Methacholine Challenge Testing: History, perspectives and where are we going?

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Disclosures

American Thoracic Society, Methapharm contributed directly to *in vitro* study and Methapharm supplied methacholine PI Allan Coates

Grant from HTX(combination of Ontario Government, Trudell International, Hospital for Sick Children Research Institute) funded the *in vivo* study – PI Dr Sharon Dell

ERS technical standards on bronchial challenge testing: general considerations and performance of methacholine challenge testing Allan L Coates, Jack Wanger, Donald W Cockcroft, Bruce H Culver et al

- Background
  - ALC drug delivery by aerosol and pulmonary function testing
  - JW and DWC decades long expertise in methacholine challenge
  - BHC long experience writing pulmonary function testing standards
- Special Thanks to Donald Cockcroft for historical background and sharing slides as well as his sense of humour

Objectives

- To review the history of direct provocation challenge testing (histamine and methacholine)
- To discuss the data that no longer supports the 5 breath dosimeter method
- To demonstrate why the PC_{20} is standardized only when using the English Wright nebulizer but the PD_{20} is delivery device independent
- To discuss future directions

METHACHOLINE TEST

- Methacholine inhalation test widely used to identify and quantitate airway (hyper) responsiveness (AHR)
  a defining feature of asthma
- Direct stimulus (as is histamine)
- Direct AHR highly sensitive (caveats)
  ∴ a negative test rules out ***current*** asthma with reasonable certainty

Compliments of Dr Cockcroft

Brief History (1)

- From the 1940's to the 1970's it was assumed that non asthmatics did not have AHR where as asthmatics did
- Some attention was paid to safety with an increasing dose administration but little to standardization of the testing
- Multiple testing protocols were developed with various delivery systems
- Methacholine slowly was replacing histamine due to greater side effects of the latter

Brief History (2)

- Finally two standardized protocols were proposed – Chai et al (JACI 1975) & Cockcroft et al (Clin Allergy 1977)
  - Chai - the 5 breath dosimeter method with a 0.6 sec pulse from a DeVilbiss modified 646 nebulizer during an inhalation from FRC to TLC
  - Cockcroft – 2 minutes of tidal breathing from an English Wright nebulizer calibrated gravimetrically for an output of 0.13 mL/min

  Both used the provocative concentration of histamine or methacholine that caused a fall of 20% in the FEV_1 (PC_{20}) as the end point

Brief History (3)

- Largely out of McMaster University (Hargreave, Juniper, Cockcroft, Ryan and others) data showed
  - Around 10% of normal subjects may show mild AHR
  - Histamine and methacholine response are very similar
  - Response is dose dependent and PC_{20} is repeatable ± 1-1.5 the concentration

  These and data from others gave rise to the ATS 1999 Guideline for Methacholine and Exercise Challenge Testing

ATS 1999 Guideline for Methacholine and Exercise Challenge Testing
The Problems

- **English Wright – 2 minute tidal breathing**
- Difficult to acquire and obsolete
- Output gravimetrically more dependent on evaporative losses than drug output – as much as 75% weight loss due to evaporation
- **The Result**
- Many laboratories claim to follow ATS guidelines but use different devices eg no standardization
- **Five Breath Dosimeter Method**
- Two major issues –bronchoprotective effect with a deep inhalation and modification of the device

The 5 breath dosimeter technique?

DeVilbiss 646 with 0.6 sec pulse for 5 breaths from FRC to TLC

Problems Recommendation of gluing arm in place would not meet any regulatory guidelines nor infection control guidelines

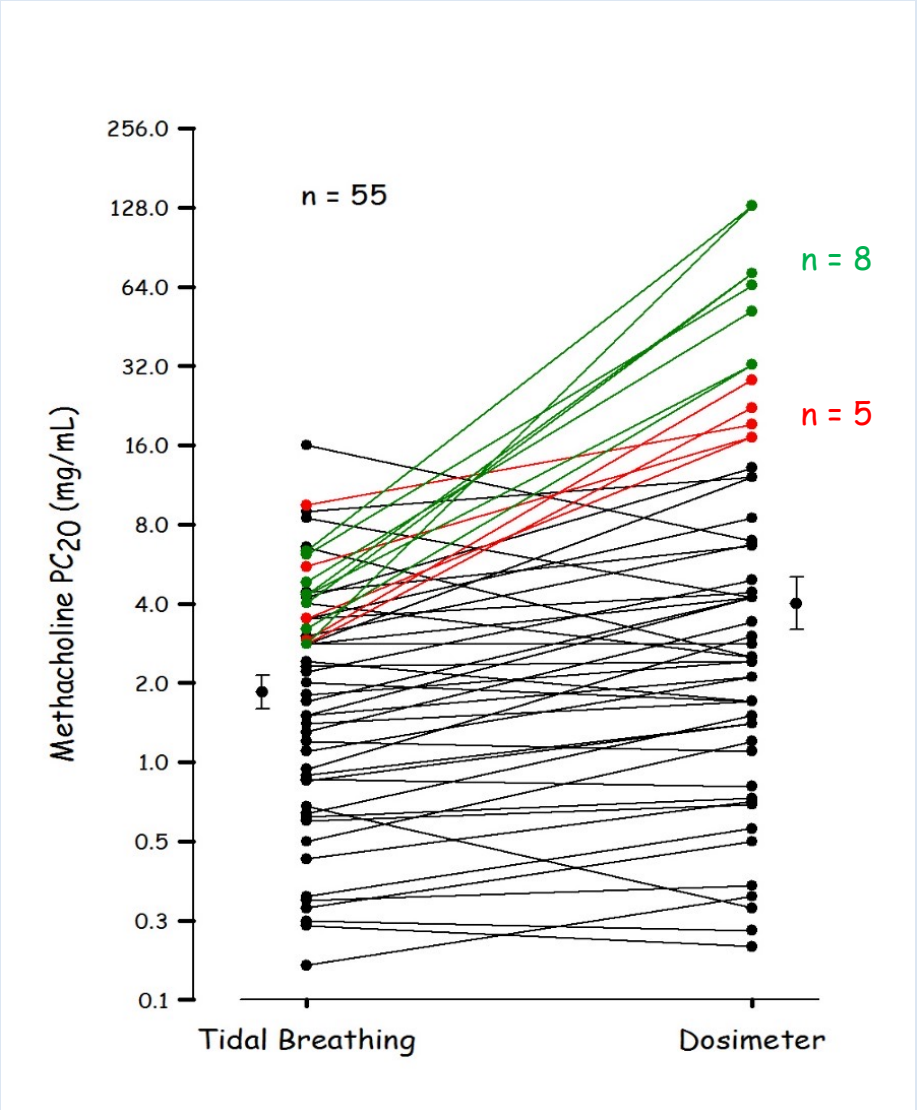
Variable output of the device

Convincing data from Cockroft's group* of the bronchoprotective effect of deep inhalation to TLC means false negatives in those with mild hyperreactivity eg those for whom the test is most indicated

