Contrast Pd/Pa

Better than resting measures?

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Coronary Pathophysiology & Microcirculation
ESC Working Group

MAISON EUROPÉENNE DU COEUR
EUROPEAN HEART HOUSE

Disclosure Statement of Financial Interest

Within the past 12+ months, Nils Johnson has had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Organizations (alphabetical)
• Grant/Research Support (to *institution*)	• St Jude Medical (for CONTRAST study) • Volcano/Philips (for DEFINE-FLOW study)
• Educational organizations (travel support for academic meetings but *never honoraria*)	• ASNC (travel award, 2007) • Canadian CPI (Montréal , 2013-15) • CRF (TCT 2012-14, CPIIS 2014) • ESC (ETP physiology courses, 2013-15) • KSIC (annual meeting, 2015) • SCAI (travel award, 2010)

Nils Johnson has *never* personally received *any* money from *any* commercial company. Specifically, he does *not accept* commercial consulting, travel, entertainment, or speaking compensation *of any kind*.

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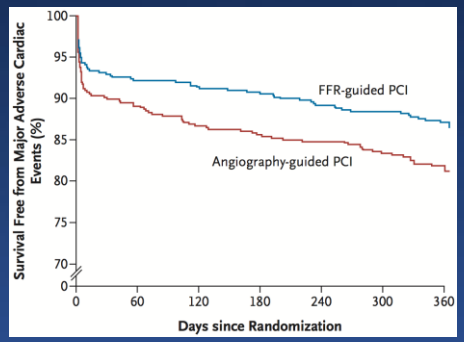
Necessity of hyperemia

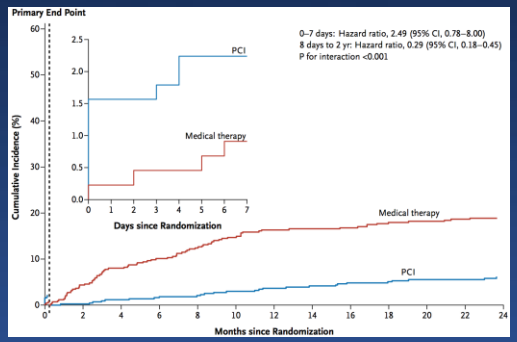
Experimental Basis of Determining Maximum Coronary, Myocardial, and Collateral Blood Flow by Pressure Measurements for Assessing Functional Stenosis Severity Before and After Percutaneous Transluminal Coronary Angioplasty

Nico H.J. Pijls, MD; Jacques A.M. van Son, MD; Richard L. Kirkeeide, PhD; Bernard De Bruyne, MD; and K. Lance Gould, MD

[FFR] applies only to maximally dilated conditions when all resistances are constant and the derivation of flow reserve from pressure is possible.



FAME 1



FAME 2

Table 31 Use of fractional flow reserve, intravascular ultrasound, and optical coherence tomography in SCAD

Recommendations	Class [a]	Level [b]	Ref. [c]
FFR is recommended to identify hemodynamically relevant coronary lesion(s) when evidence of ischaemia is not available.	I	A	399, 401, 405

Class I/A from ESC

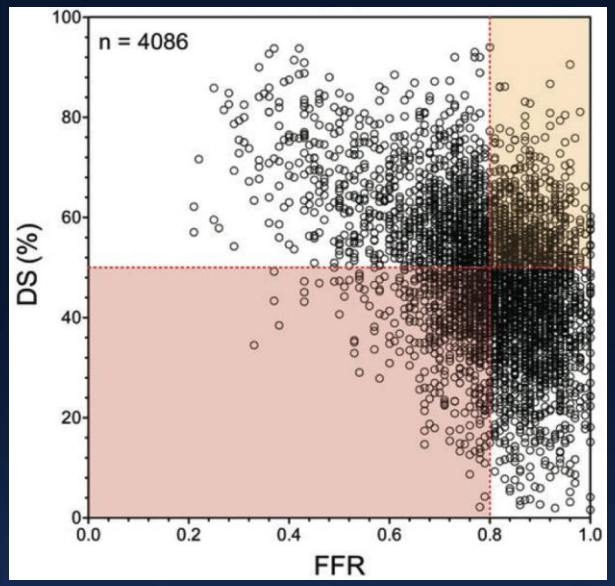
Quote = Pijls NH, *Circulation*. 1993 Apr;87(4):1354-67 (text from discussion)
FAME 1 = Tonino PA, *NEJM*. 2009 Jan 15;360(3):213-24 (Figure 3A)
FAME 2 = De Bruyne B, *NEJM*. 2014 Sep 25;371(13):1208-17 (Figure 1A)

No hyperemia ≈ 80% accuracy

- Rest Pd/Pa
  - Mamas, 528 lesions, accuracy not reported, 0.86 AUC
  - RESOLVE, 1593 lesions, 82% accuracy, 0.82 AUC
  - VERIFY 2, 120 lesions, 85% accuracy, 0.89 AUC
- iFR
  - RESOLVE, 1593 lesions, 80% accuracy, 0.81 AUC
  - ADVISE 2, 690 lesions, 82% accuracy, 0.90 AUC
  - VERIFY 2, 120 lesions, 82% accuracy, 0.87 AUC

Mamas = Mamas MA, *J Invasive Cardiol*. 2010 Jun;22(6):260-5
RESOLVE = Jeremias A, *JACC*. 2014 Apr 8;63(13):1253-61
ADIVSE 2 = Escaned J at TCT 2013 in San Francisco on October 30, 2013
VERIFY 2 = Watkins S at SCAI 2014 in Las Vegas on May 30, 2014

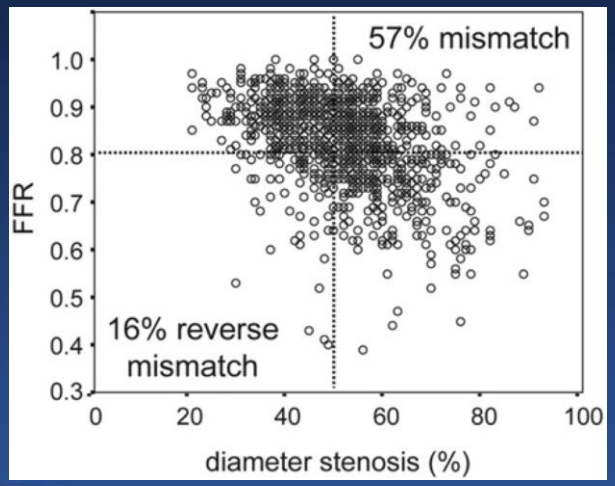
No physiology <70% accuracy



4,086 lesions with QCA

Compared to FFR≤0.8

- 50%DS threshold
  - 0.64 AUC



1,066 lesions with QCA

Compared to FFR≤0.8

- 52%DS threshold
  - 66% accuracy
  - 0.66 AUC

Top = Toth G, *Eur Heart J*. 2014 Oct 21;35(40):2831-8 (Figure 1A)
Bottom = Park SJ, *JACC Cardiovasc Interv*. 2012 Oct;5(10):1029-36 (Figure 1A)

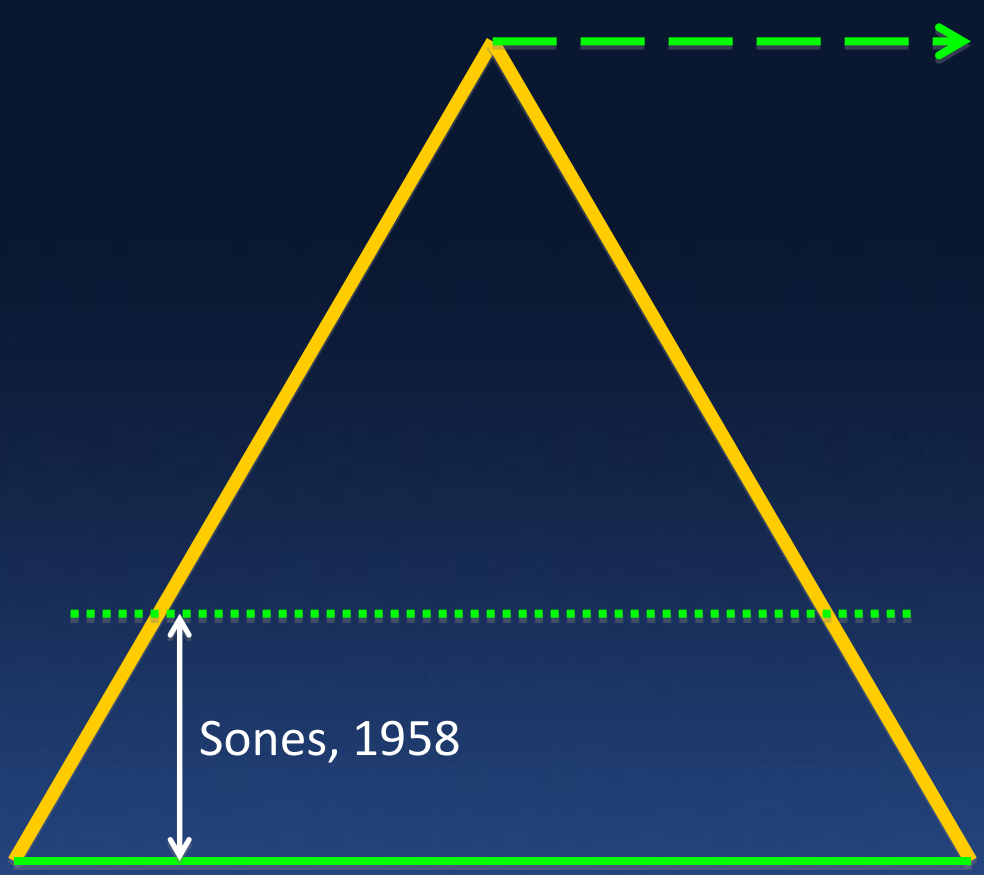
Pyramid of diagnostic accuracy

100% = gold standard

50% = coin flip

Concept from Pijls NH, ETP 2014 course, based on slide 26 of his April 24 lecture

