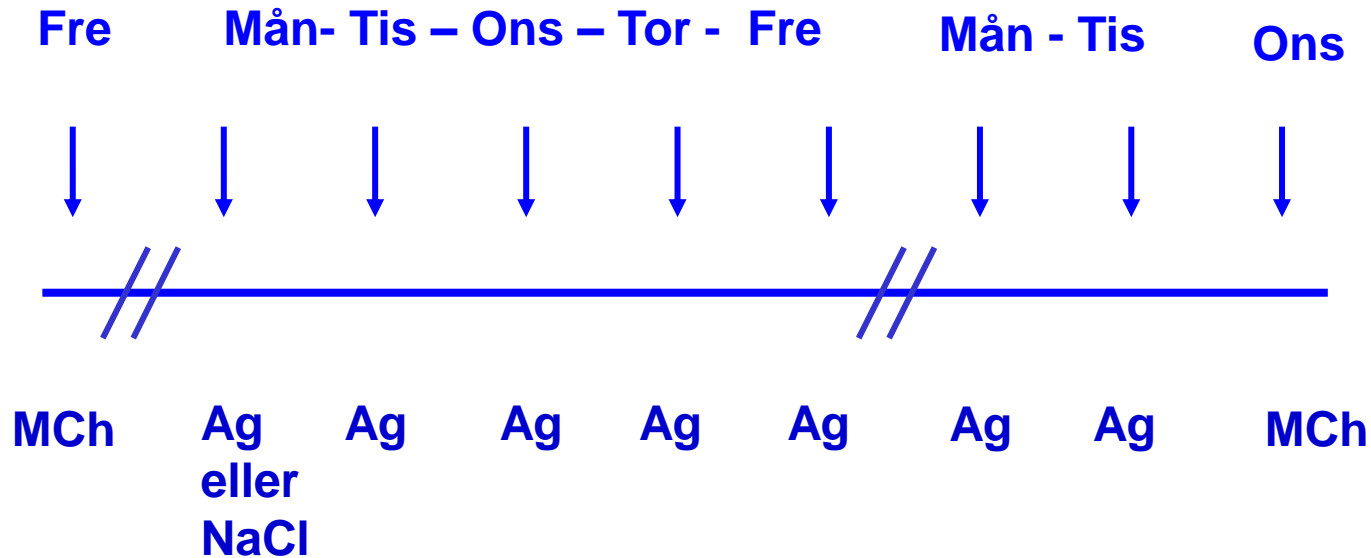
- Metodologiska aspekter

- Bronkdilaterande läkemedel adekvat utsatta
- Medverkan
- Infektionsfri (>4 veckor)
- FEV1 \geq 70% av förväntat
- Dosökning 15 - 20 min till 20% fall
- I-v infart

Konc. mg/mL	andetag	Kumulerad Dos μ g	FEV1 % fall
baslinje	0	0	
NaCl	7	0	
1000	1	7	
1000	2	21	
1000	7	71	
10000	2	213	
10000	7	710	
100000	2	2130	
100000	7	7100	