Conclusion This techniques is no longer be recommended

*** Allen et al Chest 2005**

ATS 1999 Methods Comparison: 55 asthmatic subjects from 3 studies



Cockcroft & Davis JACI 2006

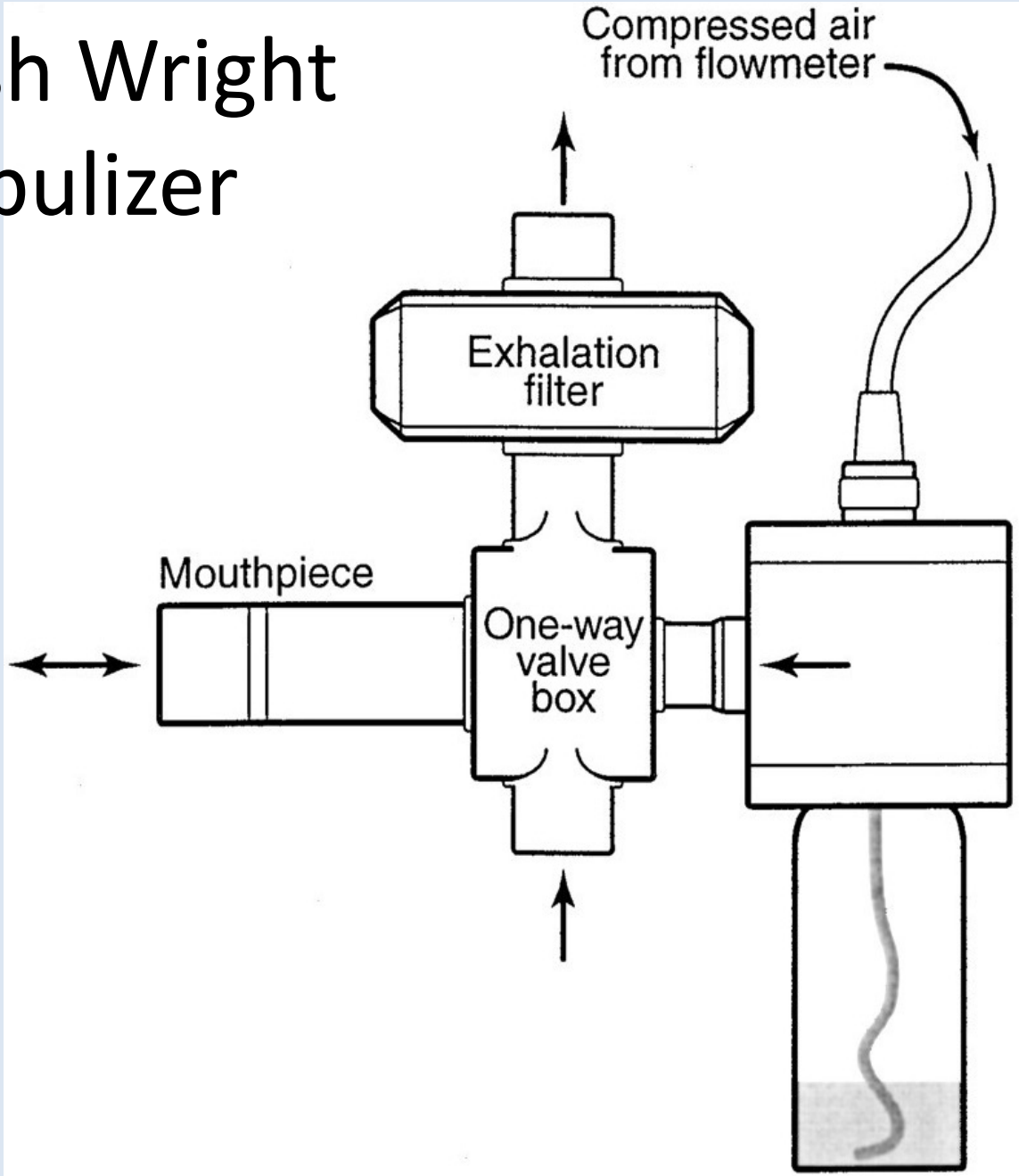
English Wright nebulizer

Used with a connection to allow room air to be added to the flow and an expiratory filter to prevent environmental contamination BUT this will occur if the subject comes off the mouth piece to cough

Subject breathes tidally from the device for 2 minutes

Spirometry 30 and 90 sec after end of nebulization

English Wright nebulizer



The Proposed Solutions

Develop *in vitro** independent evaluation standards using a breath simulator (V_T=0.75 L, RR=15 b/m, Ti/Ttot=0.4)

Compare devices both *in vitro* and *in vivo*

English Wright vs AeroEclipse II BAN

Attempt to shorten the time required for the test (could be a problem due to cumulative affect of methacholine)

* Coates et al J Aerosol Med Pul Drug Del 2014

AeroEclipse II BAN™ Nebulizer

Breath actuated so it stops nebulizing when removed from mouth so little environmental contamination – maybe no need for filter

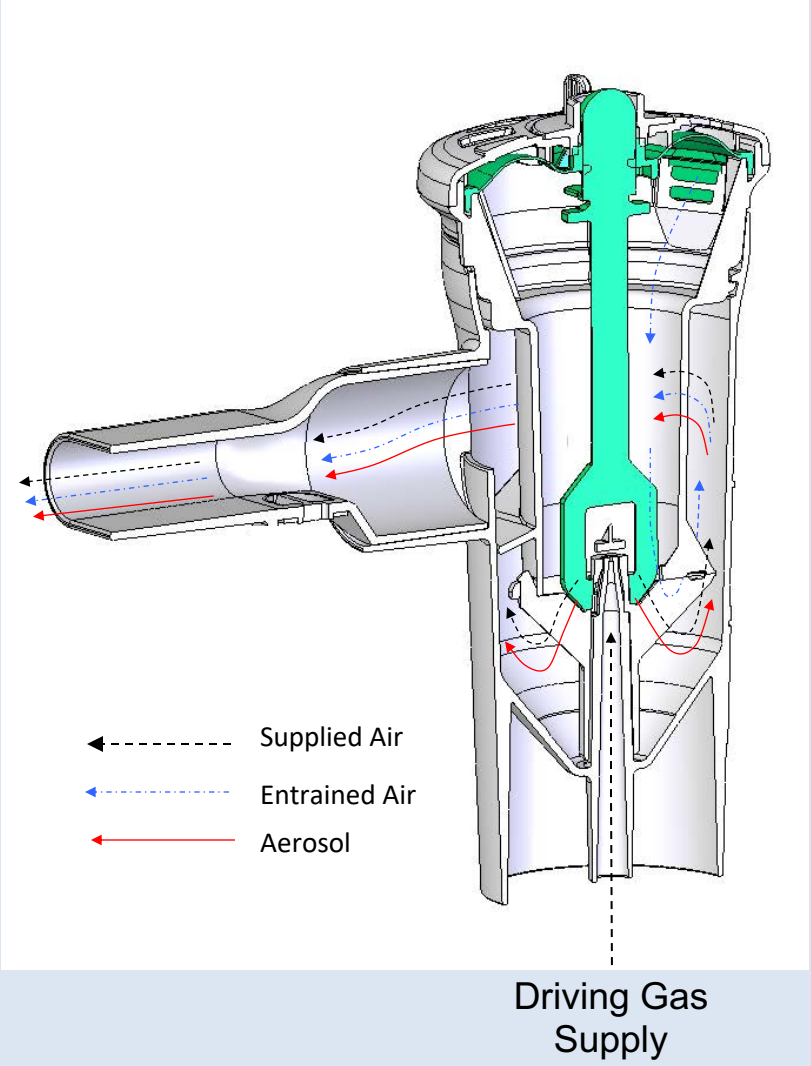
Driven by 50 psi source (8 L/min) – tank or hospital gas with a respirable fraction (by laser diffraction) measured at 0.76 with some *in vivo* correlation

Disposable – no need for cleaning

AEROECLIPSE* II BAN Schematic

Aerosol is *only* created in response to the patient's inspiratory maneuver.