Pyramid of diagnostic accuracy



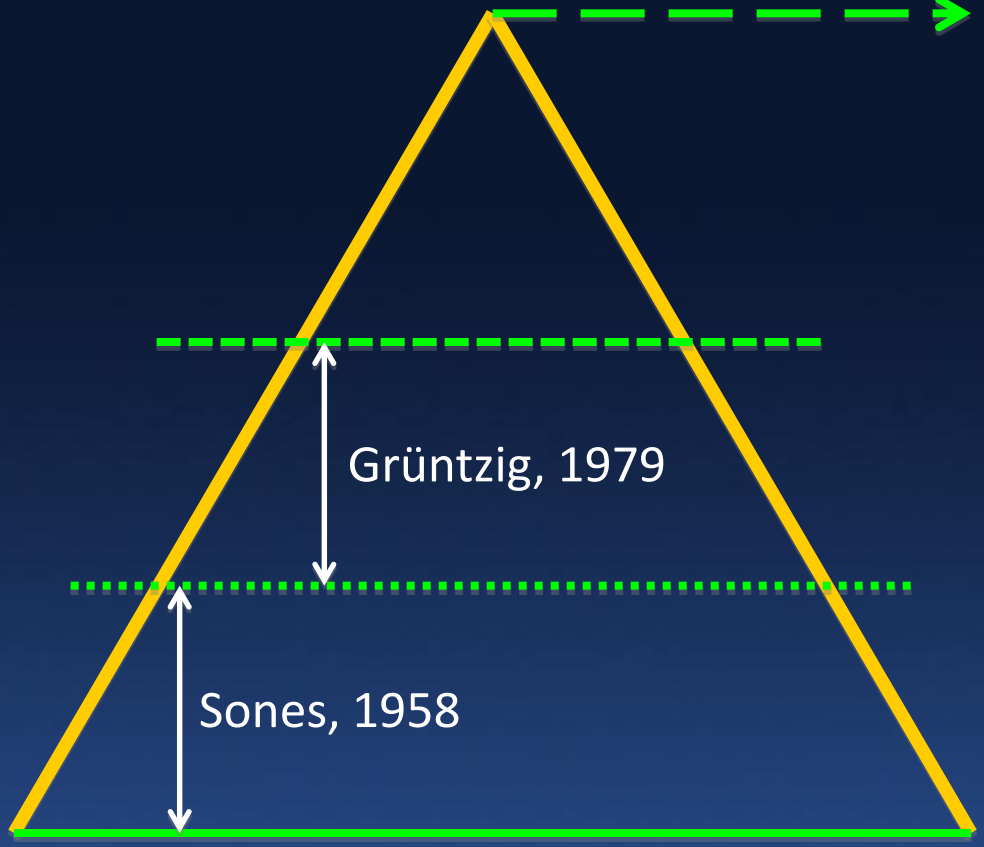
100% = gold standard

65% ≈ angiogram alone

50% = coin flip

Concept from Pijls NH, ETP 2014 course, based on slide 26 of his April 24 lecture

Pyramid of diagnostic accuracy



100% = gold standard

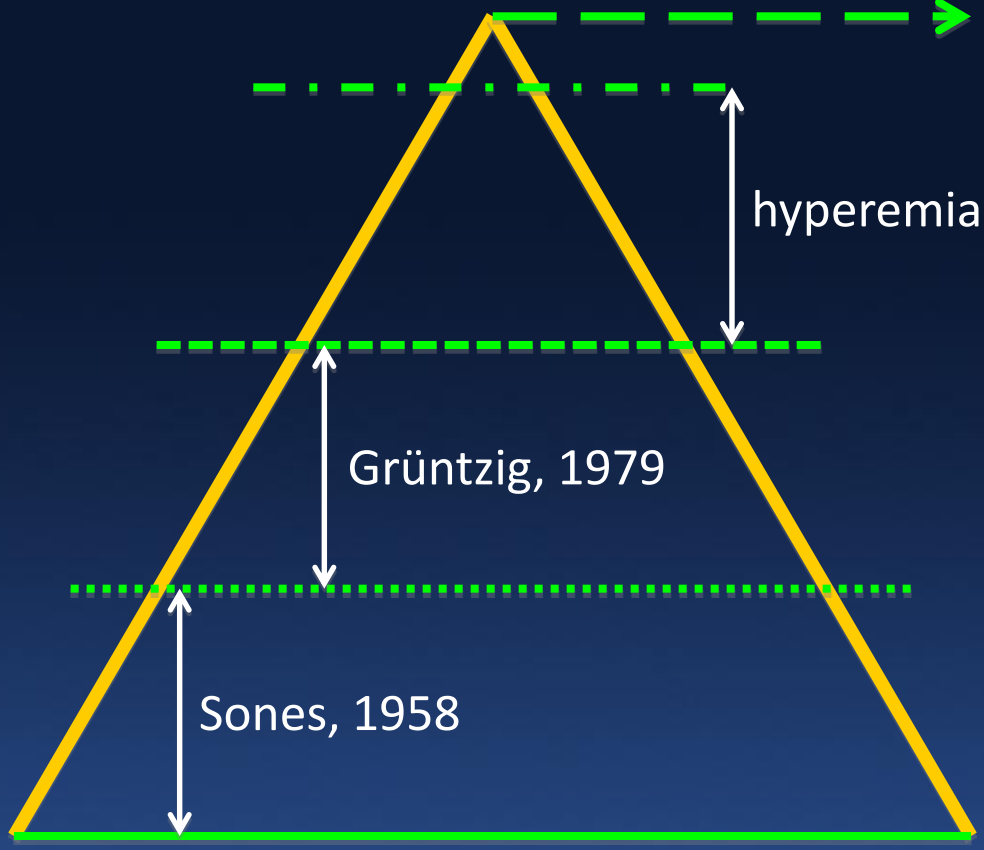
80% ≈ rest physiology
(Pd/Pa or iFR)

65% ≈ angiogram alone

50% = coin flip

Concept from Pijls NH, ETP 2014 course, based on slide 26 of his April 24 lecture

Pyramid of diagnostic accuracy



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Vasodilators in human physiology

- dipyridamole (1978, Gould KL, *Am J Cardiology*)
- *contrast medium (1983, Ganz P, Am Heart J)*
- coronary occlusion (1984, Marcus ML, *NEJM*)
- papaverine (1986, Wilson RF, *Circulation*)
- adenosine (1990, Wilson RF, *Circulation*)
- ATP (2003, De Bruyne B, *Circulation*)
- nitroprusside (2004, Kern MJ, *Circulation*)
- nicorandil (2006, Kang JC, *Int J Cardiology*)
- regadenoson (2011, Nair PK, *JACC Interventions*)

1959 paper on contrast hyperemia

Effects on Coronary Blood Flow.—A total of 48 observations in 5 dogs was made on the effects of intracoronary contrast injections on coronary blood flow. Each dog received 2 to 4 injections of each of the dyes (0.025 to 0.25 c.c./Kg). Injections were given only when coronary blood flow varied less than 5 per cent over a period of 5 minutes. Immediately following the response, sufficient time was allowed for the coronary blood flow to return to the preinjection rate. The results indicate that all of the contrast media increased coronary blood flow, averaging a 60 per cent increase from the control.