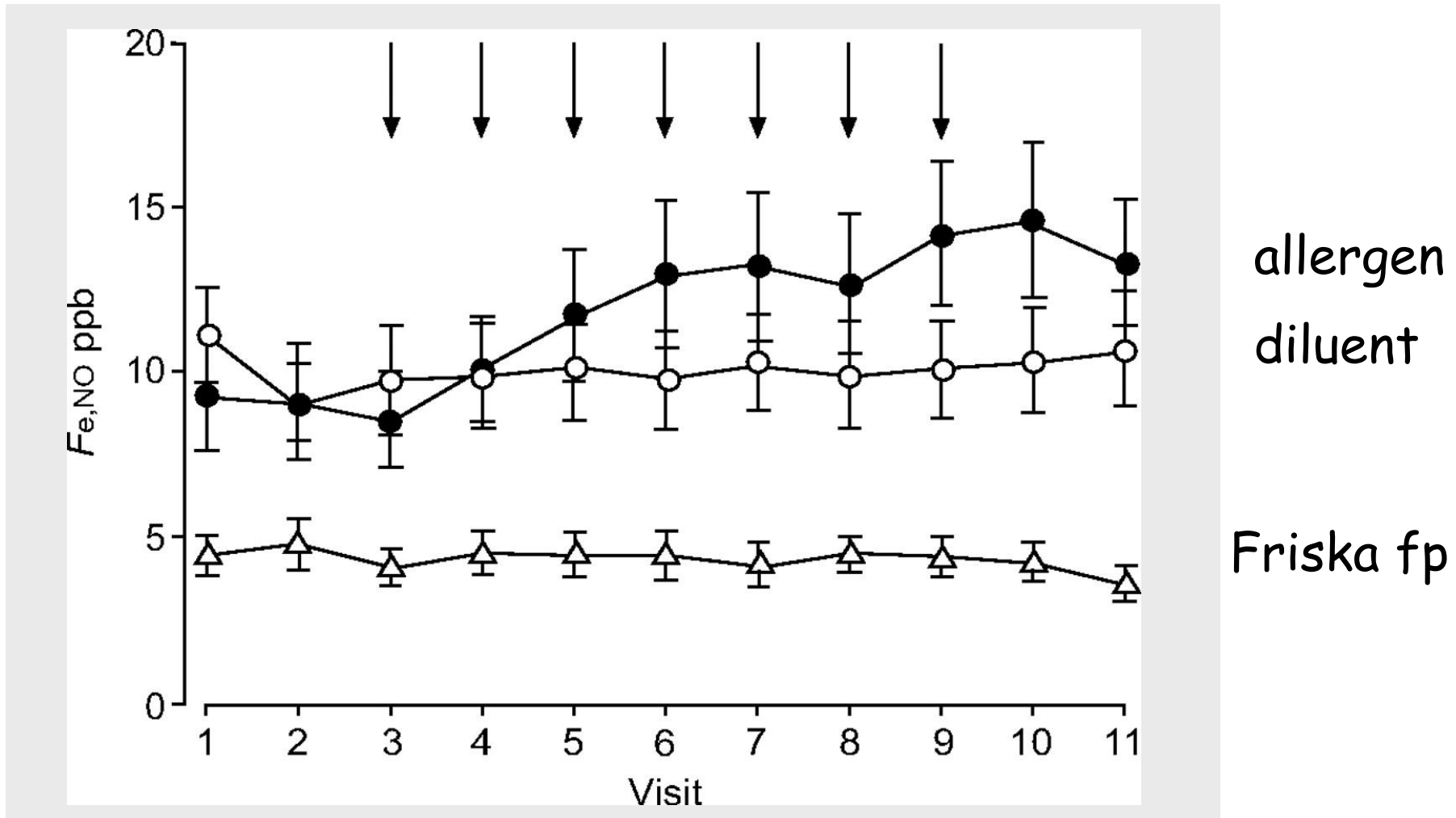


Lågdos allergen provokation (PD₅)