1. Patient is inhaling
2. Negative pressure in the nebulizer pulls the diaphragm down
3. The actuator has moved all the way down sealing around the nozzle cover
4. Aerosol is produced



Summary of *in vitro*[*] Results

AeroEclipse II BAN will deliver the equivalent estimated pulmonary dose of the English Wright in 12 vs 120 seconds

Note: 10% of the output of the AeroEclipse was collected on the expiratory filter

* Coates et al J Aerosol Med Pul Drug Del 2014

In Vivo Research Question 1

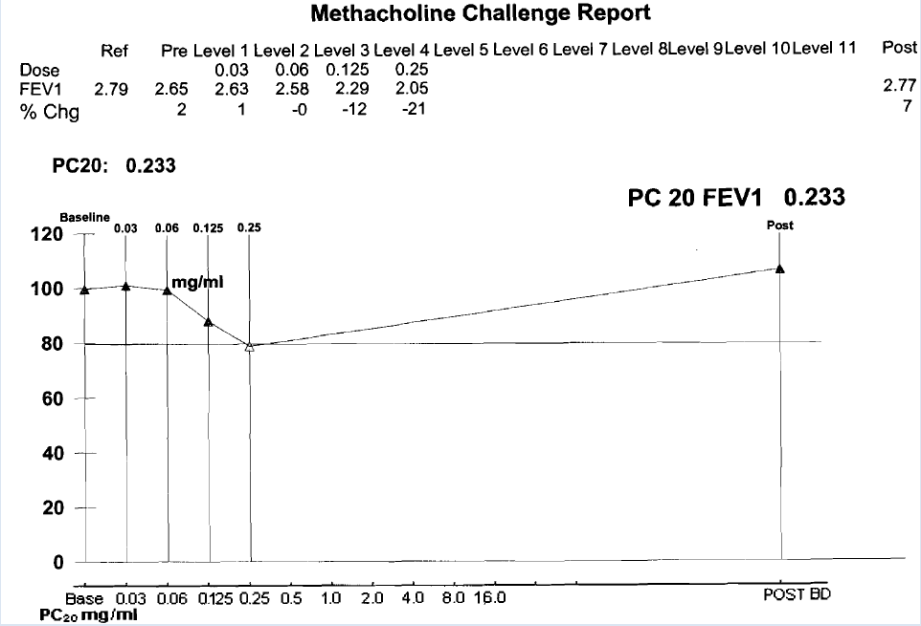
Dell et al

Is there a cumulative dosing effect using a shortened inhalation time protocol which, if we shorten the time between doses, will it affect our test results?

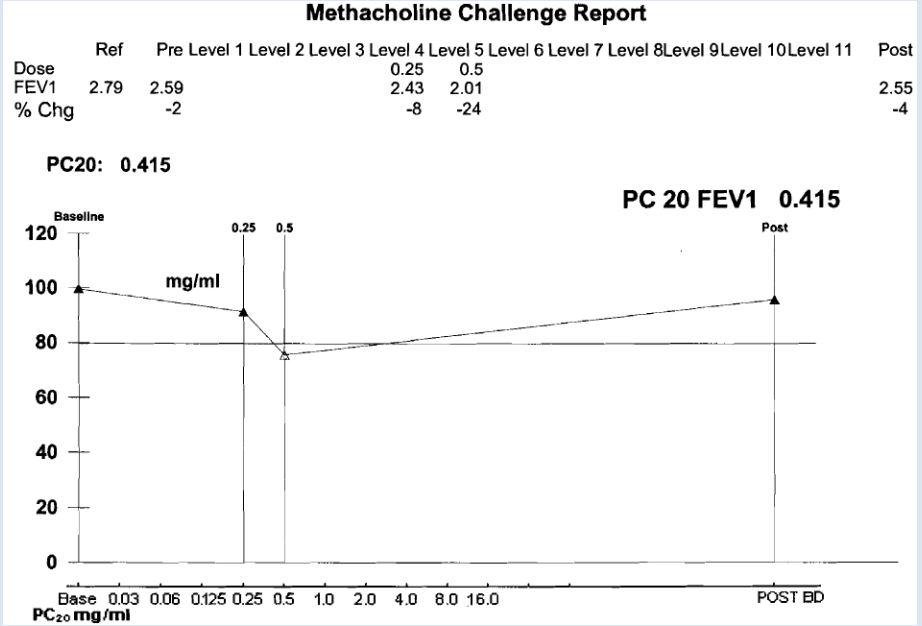
Subjects - children with known positive Methacholine Challenge Test (MCT)

First test, PC_{20} determined from 30 s tidal breathing with AeroElcipse then test repeated starting with the PC_{20} dose

The PC_{20} is higher if starting at previous PC_{20} – cumulative effect

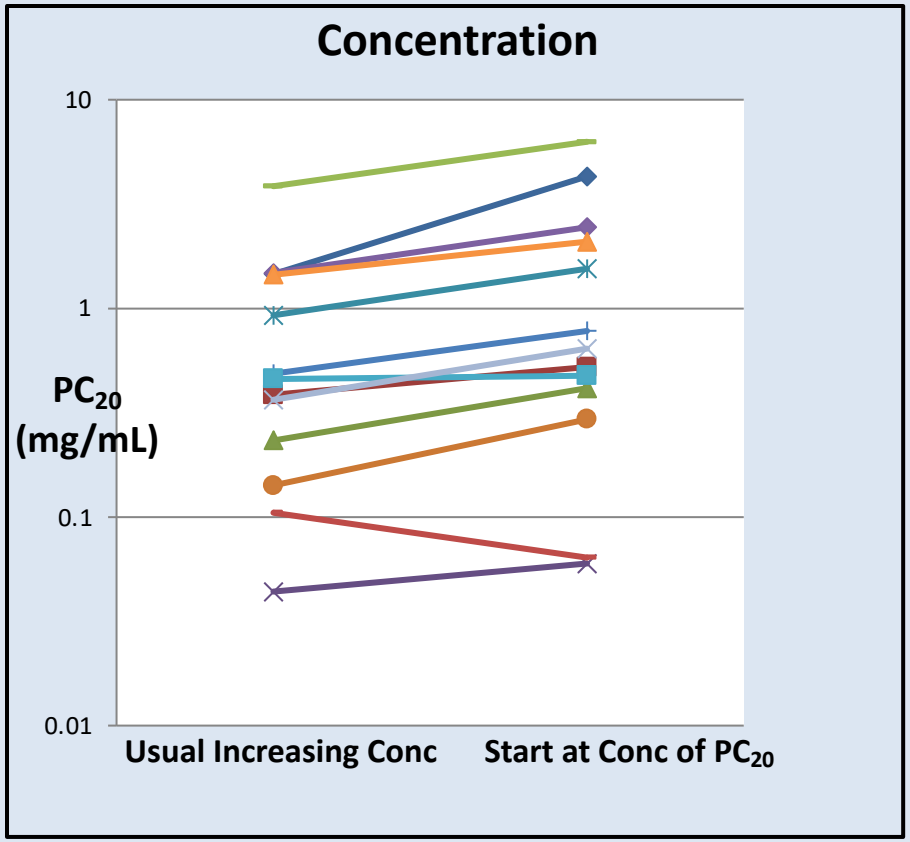


AeroEclipse (Visit 1)

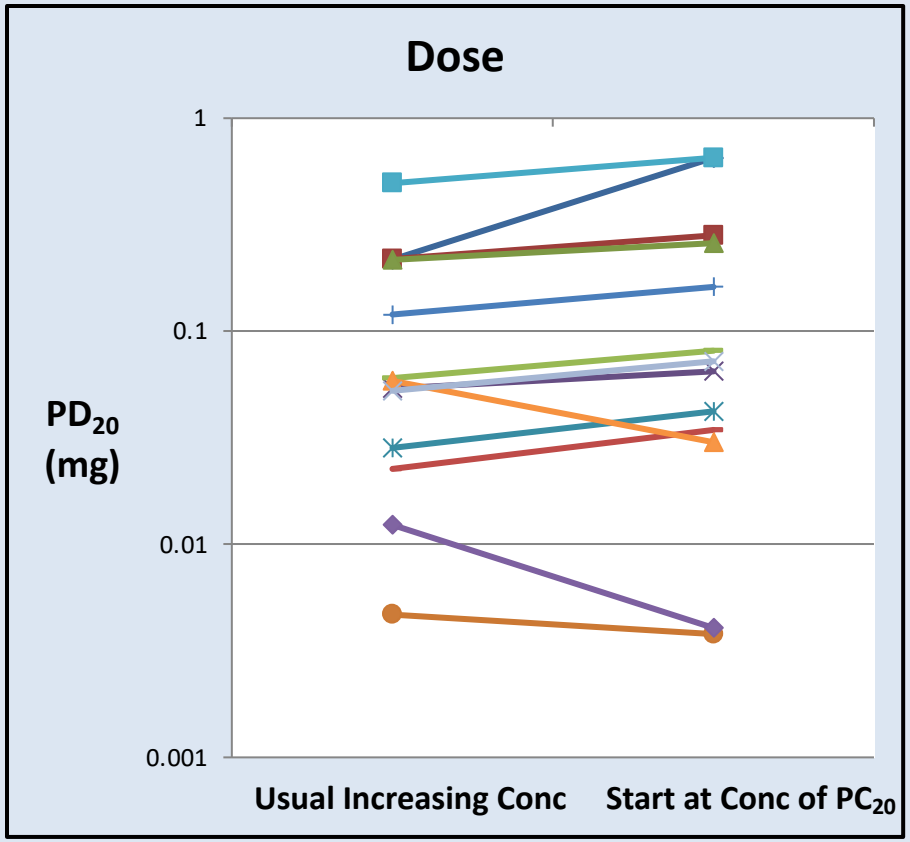


AeroEclipse (Visit 2)

