METHACHOLINE GUIDELINES 2016

Don Cockcroft

April 16, 2016

The Goon Show

1951-1960
Spike Milligan
Peter Sellers
Harry Secombe
Spike Milligan
Creator and
chief writer
b. April 16 1918

COI

No conflict of interest (4 years)

Member guideline update

task force

I have previously been a consultant for Methapharm (makers of Provocholine®, methacholine)

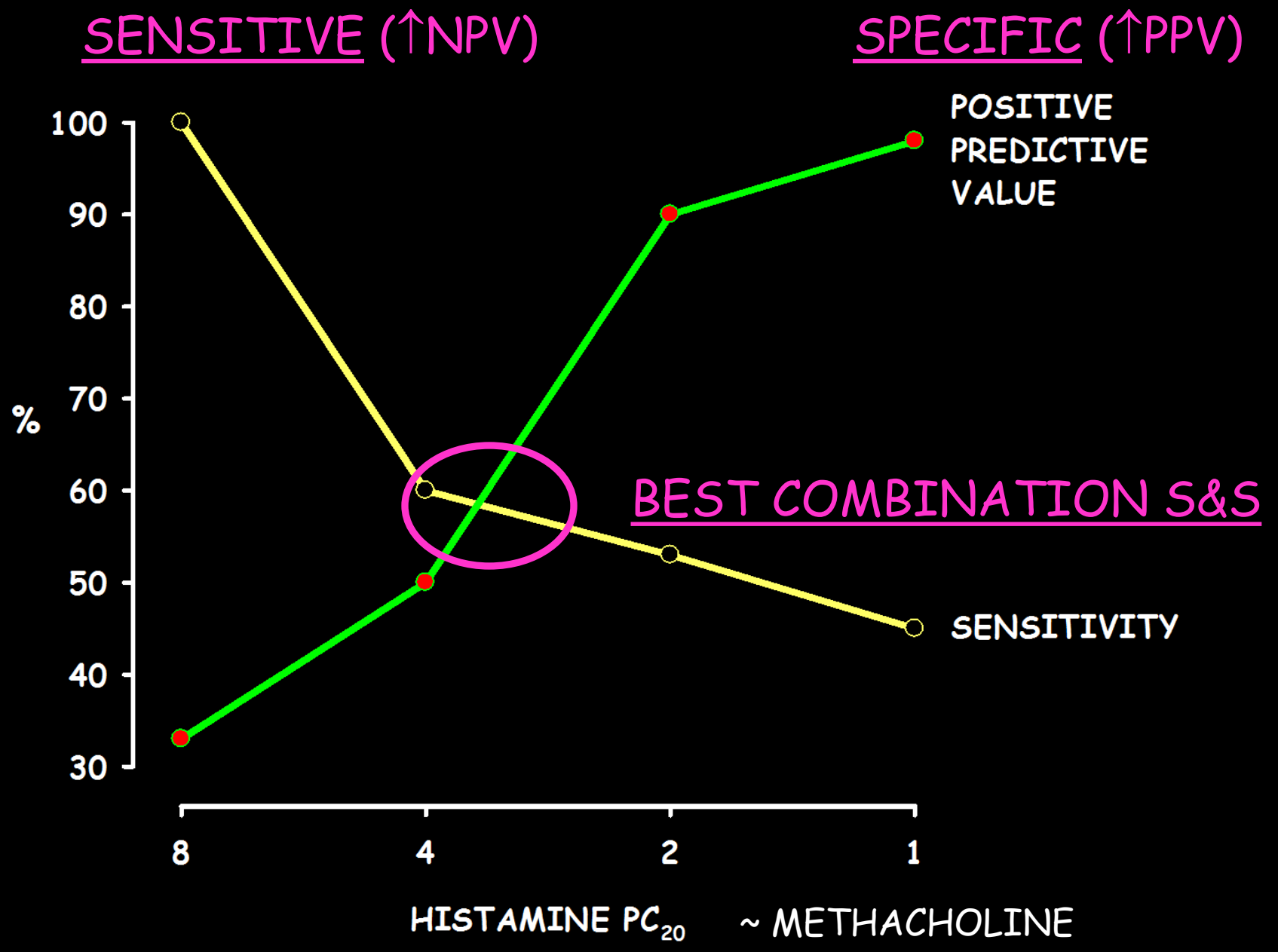
OBJECTIVES

To review and understand:

1. Methacholine challenges: a brief review of the methacholine challenge
2. The 1999 guidelines published in 2000
3. A preview of the principles involved in the (almost complete) updated guidelines (2016)