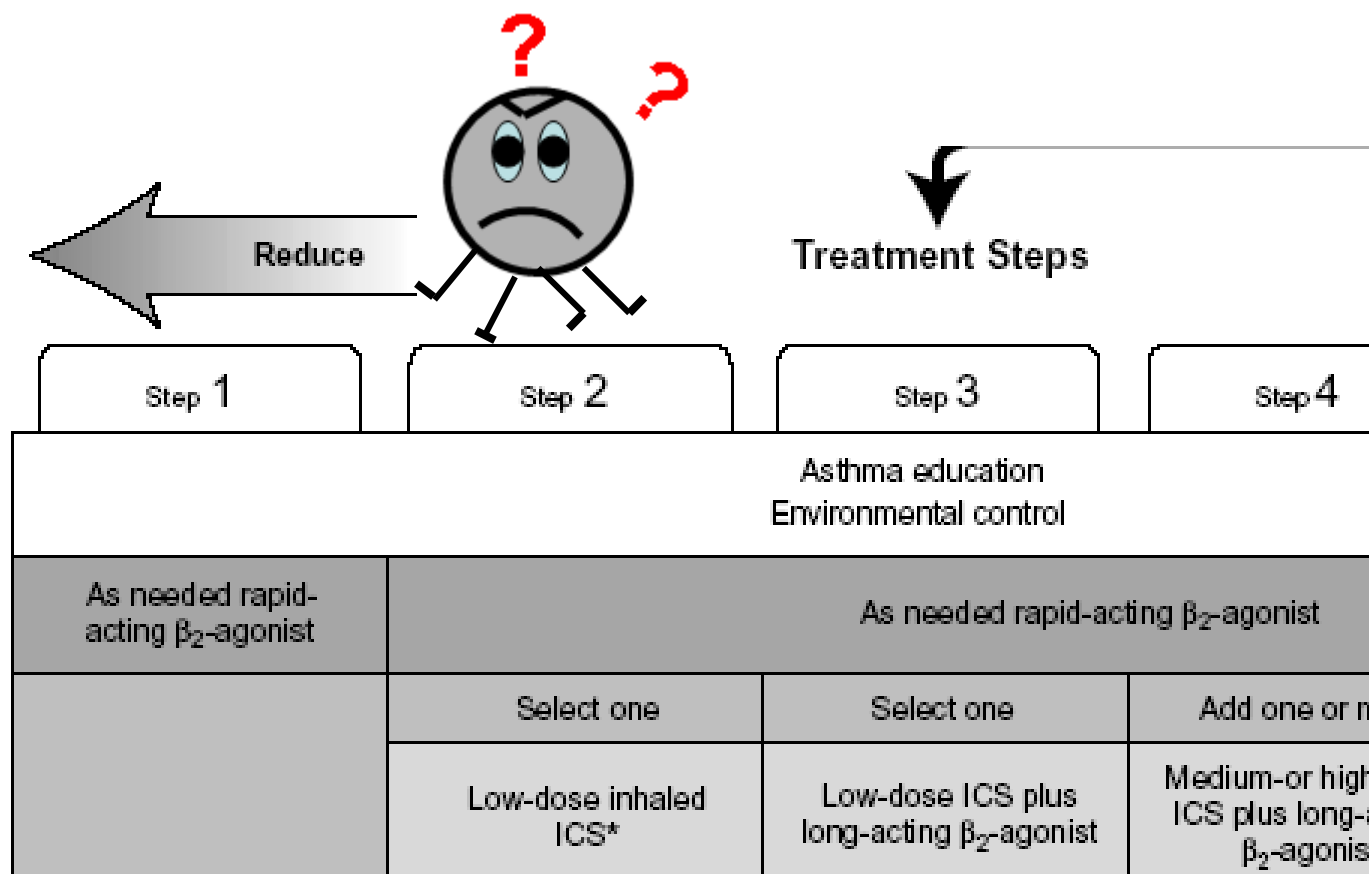
Allergen → **Ökad BHR för Hi/MCh**

Utandat NO under lågdos