Comparison of Concentration (PC_{20}) and Dose (PD_{20}) for Aero30 (cumulative effect)



n=13
p=0.0014



n=13
p=0.1002

Conclusion In Vivo Research Question 1

- The preceding dose influences the subsequent dose
- Greatly shortening the test time due to shorter inhalation times would enhance the cumulative effect making any comparisons to previous methods difficult
- Corollary THE TIME BETWEEN INHALATION IS IMPORTANT AND MUST BE STANDARDIZED

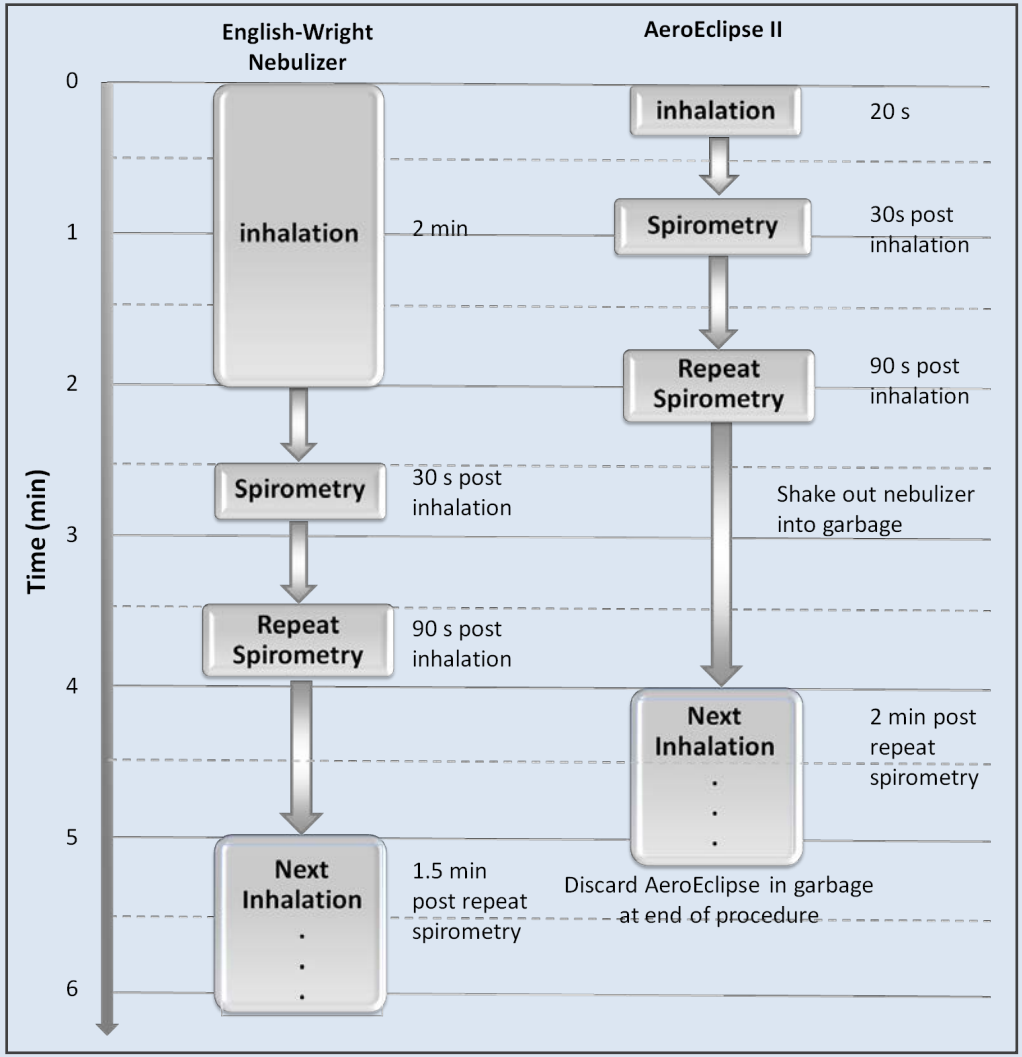
In Vivo Research Question 2

Will the AeroEclipse II with 20 second inhalation time give a similar result to the Wright nebulizer with 2 minutes tidal breathing?

Subjects -27 children with known positive Mch Test

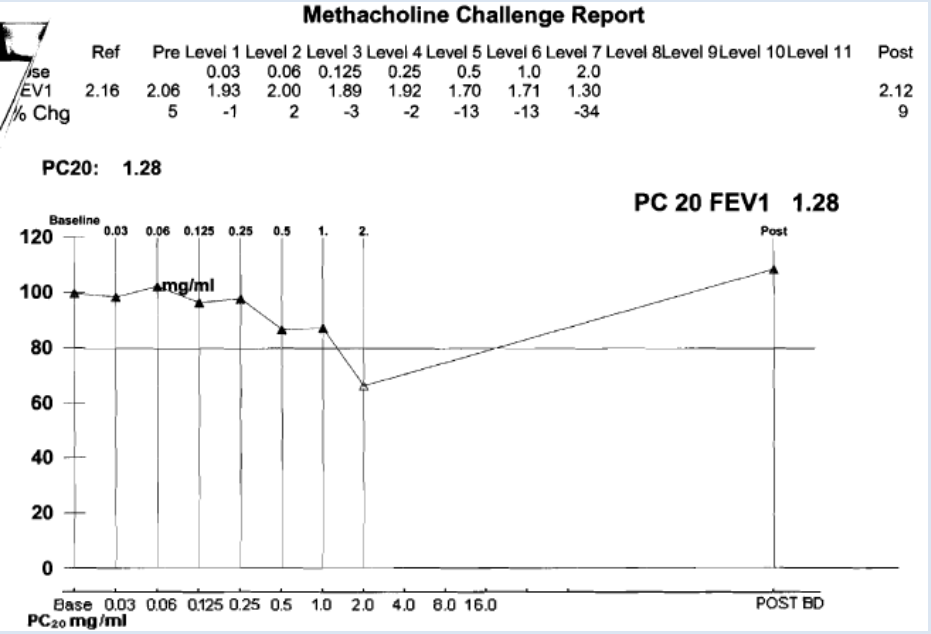
Concern about variability in number of breaths if time was reduced to 12 seconds for the AeroEclipse (which would have been *in vitro* equivalence)