BACKGROUND

- Methacholine challenge a widely used *direct* bronchoprovocation test
- Use: symptoms and normal spirometry
- Highly sensitive: some caveats
- Functions best to exclude disease
- Not very specific (unless low cutpoint)
- Misunderstandings re interpretation


SENSITIVE (↑NPV)
SPECIFIC (↑PPV)
POSITIVE PREDICTIVE VALUE
100
90
80
70
60
50
40
30
%
BEST COMBINATION S&S
SENSITIVITY
8
4
2
1
HISTAMINE PC20 ~ METHACHOLINE

MCT: CHALLENGES (1999)

- A means to confirm asthma that is both *independent* and *objective* is frequently lacking: ergo assessment of S&S difficult

  insoluble and not discussed further
- Multiplicity of methacholine methods which has made comparison of results a challenge

METHOD MULTIPLICITY

Background to the 1999 guidelines

- Methacholine response *dose* dependent
- Methacholine inhaled at 5 min intervals is partially *cumulative*: effect ↑ with time ↓
- PC_{20}s are not comparable unless care re inhalation time/neb output & time interval

to standardise dose and cumulative effect

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MCT 1999 GUIDELINES

Tidal Breathing

- 2 min tidal breathing
- Neb @ 0.13 mL/min
- **90 µL** per dose step

Dosimeter

- 5 Breaths B-hold (@TLC)
- 9 µL per breath
- **45 µL** per dose step

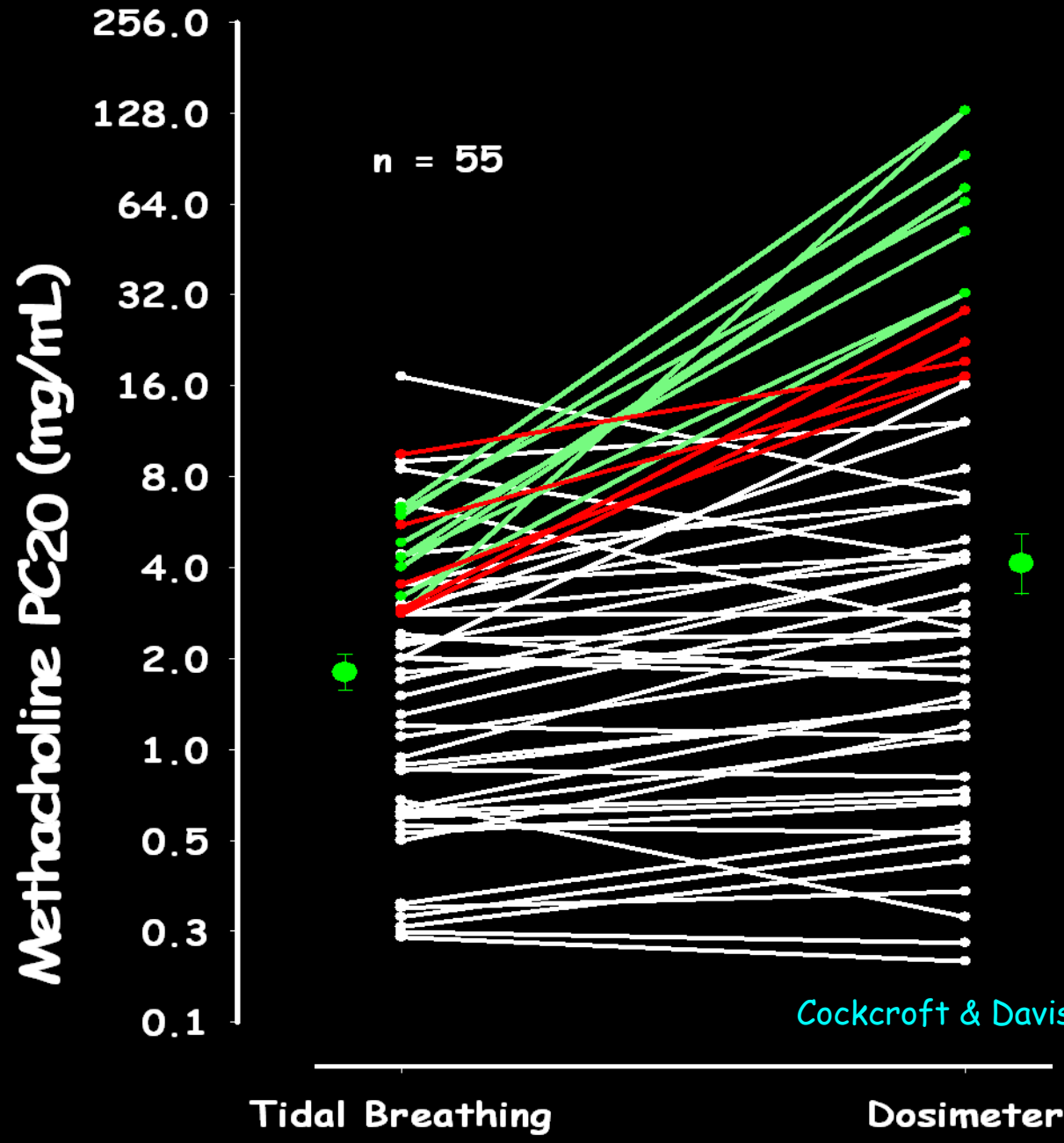
Other aspects identical:

- Concentrations (doubling 0.03-32 mg/mL)
- Timing between doses (5 min)
- Timing of FEV_1 (30 & 90 sec)
- Calculation of PC_{20}

DEFINITIONS (both methods)

PC_{20}	>16	mg/ml – normal (negative)
PC_{20}	< 16	mg/ml = *non-negative* (dwc)
PC_{20}	4-16	mg/ml – borderline
PC_{20}	1-4	mg/ml – mild AHR
PC_{20}	0.25-1	mg/ml – moderate AHR
PC_{20}	< 0.25	mg/ml – marked AHR

Methods
Comparison
55 asthmatic
subjects
from
3 studies



Cockcroft & Davis JACI 2006

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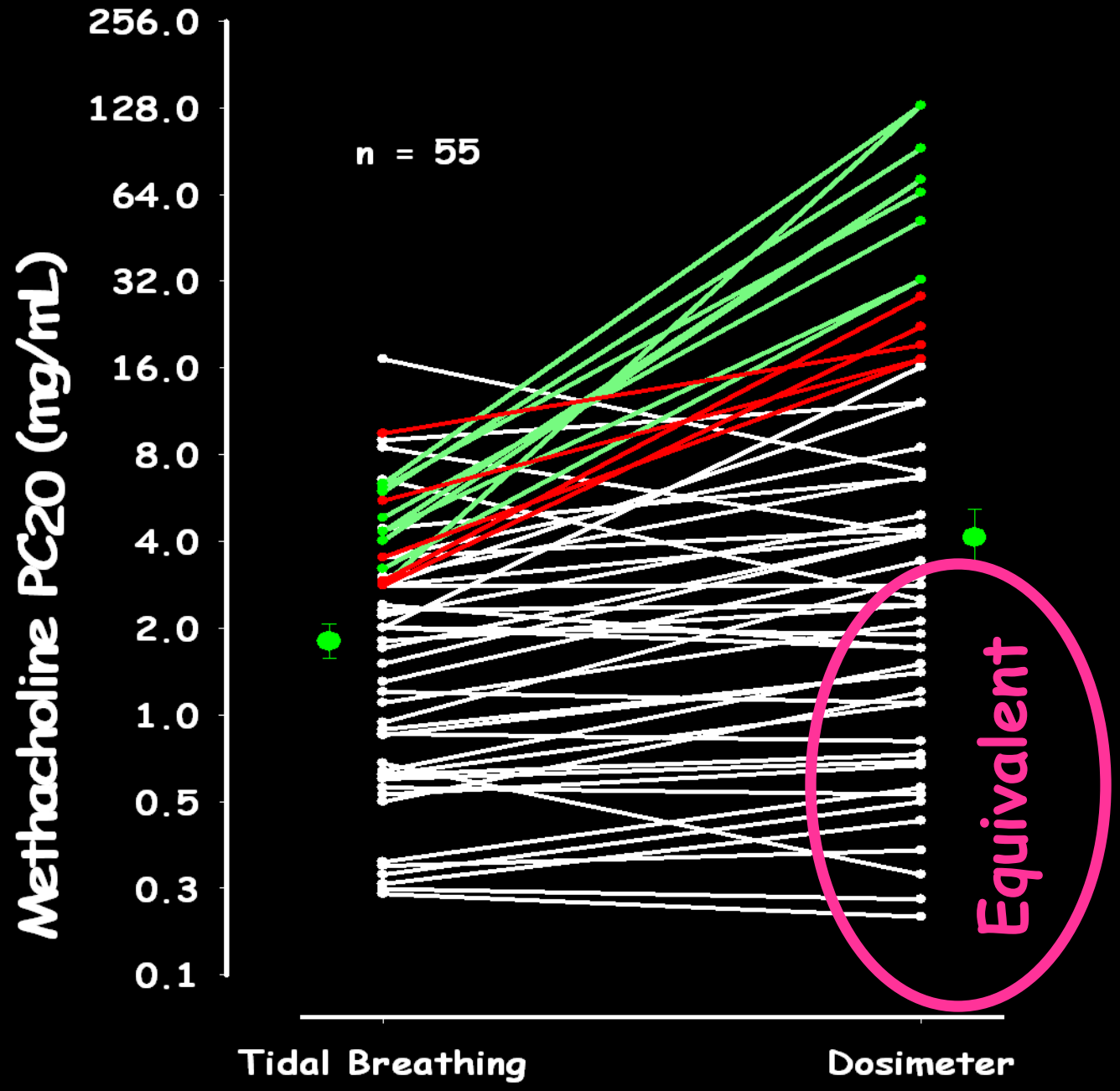