provokation - vid allergisk astma

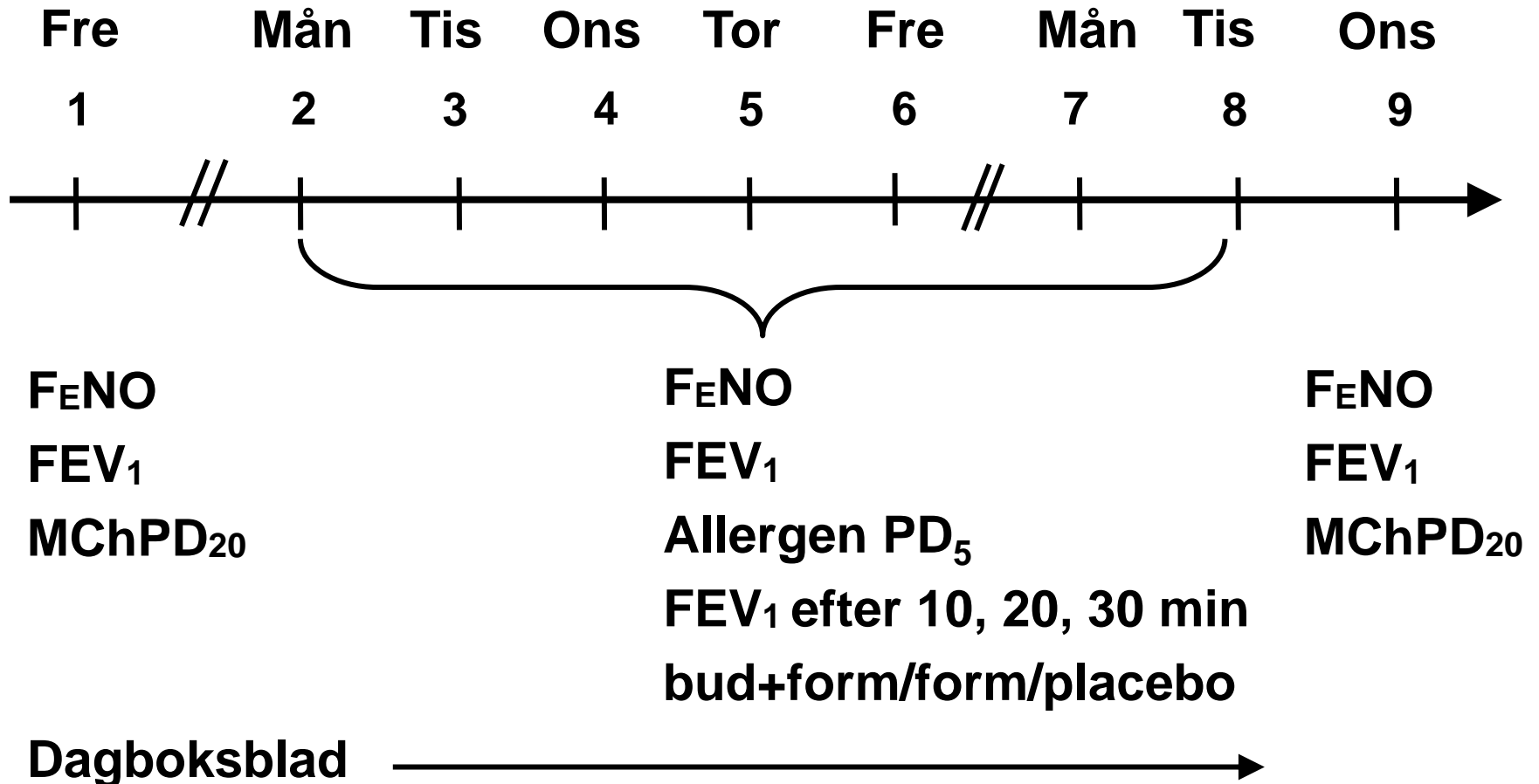


Lågdos allergen exponering