Protocol

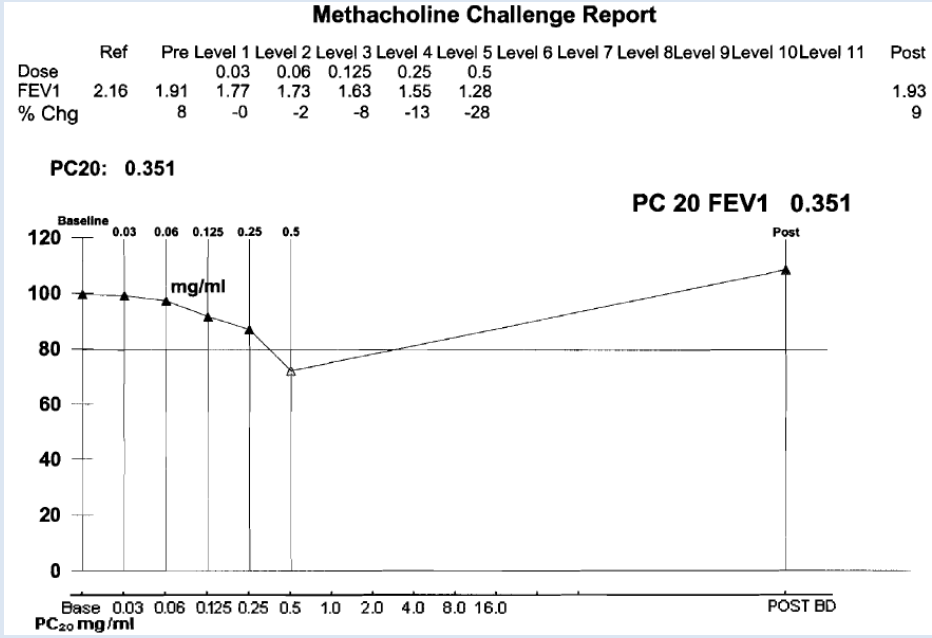


Note – This does not exactly follow the current guidelines of 5 minutes between doses

Comparison of EW to AeroEclipse

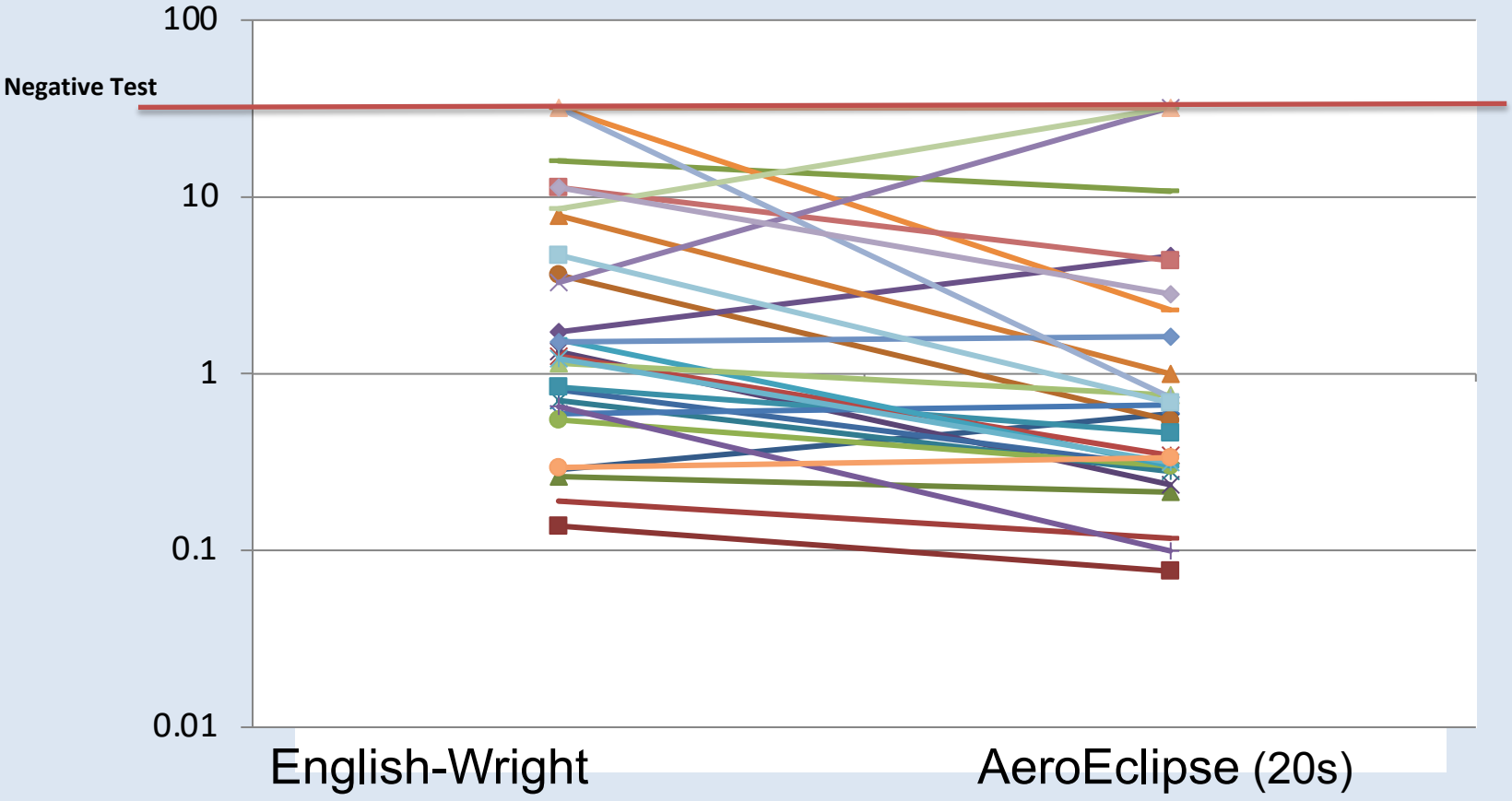


English Wright (2minutes inhalations)



Aeroeclipse (20 second inhalation)

Comparison of PC_{20} for English-Wright and AeroEclipse II BAN



n = 27 p < 0.003

The Problem

With inhalation time of 20 seconds, the PC_{20} for the English Wright was greater than for the AeroEclipse II

Concern about variability in number of breaths if time reduced even more

Difference were most marked for those with the higher PC_{20} which are the patients where the question of asthma is greatest