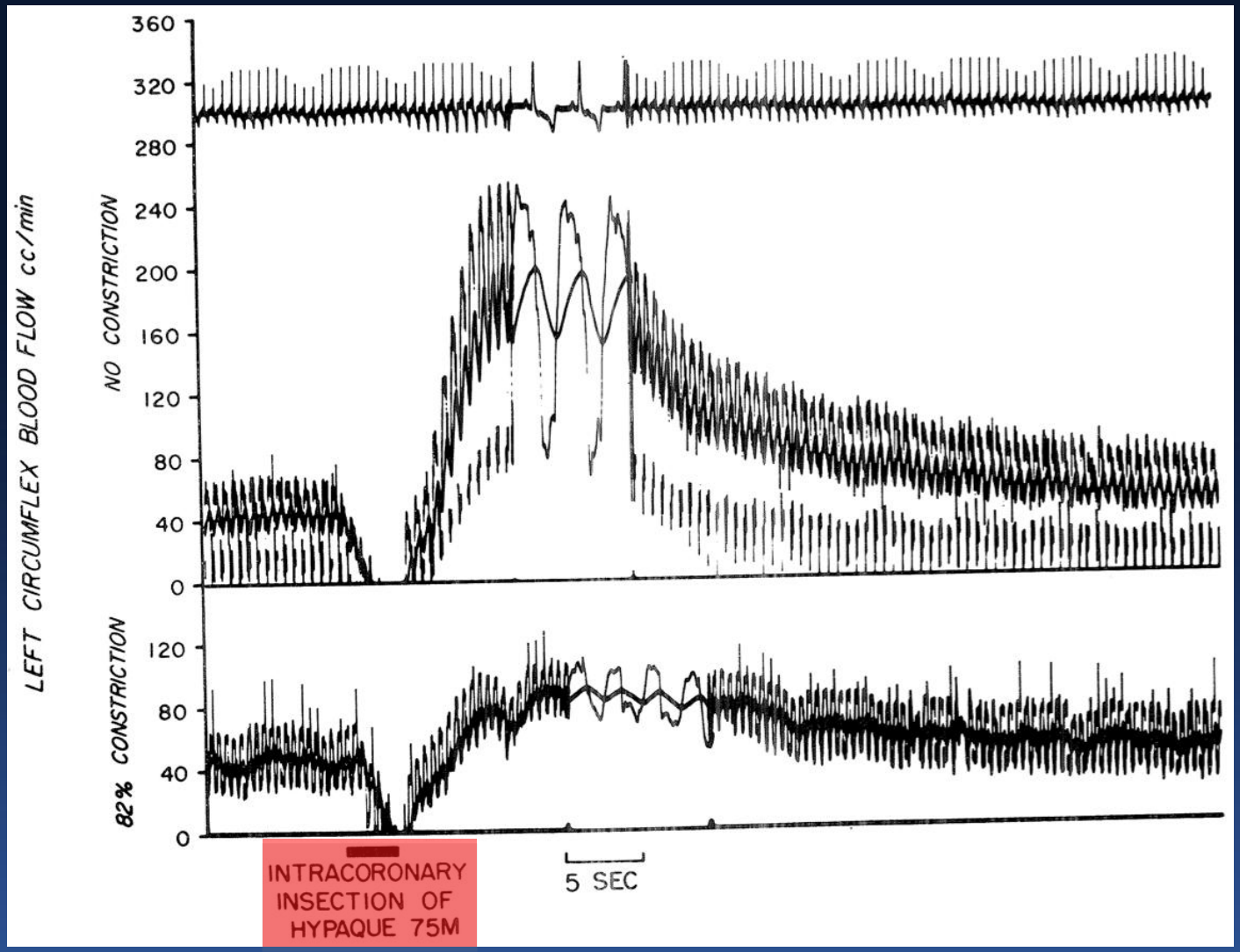
70 kg * (0.025 to 0.25 cc/kg) =

1.8 to 18cc ≈ *10cc of IC contrast*

gave *60% increase* in flow

Guzman SV, *Am Heart J*. 1959 Oct;58(4):597-607 (taken from results, page 602)

1974 introduction of CFR



Gould KL, *Am J Cardiol*. 1974 Jan;33(1):87-94 (Figure 1)

1983 and 1985 coronary ΔP in humans

Table I. Effect of intracoronary injection of Renografin 76 on mean coronary stenosis pressure gradients

% Angiographic stenosis	Gradient at rest (mm Hg)	Gradient after Renografin 76 (mm Hg)
30% LM	0	0
30% RCA	6	17
50% Graft	0	0
50% LAD	0	3
50% LAD	5	21
55% LAD	0	27
60% RCA	0	0
60% LAD	5	20
60% LAD	8	24
60% LAD	10	23
65% LAD	13	34
70% LAD	26	37
75% LAD	16	34
80% LAD	0	22
80% LAD	16	30
80% LAD	17	48
80% RCA	25	44
85% CX	7	20
85% RCA	8	26
85% CX	24	38
85% LAD	52	52
85% LAD	57	60
90% LAD	37	41
90% LAD	40	58
90% LAD	41	51
90% LAD	43	60
90% LAD	57	59
90% LAD	50	61
	20 ± 4 (Mean ± SE)	33 ± 4 (Mean ± SE)

Abbreviations: LAD = left anterior descending; LM = left main; RCA = right coronary artery; CX = circumflex.

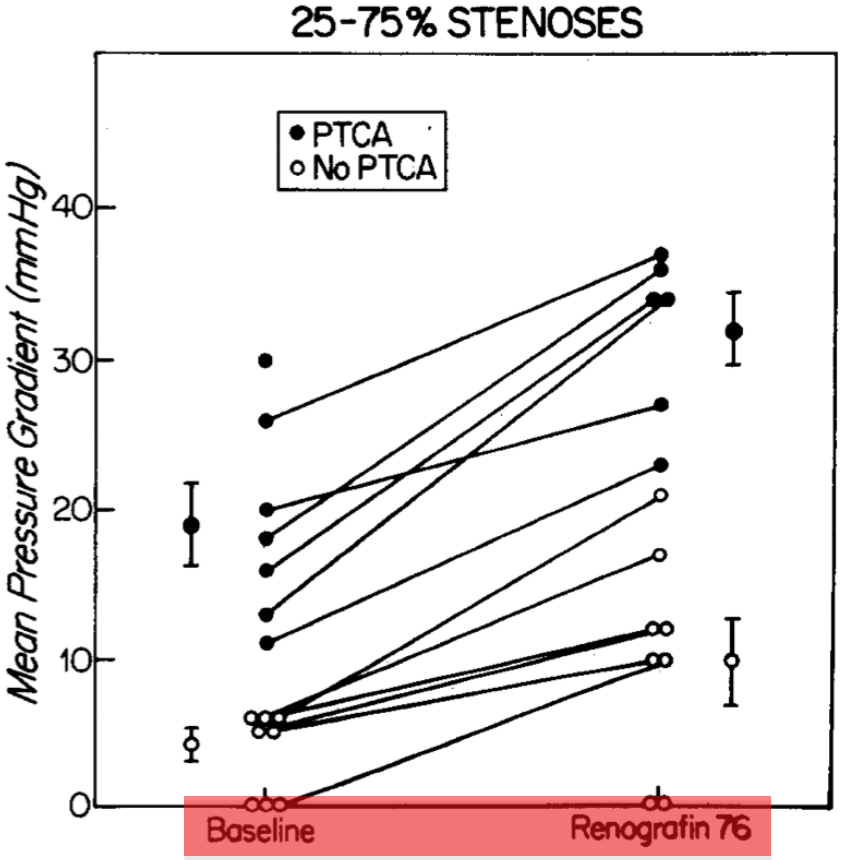
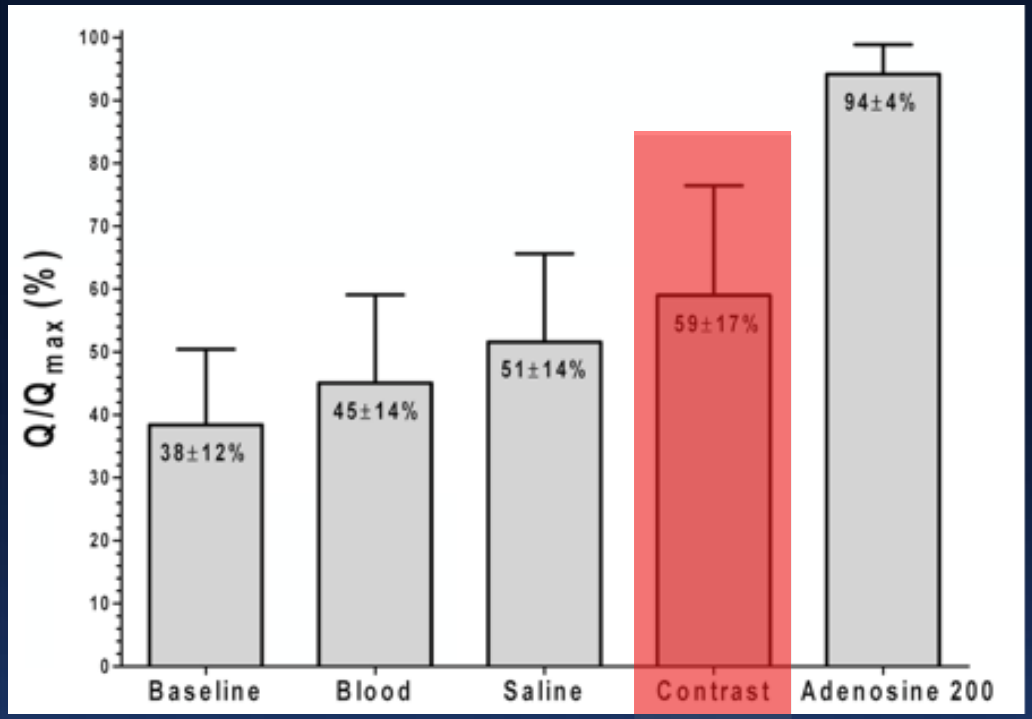


FIGURE 1. Mean transstenotic coronary pressure gradients in 15 patients with moderate stenoses. The gradients are shown basally (n = 15) and after injection of Renografin 76 (n = 14). **Closed circles,** percutaneous transluminal coronary angioplasty (PTCA) performed; **open circles,** PTCA not performed. Values are mean ± standard error of the mean.