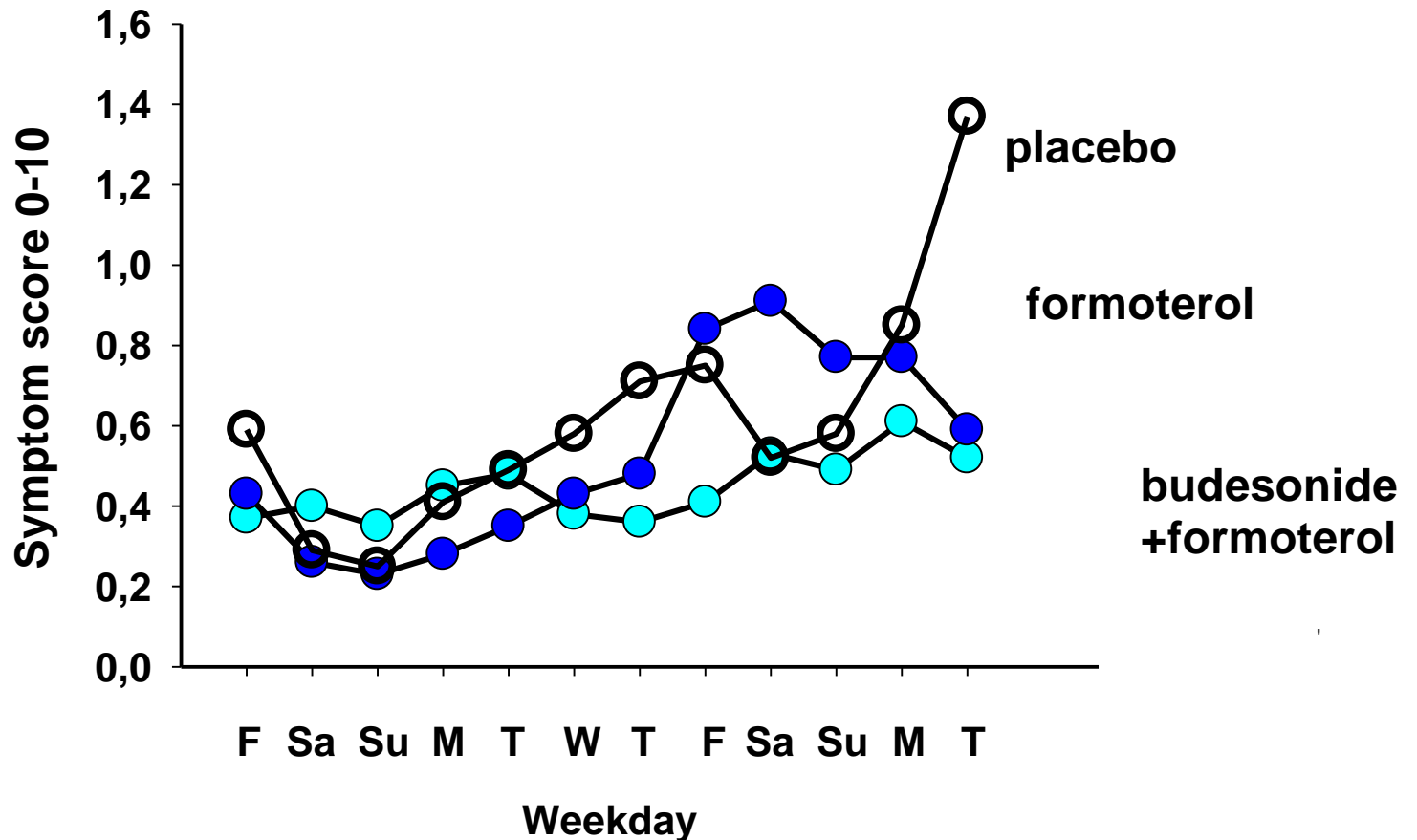
- Formoterol enbart
vs formoterol och budesonid i kombination