Let Us Look at this Differently

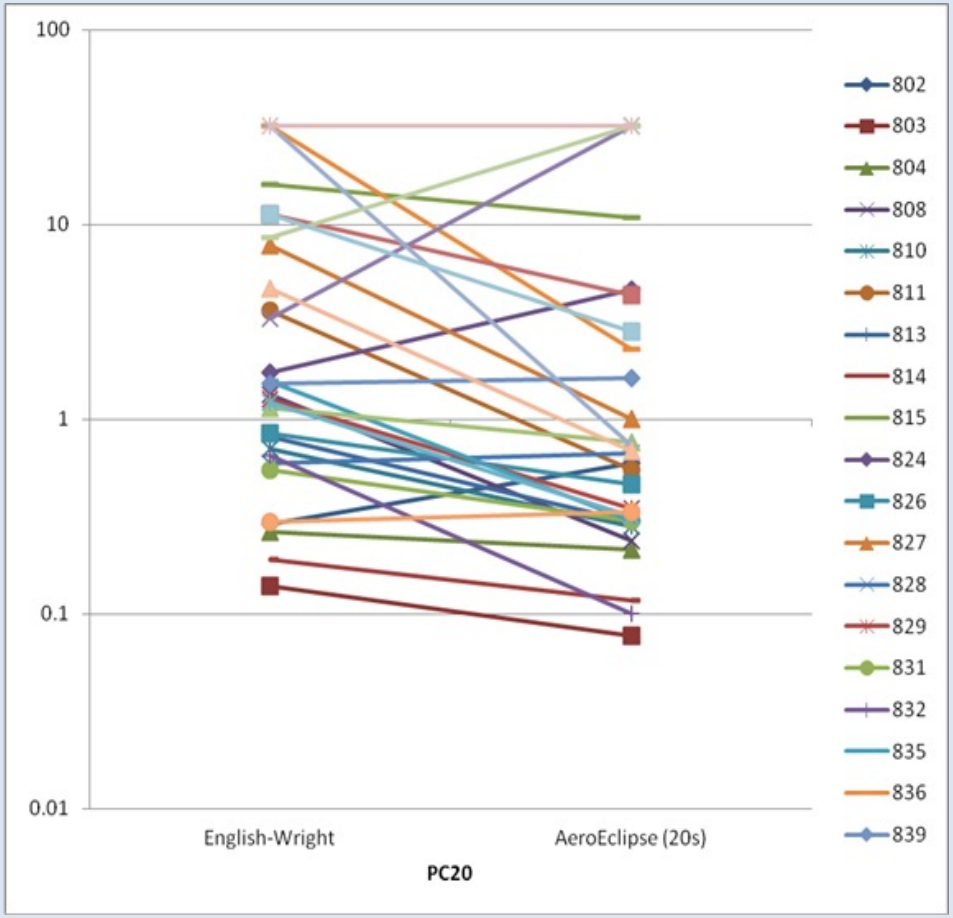
We know how many breaths they took

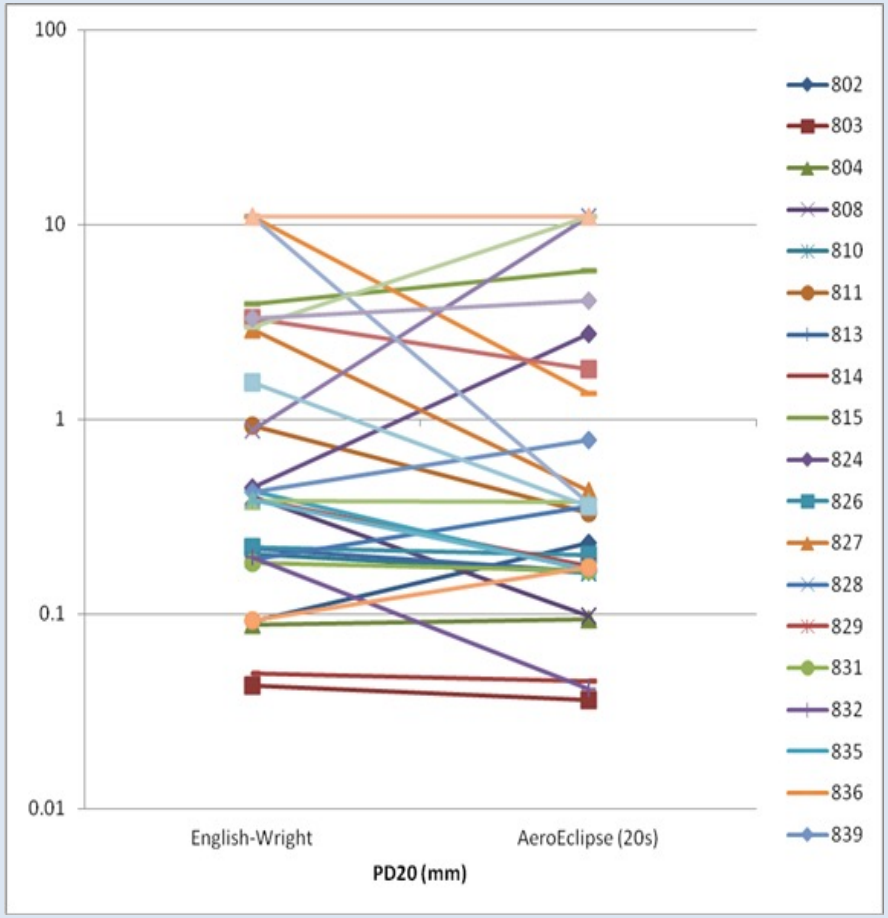
We know (can estimate) the time spent in inspiration

We measured the rate of output of both the English Wright and the AeroEclipse II

We can calculate the cumulative dose that caused the 20 % fall in FEV_1, the PD_{20}

Comparison of Concentration (PC_{20}) mg/mL and Dose (PD_{20}) µm for English-Wright and Aero20



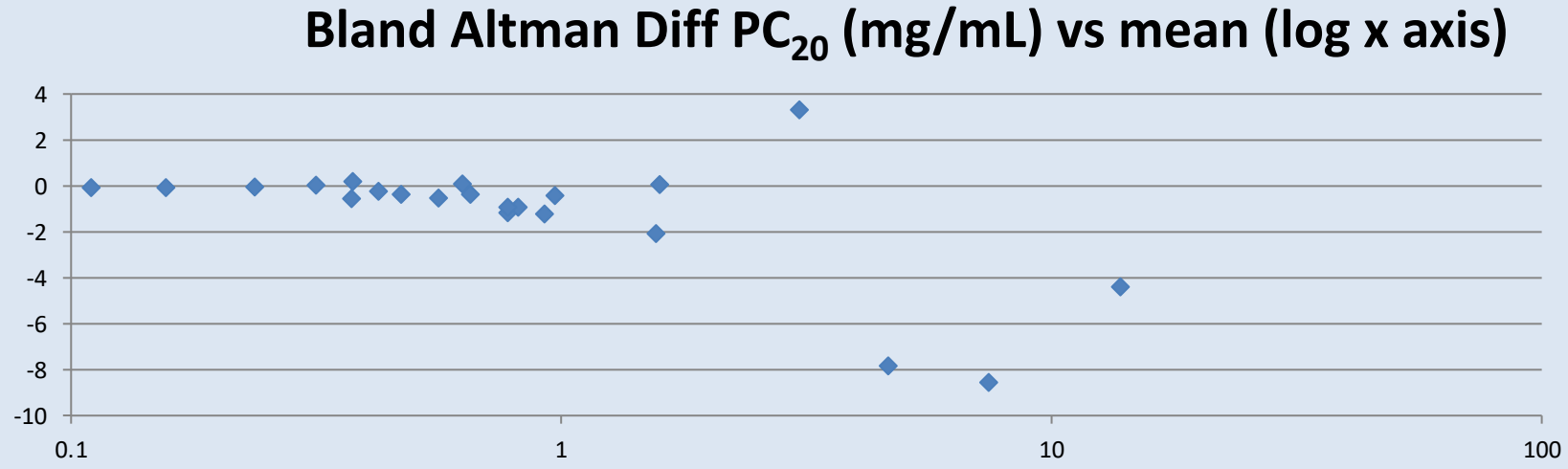


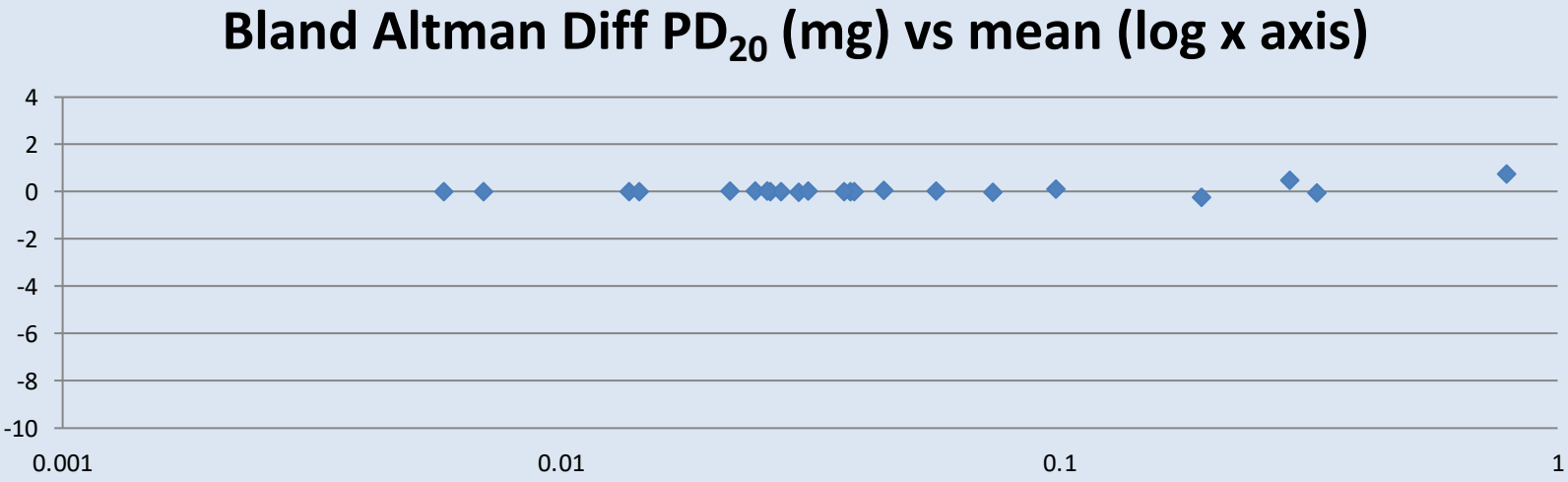
N = 27
P = 0.0073

n=27
P= 0.39

*Used conservative estimate of PC_{20}=32 mg/mL and PD_{20} = 8 µmoles for negative