1983 table = Ganz P, *Am Heart J*. 1983 Dec;106(6):1399-406 (Table 1)
1985 figure = Ganz P, *Am J Cardiol*. 1985 Apr 1;55(8):910-4 (Figure 1)

2015 contrast hyperemia



"8 mL IC bolus administration of … contrast medium (iodixanol 270 mg/mL)"

- *59% of maximum flow*

Adjedj J, *in submission* (methods and Figure 4)

2003 contrast Pd/Pa

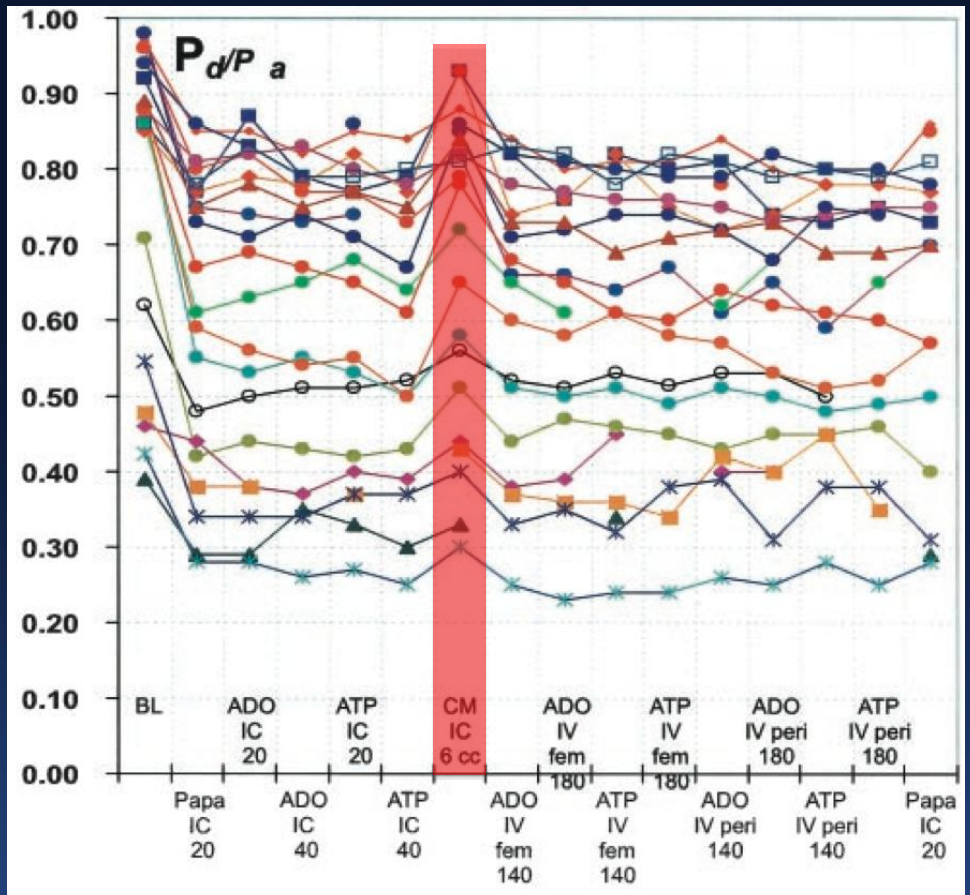


Figure 2. Individual values of P_d/P_a ratios in the 21 study patients from group 1 at baseline and during vasodilation induced by the different vasodilators. BL indicates baseline; other abbreviations as in Figure 1.

"intracoronary bolus administration of *6 mL of Iohexol* did produce a *significantly weaker effect* than all other stimuli"

- 10 seconds to effect
- 2 second plateau

(vs 22 for papaverine, or 5-7 for adenosine)

De Bruyne B, *Circulation*. 2003 Apr 15;107(14):1877-83 (Figure 2, data from Table 2 and results)

2014 contrast Pd/Pa

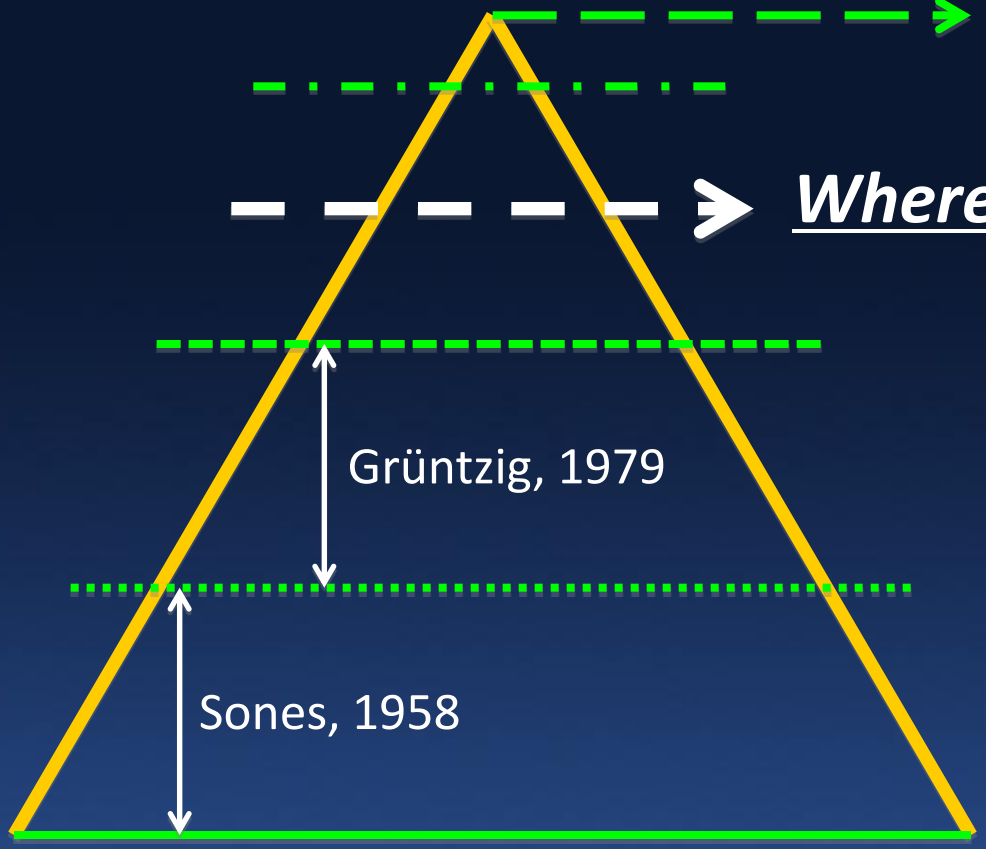
- 328 lesions (Spain), ESC abstract P6374
  - *cutoff 0.90*, ROC area 0.92
- 104 lesions (Italy), RINASCI
  - *cutoff 0.83*, ROC area 0.97
- 102 lesions (France), ESC abstract P4541
  - *cutoff 0.85*, ROC area 0.92, 86% accuracy
- 98 lesions (Portugal), ESC abstract P4537
  - *cutoff 0.84*, ROC area 0.97, 90% accuracy

RINASCI = Leone AM, *EuroIntervention*. 2014 Jul 10. [Epub ahead of print]

Motivations for contrast Pd/Pa

- Contrast Pd/Pa *might* provide superior diagnostic performance than Pd/Pa or iFR
- As operators document FFR wire position anyway, contrast Pd/Pa *potentially* offers valuable information at no extra cost and time
- In *rare* centers adenosine is *expensive* or *not available*, and in *rare* patients adenosine is *contraindicated*
  - Here, contrast Pd/Pa *could* increase feasibility, reduce cost, and improve adoption of functional testing of CAD severity as endorsed by guidelines

Pyramid of diagnostic accuracy



100% = gold standard

95% ≈ FFR

Where does contrast fit?

80% ≈ rest physiology (Pd/Pa or iFR)

65% ≈ angiogram alone

50% = coin flip

Concept from Pijls NH, ETP 2014 course, based on slide 26 of his April 24 lecture

CONTRAST study

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

Home > Find Studies > Study Record Detail

CONTRAST (Can cONTrast Injection Better Approximate FFR compAred to Pure reSTing Physiology?)

This study is enrolling participants by invitation only.

Sponsor:
The University of Texas Health Science Center, Houston

Collaborator:
St. Jude Medical

Information provided by (Responsible Party):
Nils Johnson, The University of Texas Health Science Center, Houston

ClinicalTrials.gov Identifier:
NCT02184117

First received: July 2, 2014
Last updated: July 17, 2014
Last verified: July 2014
History of Changes

Full Text View | Tabular View | No Study Results Posted

Purpose

The purpose of this study is to determine the diagnostic performances of iodine contrast medium and resting conditions to predict fractional flow reserve (FFR). Reference FFR will be measured using standard adenosine. We hypothesize that contrast FFR will offer superior diagnostic agreement compared to resting conditions.