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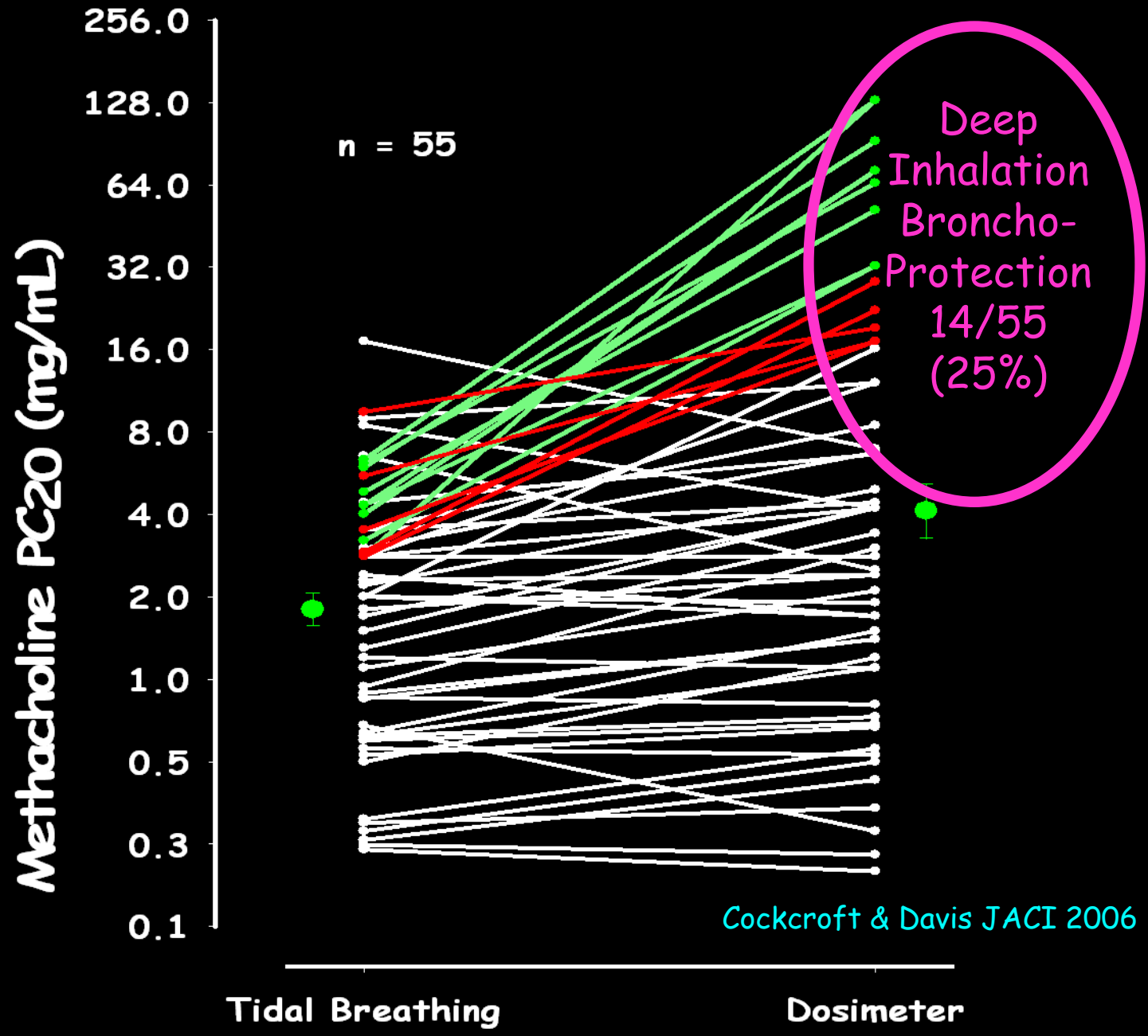