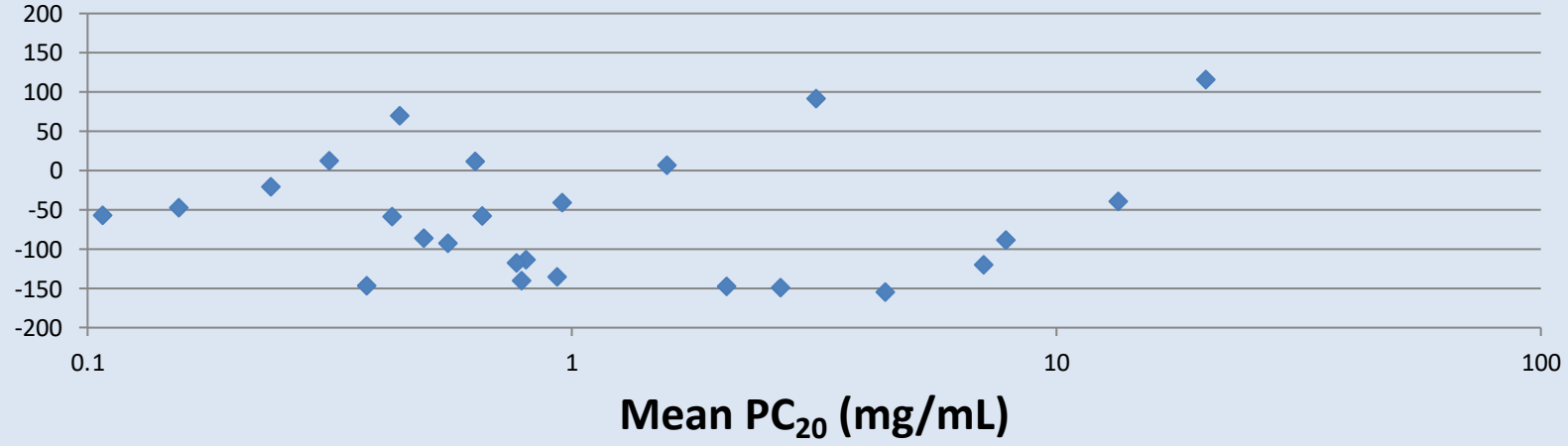
Are These Findings Clinical Relevant? (Aer20 – EW) vs mean



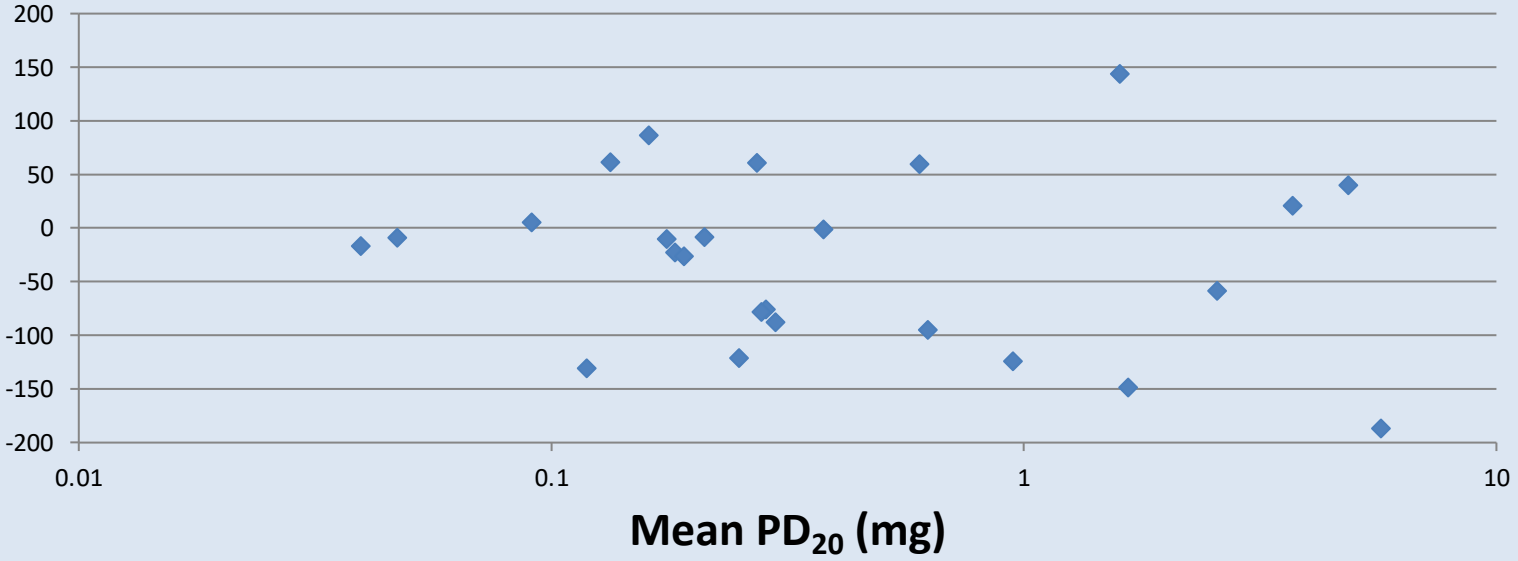


Are These Findings Clinical Relevant?
Percent difference Aero to EW (y axis) plotted against the mean (x axis)