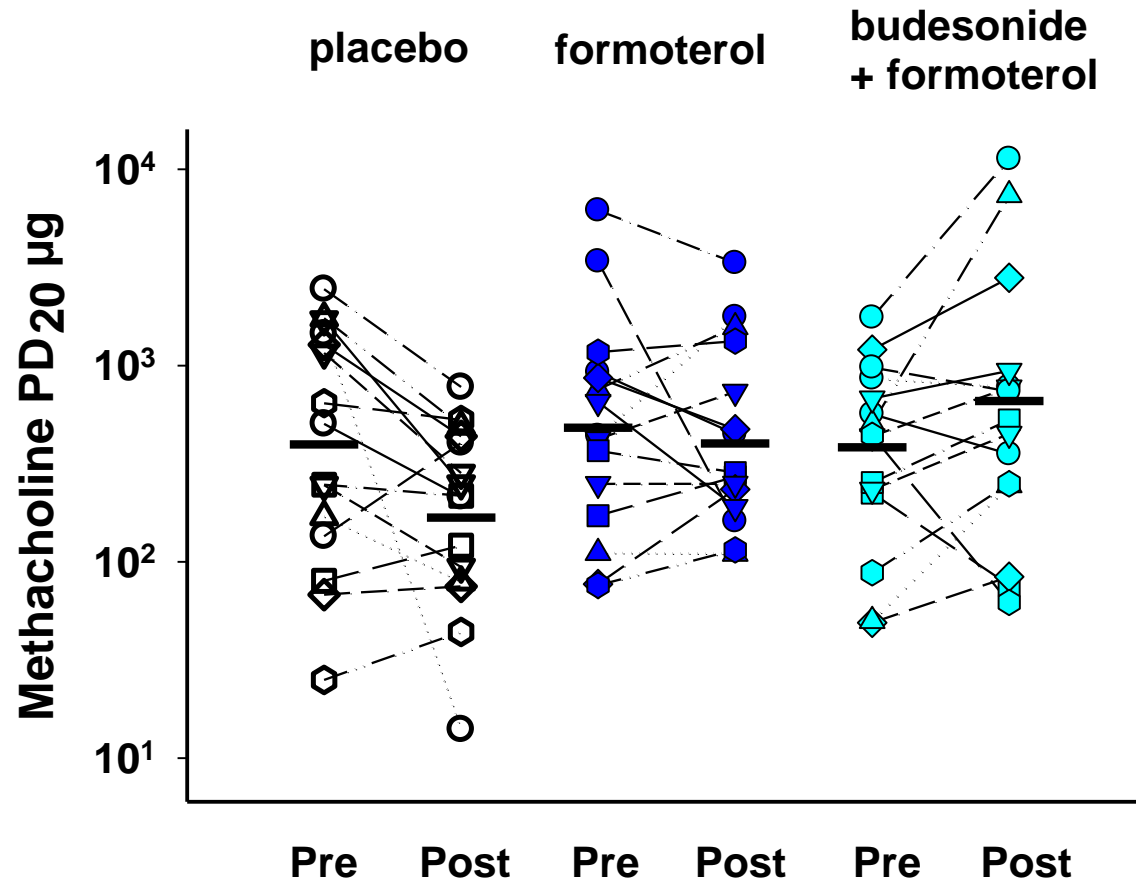
Studie design



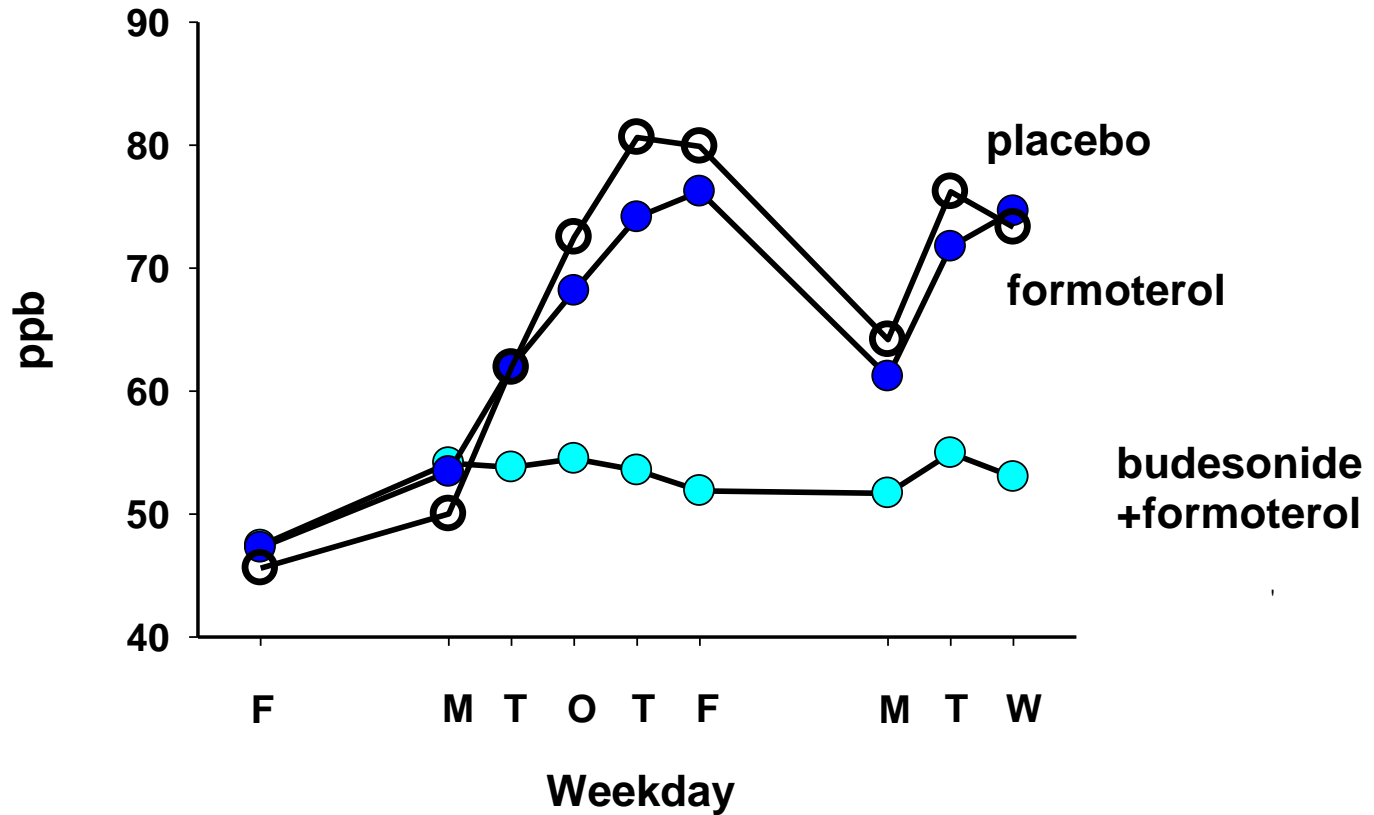
Symptom score during repeated low dose allergen challenge