Cockcroft & Davis JACI 2006

MCT: CHALLENGES (2016)

- A means to confirm asthma that is both *independent* and *objective* is lacking
- Multiplicity of methacholine methods still make comparison between labs problematic
- The Wright is inefficient and hard to find also true for deVilbiss and Bennett Twin
- The two ATS (1999) methods yield vastly different results regarding S & S

NEW GUIDELINES

- PD_{20} vs PC_{20}
- Dose calibration
- Inhalation pattern
- Inhalation time
- Time interval between doses
- Nebuliser type(s)
- Medication withhold times

METHACHOLINE DOSE

- Methacholine response *dose* dependent
- There are several studies that confirm this including old studies by DWC (same neb) and more recent studies from Dell & Coates and Gauvreau (different nebs)
- It therefore makes empiric sense that expressing the result as the PD_{20} would allow better between method comparison

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CALIBRATION

- A lot of *output* of jet nebulisers is evapouration; this is as much as 50 to 75%
- Conventional calibration (weigh before and after nebulisation) overestimates dose because of the evapouration
- Solute output can be measured but not routine; alternately supplied by makers

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INHALATION

- The major difference between the two 1999 methods is DI bronchoprotection
- This happens in the area where results of most Dx tests occur (i.e. mild AHR)
- This greatly reduces the diagnostic sensitivity of the methacholine challenge (which is its major diagnostic value)

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- This greatly reduces the diagnostic sensitivity of the methacholine challenge
- Avoid Deep Inhalations (can still use dosimeter)

INHALATION TIME

- Freddy Hargreave modified the Dutch method from 30 sec to 2 min because we thought 30 seconds was too short
- Very small (old) study suggested 2 min PC_{20} more repeatable than 30 sec PC_{20}
- Consensus was that 60 sec (one min) would be ideal

NEBULISER

- There are new more efficient nebulisers
- Many are disposable (can't calibrate each one)
- When using PD_{20} there is no need to use 1999 methacholine concs (0.03 to 16 mg/ml)
  (that → unacceptably short inhalations)
- Need to know solute dose nebulised
- Vibrating mesh nebs and ultrasonic nebs avoid the evapouration issue

TIME INTERVAL

- Time interval needs to be consistent so that the cumulative effect consistent
- We do not recommend shortening time; that will increase the cumulative effect
- We have discussed 5 minutes between the start of each inhalation vs 4 min between mid-point of inhalations (4.5 min re 60 s inhalation)

CUMULATIVE EFFECT

- Re-analysis of Liz Juniper's data (1978) suggest that at 5 min intervals (doubling doses) the cumulative effect is about half way between nil and complete
- The non-cumulative PD_{20} will always be $\leq$ half the cumulative PD_{20}
- Non-cumulative makes more sense (dwc) when using quadrupling dose step ups

DRUG HOLDING

Updated Guidance:	1999
▪ LTRA: no effect	24h
▪ Caffeine: little effect	12h
▪ H1 blockers: including high dose Benadryl did not influence methacholine PC_{20}	3d
▪ Ipratropium: withhold time 12 h	24h
▪ Long acting anti-muscarinics: need to be withheld for at least a week	48h

NEW GUIDELINES

PD_{20} vs PC_{20}	PD_{20} (in mcg: cum or non)
Dose calibration	Solute output
Inhalation pattern	Tidal breathing
Inhalation time	60 sec
Time interval	4.5-5 min
Nebuliser type(s)	New efficient nebs
Medication holding	new data

PC_{20} vs PD_{20}

PC_{20}(mg/ml)	PD_{20} (μg)	
16	800	1999 slide (dwc)
4	200	Non-cumulative
1	50	(evapouration
0.25	12.5	not considered)

PD_{20} PC_{20} COMPARISON (2016)

PC_{20} (mg/ml)	PD20 (µg) non-cumulative	cumulative
16	400	800
4	100	200
1	25	50
0.25	6	12.5

NEW DEFINITIONS

	Non cum PD_{20}	Cum PD_{20} (mcg)
Negative	>400	>800
Borderline	100-400	200-800
Mild AHR	25-100	50-200
Mod AHR	6-25	2.5-50
Marked AHR	<6	<12.5

My outdated license plate

GO RIDERS GO !!!!