Aero – English Wright



Aero – English Wright

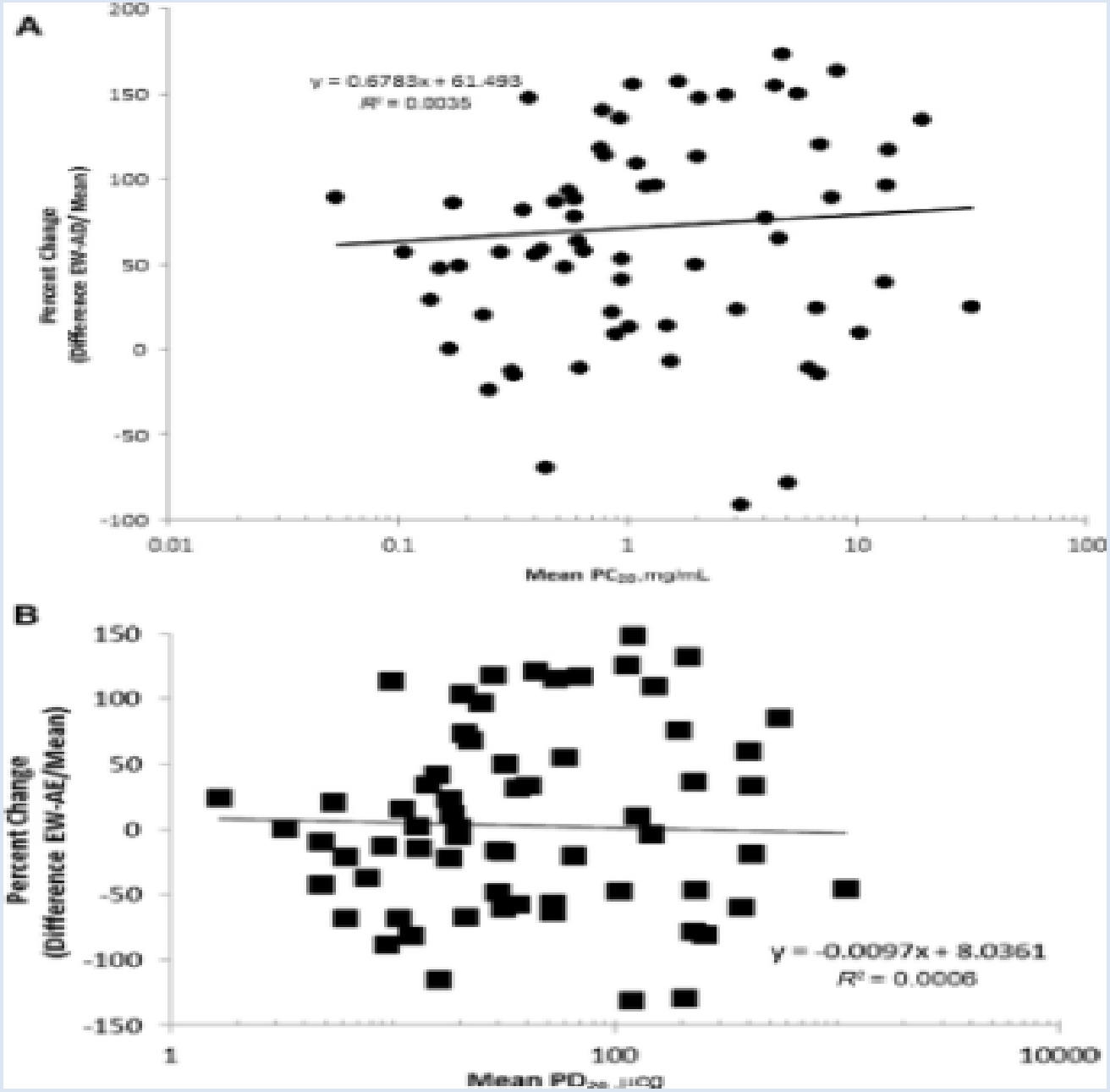


What about Adults?

- Gail Gauvreau's group duplicated the study in asthmatic adults and found virtually similar results (El-Gammal et al Ann Am Thor Soc 2015)
- Coates et al combined the pediatric and adults data

Combined Pediatric and Adult Data

Coates et al Ann Allergy Asthma Immunol 2017



Conclusions

The was an approximate two doubling dose difference in PC_{20} for the E-W compared to the AeroEclipse .

In is those with mild hyperreactivity this could be the difference between positive and normal (eg problems with negative predictive value)

These differences disappear if the PD_{20} is used instead of the PC_{20}

ATS/ERS Proposal

Use PD_{20} instead of PC_{20}

Corollary – should be device independent as long as the delivery characteristics of each device are known

Hence, for any proposed new delivery system, as long as the *in vitro* performance characteristics are known, there should be equivalence among devices

Epidemiological studies will be needed to define normals for PD_{20} – proposed > 2 µmoles (0.4 mg)

Summary

Five breath dosimeter method no longer recommended

For tidal breathing method

Use PD_{20} instead of PC_{20} (should be device independent)

Clearly more *in vitro* and *in vivo* studies will be needed to better define devices and population standards

What About Other Devices?

Methacholine is technically very difficult to assay so quantification of performance data is sparse –could gravimetric assays be used?

The variable degree of evaporative losses with jet nebulizers make this method inaccurate

Vibrating mess nebulizers have little to no evaporative losses so gravimetric assays are applicable

Vibrating Mesh Nebulizers

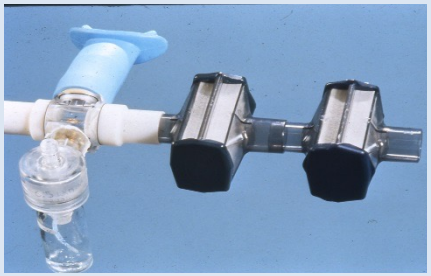
- Beth Davis et al (Cockcroft group) compared a vibrating mesh nebulizer (Aerogen Solo®) to the English Wright
- Unlike the relatively inexpensive disposable AeroEclipse, the Solo is not disposable and is recommended for single patient use only (no manufacturer support for sterilization making it a relatively expensive option in the PFT lab)

- Chest 2017

VIBRATING MESH NEB

- Aerogen Solo® vibrating mesh nebuliser
- No evaporation eg output can be measured gravimetrically
- Intended to be disposable
- No compressed gas
- Preliminary study (Blais 2017) showed it could be used to deliver methacholine

Compliments of Dr Cockcroft



Wright® vs Solo®

WRIGHT ®	SOLO®
• 2 min tidal breathing	• 0.5 mL to completion by tidal breathing
• Neb @ 0.13 g/min	
• Saline followed by 0.125-16 mg/mL	• Saline followed by 0.016-2 mg/mL

Other aspects identical:

- Timing between doses (5 min)
- Timing of FEV_1 (30 & 90 sec)
- Calculation of PC_{20} / PD_{20}

Compliments of Dr Cockcroft

AEROGEN® SOLO® METHOD

- ERS guideline compatible method
- 0.5 mL (exactly) nebulised to completion
  and inhaled by tidal breathing;
  this requires approximately 1.5-2.5 m
- 2 mg/mL x 0.5 mL x 0.4 = 400 μg
  (0.4 is the duty cycle, Ti/Ttot)
- Doubling conc/dose @ 5 min intervals
  up to 2 mg/mL (i.e. 400 μg)

Compliments of Dr Cockcroft

RESULTS

Results are geometric mean & average of 2

(n = 15 stable subjects)

- Wright® PC_{20} = 4.4 mg/mL
- Solo® PC_{20} = 0.48 mg/mL ($p < 0.001$)
- Wright® PD_{20} = 110 μg
- Solo® PD_{20} = 96 μg ($p > 0.05$)
- Repeatability (interclass correlation coef) 0.96&0.97

Compliments of Dr Cockcroft

SOLO®: SUMMARY

- The Solo® method showed similar PD_{20} vs the Wright 2 m tidal breathing method
- Validates the ERS Guideline Table 6
- Advantages
  - Dose can be calculated
  - Calibration not required
  - Compressed gas not needed
  - Quiet and easy to use
- A valuable alternative method

Compliments of Dr Cockcroft

Adapting to New Data

- Change is often challenging and can bring unexpected problems
- Moving to PD_{20} from PC_{20} may have consequences well beyond the PFT lab
- BUT
- The love for the Saskatchewan Roughriders helps

vs

Definitions	PC_{20} (mg/mL)	PD_{20} (µg)
Negative	> 16	~ > 400
Borderline	4-16	100-400
Mild AHR	1-4	25-100
Mod AHR	0.25-1	6-25
Marked AHR	< 0.25	< 6

Compliments of Dr Cockcroft

ERS Guidelines Table 6 Coates ERJ 2017

Future Directions

- One of the issues is that both the recent pediatric and adult studies have used known asthmatic to compare the tests
- The data is sparse concerning where the cut off should be for normal subjects
- Preliminary data in a large children's cohort study (CIHR funded, PJ Subbarao PI) suggests that the ERS current cut off for normal may be too high – no data on adults
- Device manufacturers need to provide performance data on their devices

Take Home Message

- The data no longer support the use of the 5 breath dosimeter method
- The PC_{20} is very delivery device dependent where as the PD_{20} can be standardized for many devices as long as the device performance is known
- Because of the cumulative effects of methacholine standardizing the time (5 minutes) between doses is important