URL https://clinicaltrials.gov/ct2/show/NCT02184117, accessed April 8, 2015

Hypothesis

- Contrast Pd/Pa *agrees with adenosine FFR better than resting metrics* (rest Pd/Pa or iFR)
- Unique features of current study
  - Larger *sample size* (improves precision)
  - International and *multicenter* (widely applicable)
  - Blinded *core lab analysis* (minimizes bias)
  - Pragmatic protocol (*real-world scenarios*)
  - Two measurements (*test/retest stability*)
  - *IC and IV adenosine* (route of hyperemia)
  - Rest Pd/Pa and iFR (*both resting metrics*)

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CONTRAST: participating centers

Belgium (Aalst)
- B De Bruyne
- E Barbato

France (Lyon)
- G Rioufol

Italy (Naples)
- G Esposito
- B Trimarco

Korea (Seoul)
- BK Koo (SNUH)
- SJ Park (Asan)

Netherlands (Eindhoven)
- N Pijls
- F Zimmermann

Portugal (Lisbon)
- S Baptista

Scotland (Glasgow)
- C Berry
- K Oldroyd

Sweden (Stockholm)
- N Witt

USA
- *W Fearon (Palo Alto)*
- G Chrysant (OKC)

UT-Houston (sponsor)
- *N Johnson*
- R Kirkeeide
- KL Gould

CRF (physiology core lab)
- A Jeremias
- A Maehara
- M Matsumura

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CONTRAST study: methods

- *750 subjects* with 1 lesion/patient
- Any lesion fulfilling a *clinical indication for FFR*
- *6 to 10 mL* of IC contrast (per operator preference)
- Contrast medium *per local practice*
- Protocol steps (*see example on next slide*)
  - Resting period (at least 1 minute)
  - IC contrast, then IC and/or IV adenosine (each repeated)
  - Pull back wire to guide (check for drift)
- *Tracings blinded* then its parts sent to the core lab

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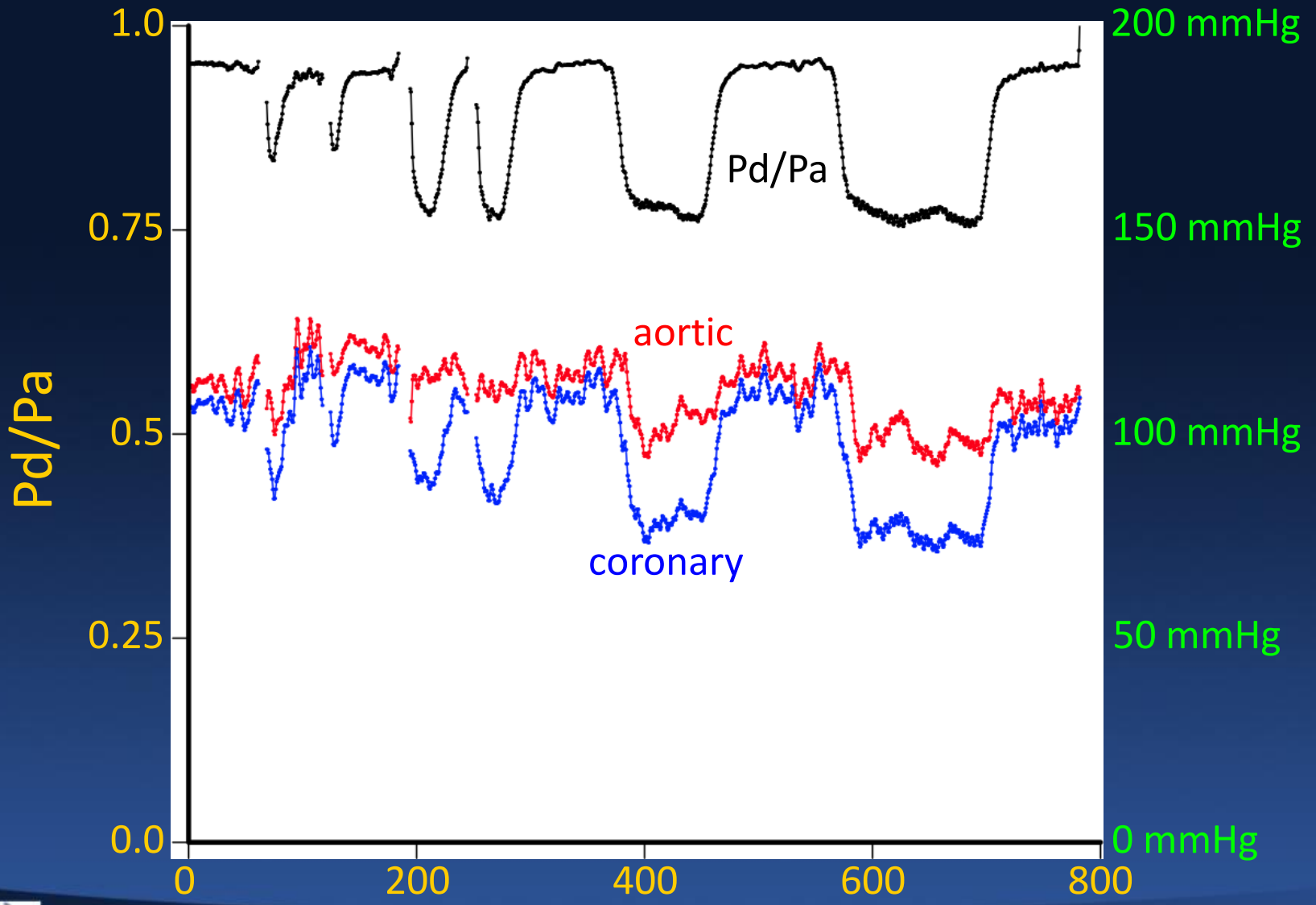
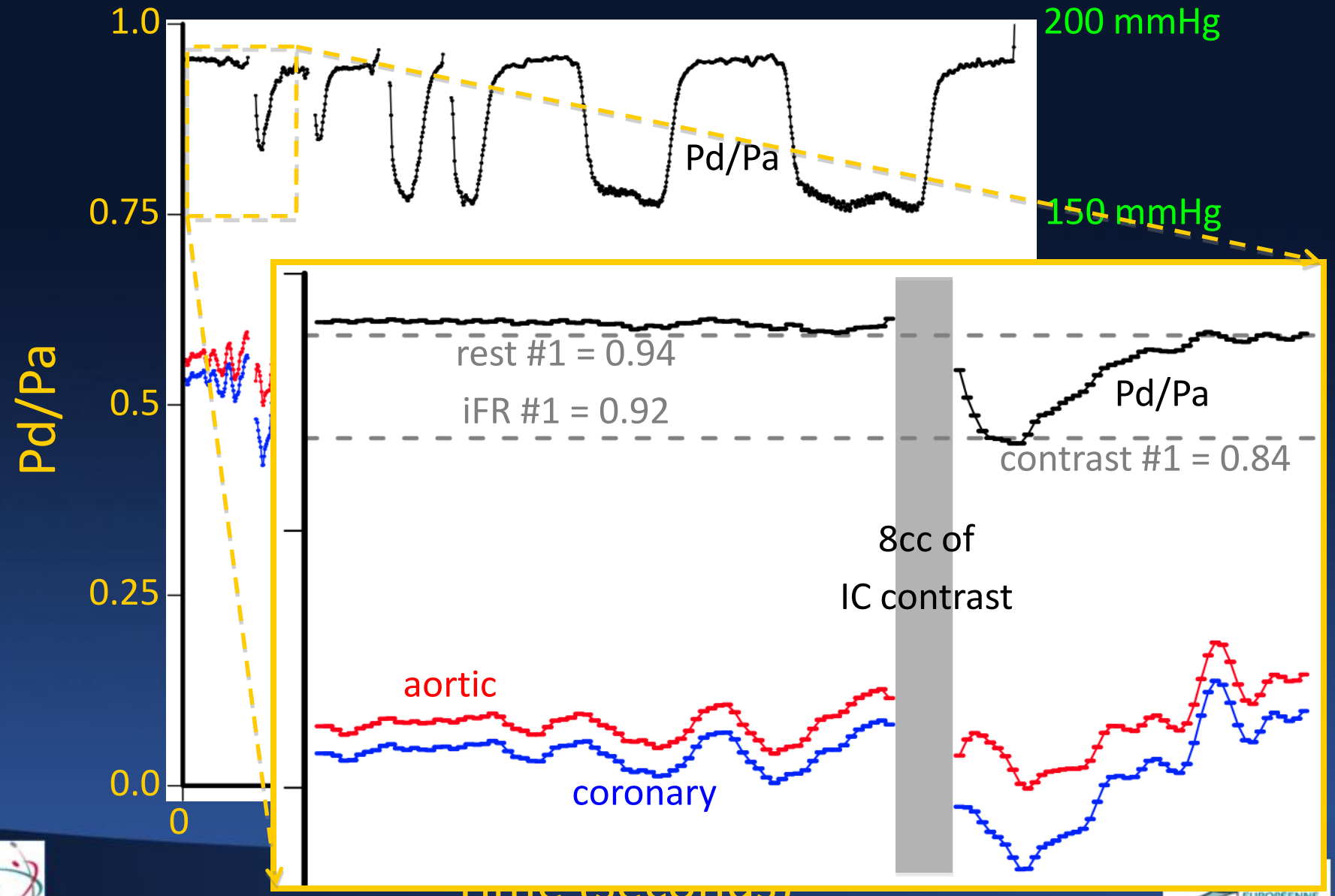
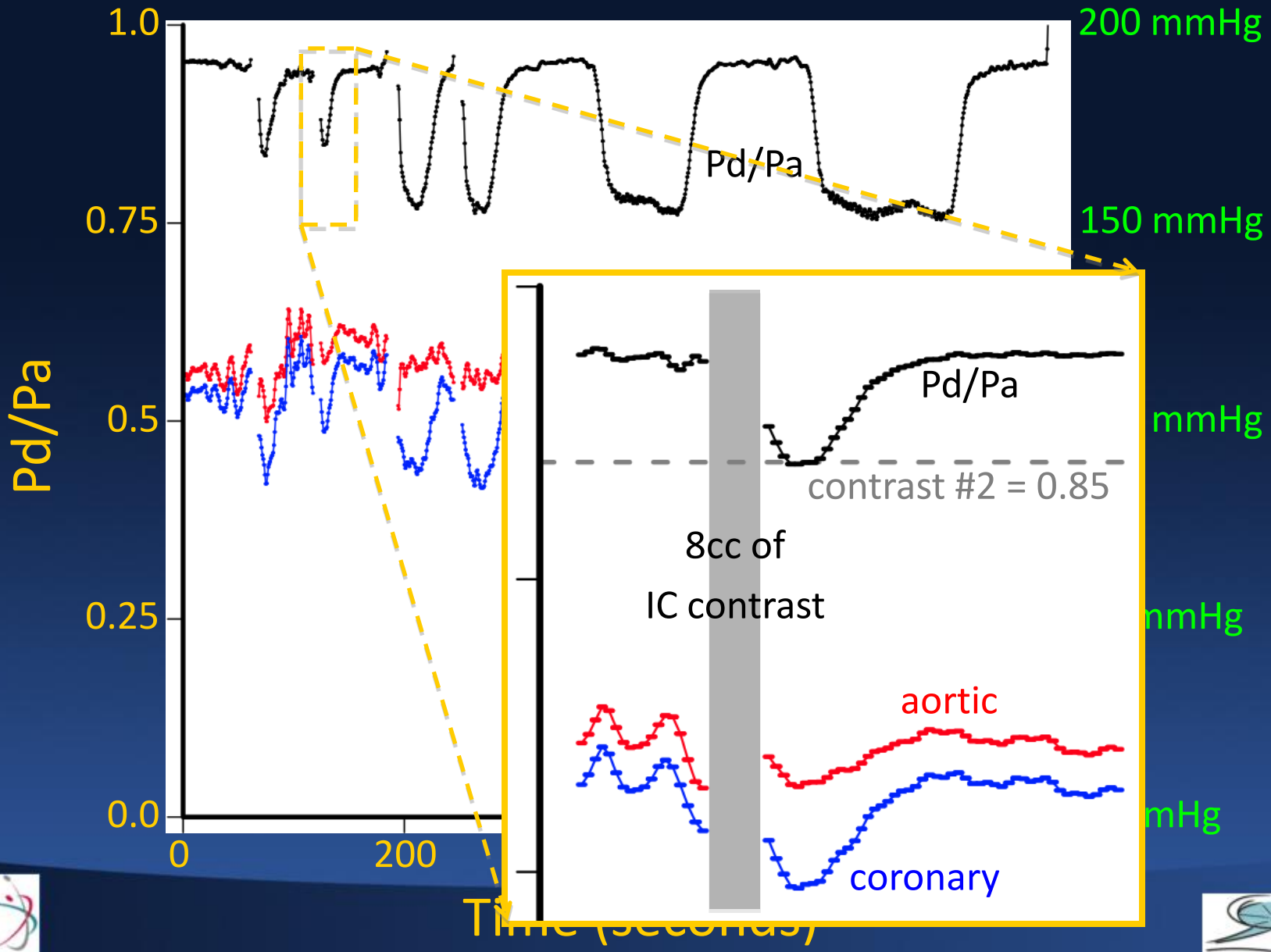
CONTRAST example: protocol