Airway responsiveness to methacholine during repeated low dose allergen challenge



Exhaled NO during repeated low dose allergen challenge



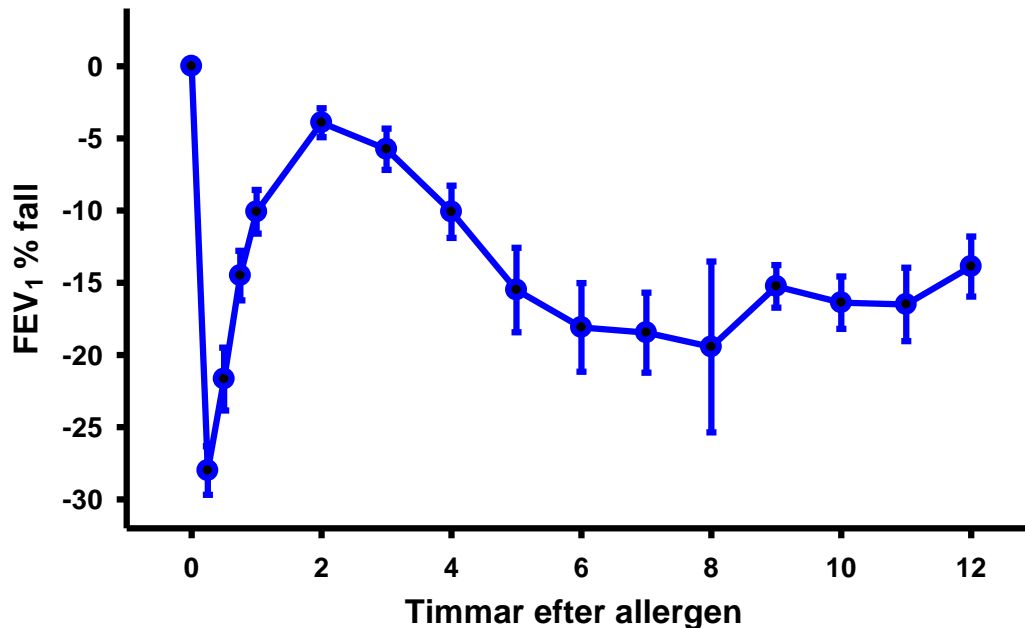
Summary

- Placebo
 - ↑ BHR, symptom, FENO
- Formoterol
 - ↓ symptom - Risk för maskering av inflammation
- Bud+form
 - ↓ AHR, symptom, FENO
 - Stöd för korttidsanvändning

Allergen provokation

En in vivo, human modell:

- explorera astmans patofysiologi
- undersöka behandlingseffekter



Genom att mäta:

Lungfunktion

- tidig reaktion
- senreaktion

Inflammation

- tex eosinofiler

Hyperreaktivitet

Patientutbildning!