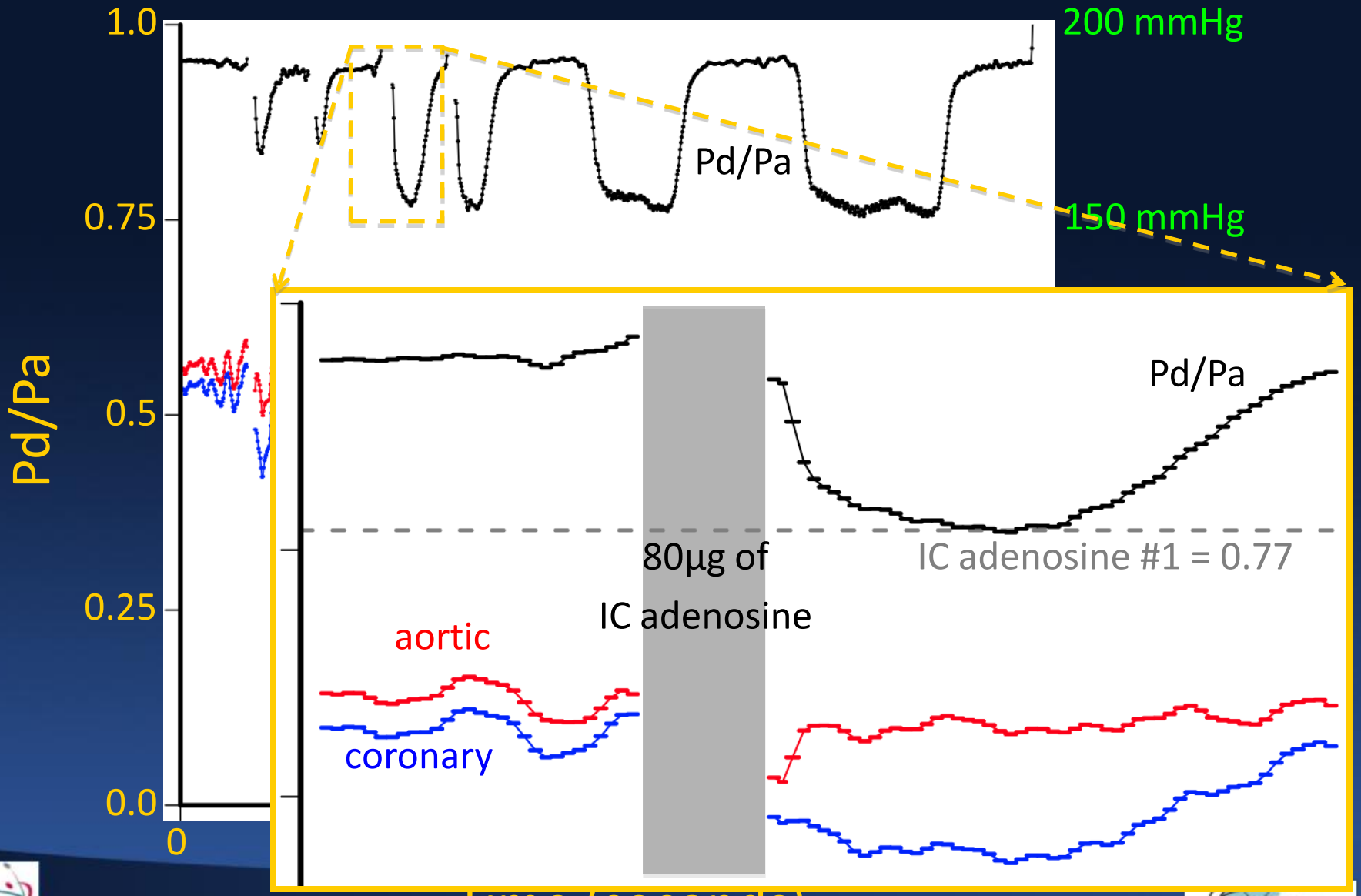
CONTRAST example: IC contrast #1



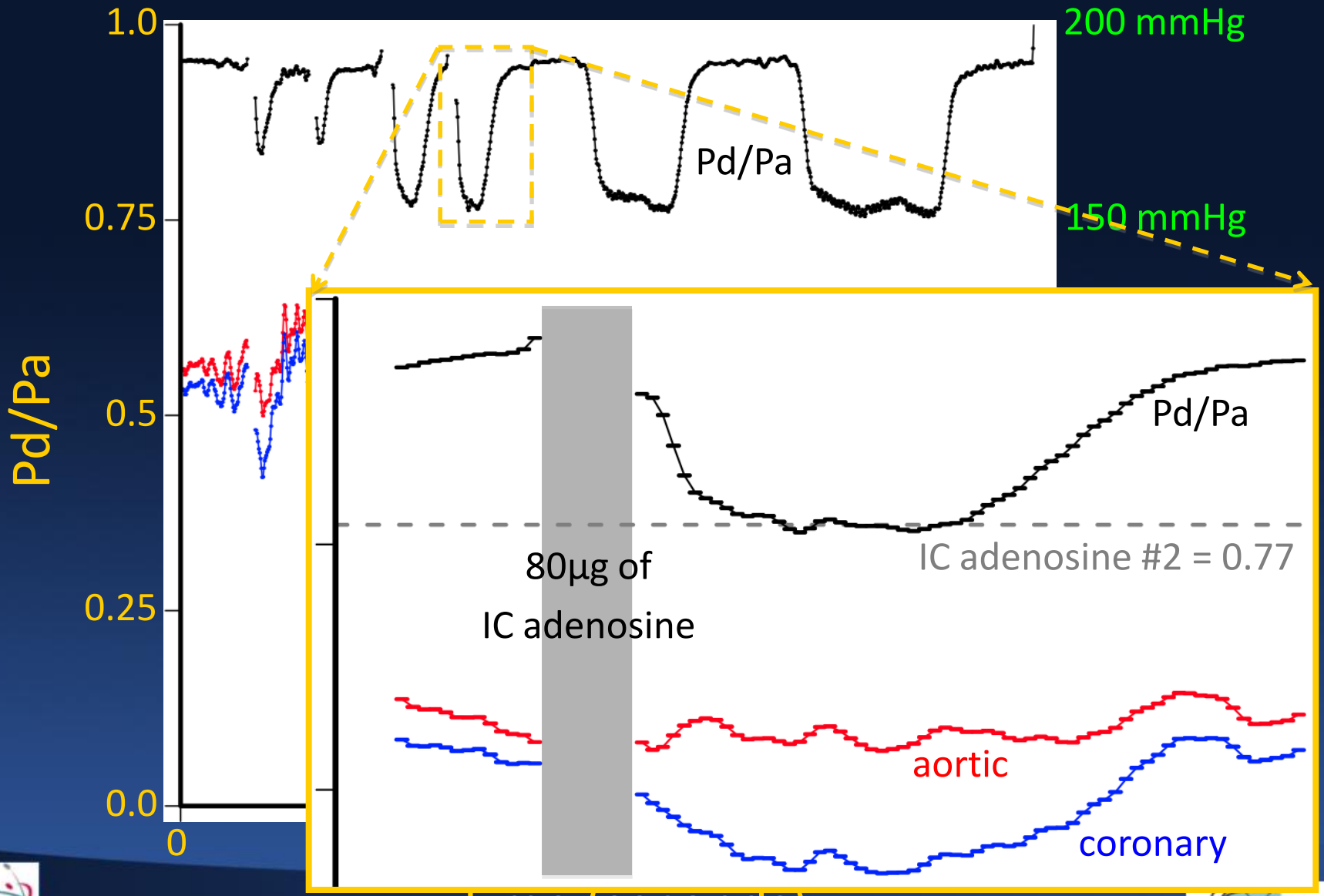
CONTRAST example: IC contrast #2



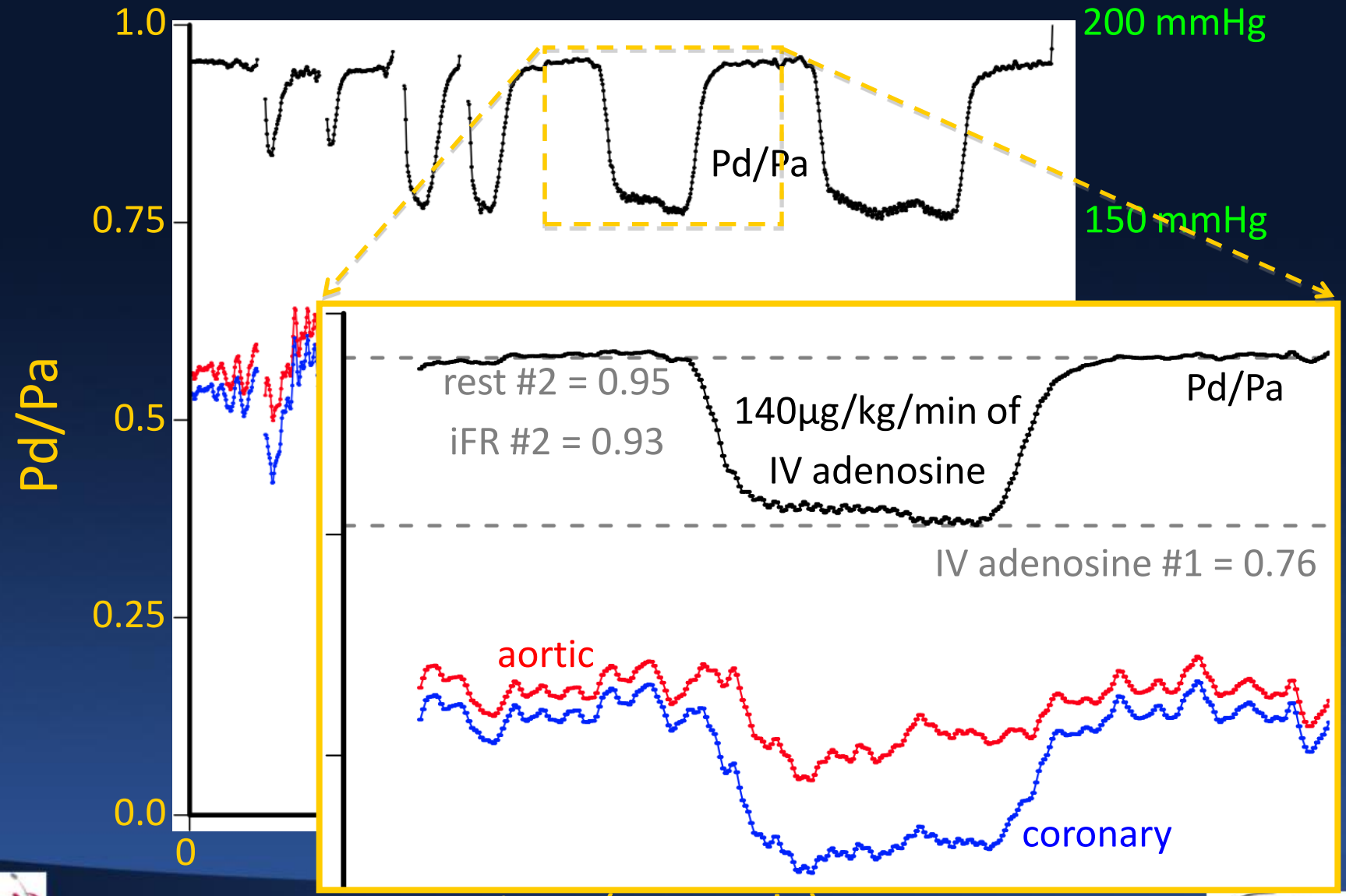
CONTRAST example: IC adeno #1



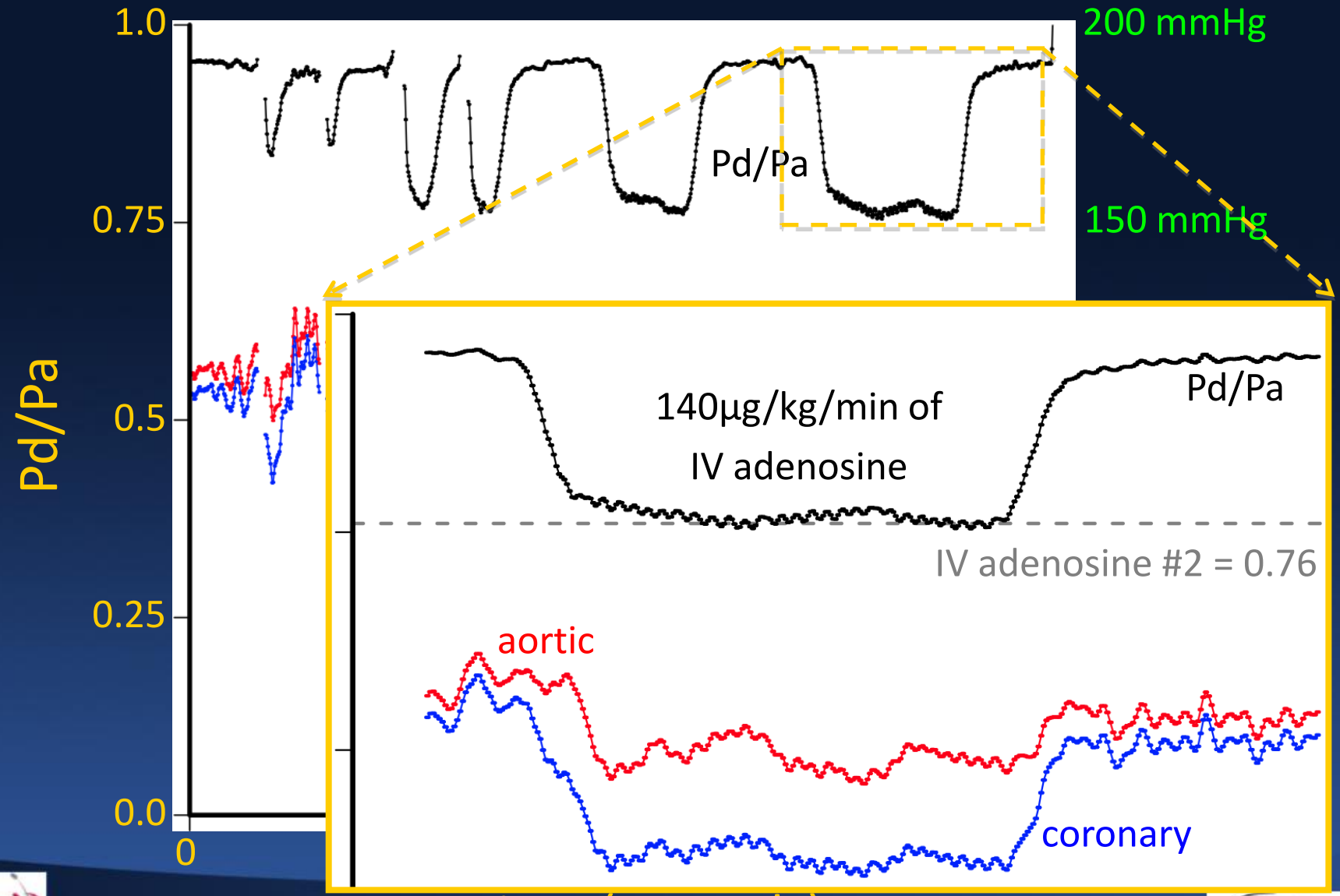
CONTRAST example: IC adeno #2



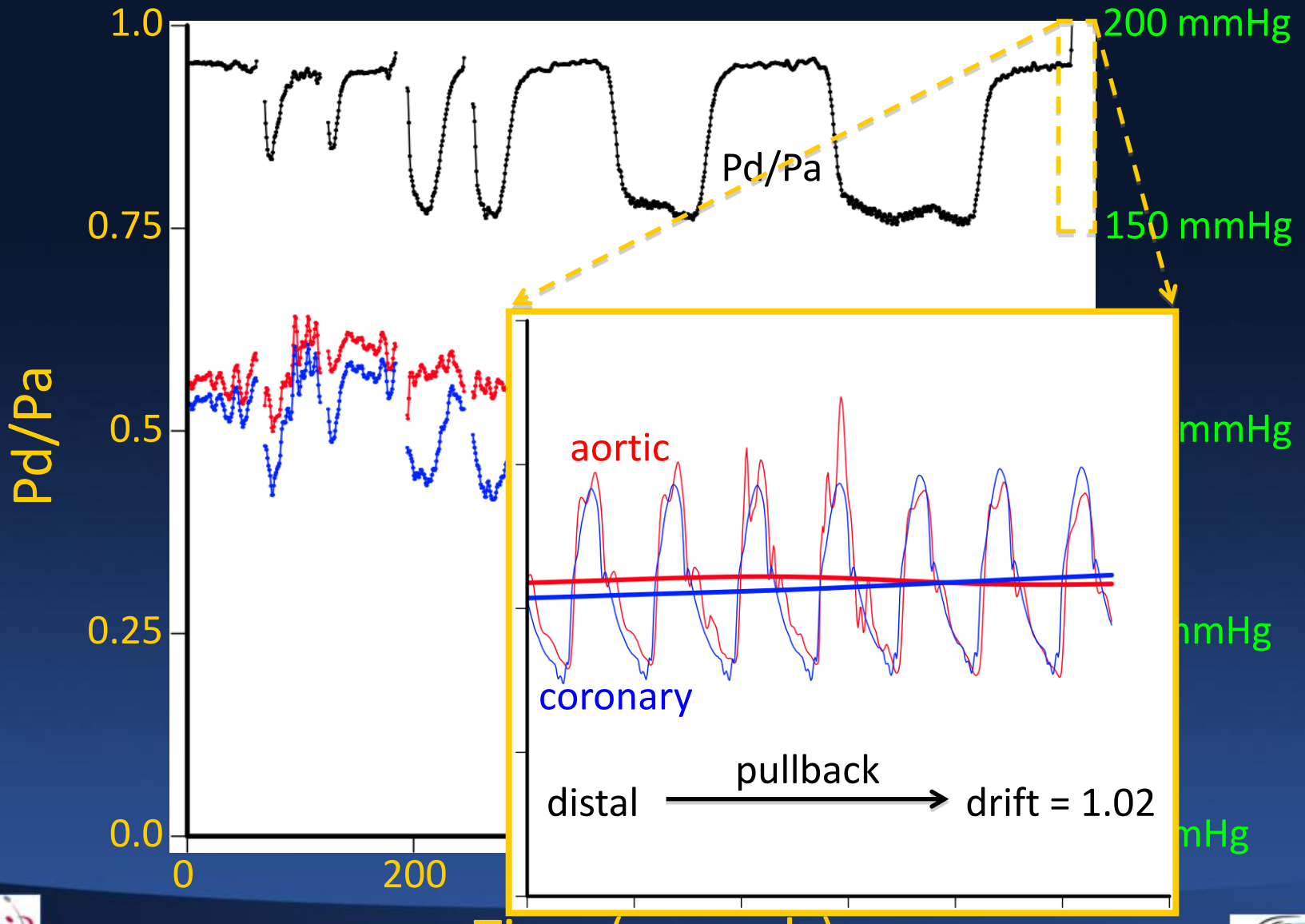
CONTRAST example: IV adeno #1



CONTRAST example: IV adeno #2



CONTRAST example: drift check



CONTRAST example: summary

- Rest
  - Pd/Pa = 0.94 and 0.95
  - iFR = 0.92 and 0.93
- IC contrast
  - 0.84 and 0.85
- IC adenosine
  - 0.77 and 0.77
- IV adenosine
  - 0.76 and 0.76
- Drift check
  - 1.02 at guide

CONTRAST study: TCT

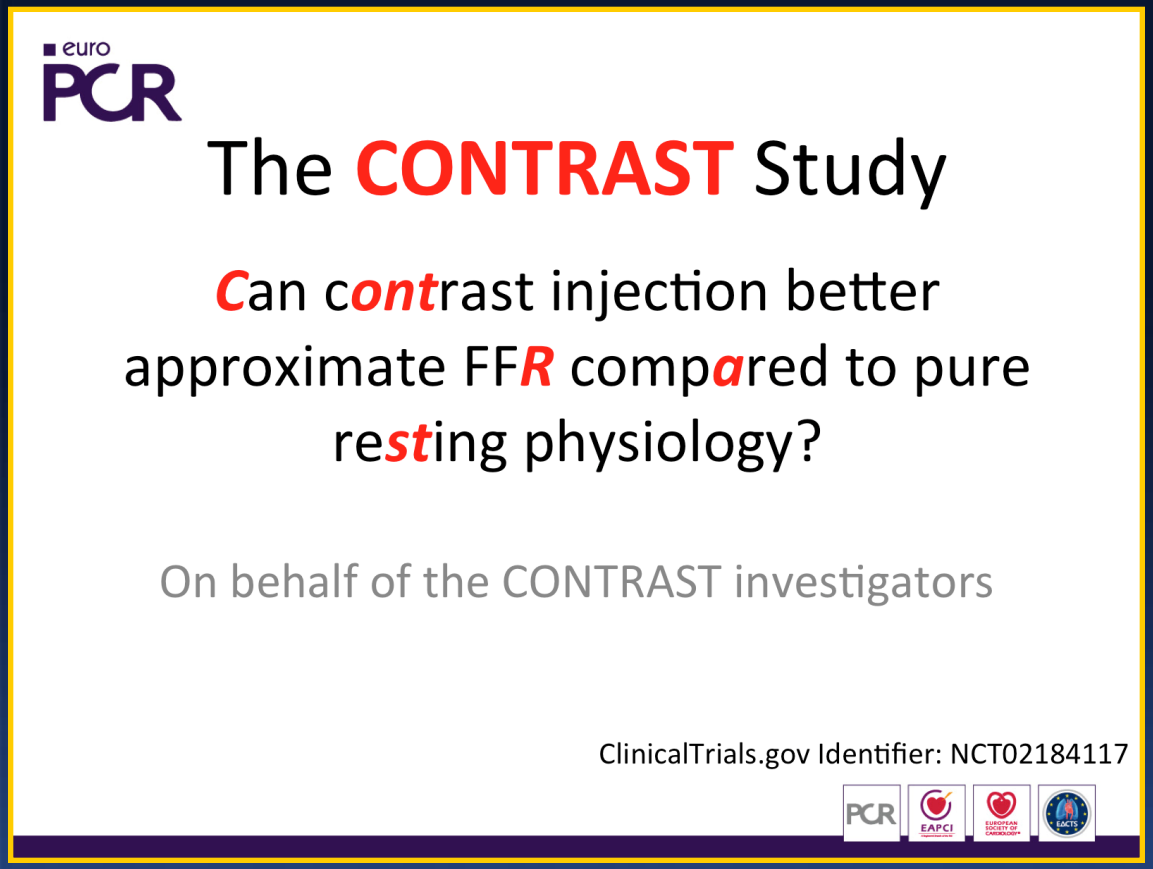
TCT 2014 taped case

September 13, 2014

Presented by

Dr. Keith Oldroyd

CONTRAST study: EuroPCR



EuroPCR 2015

Late-breaking trial

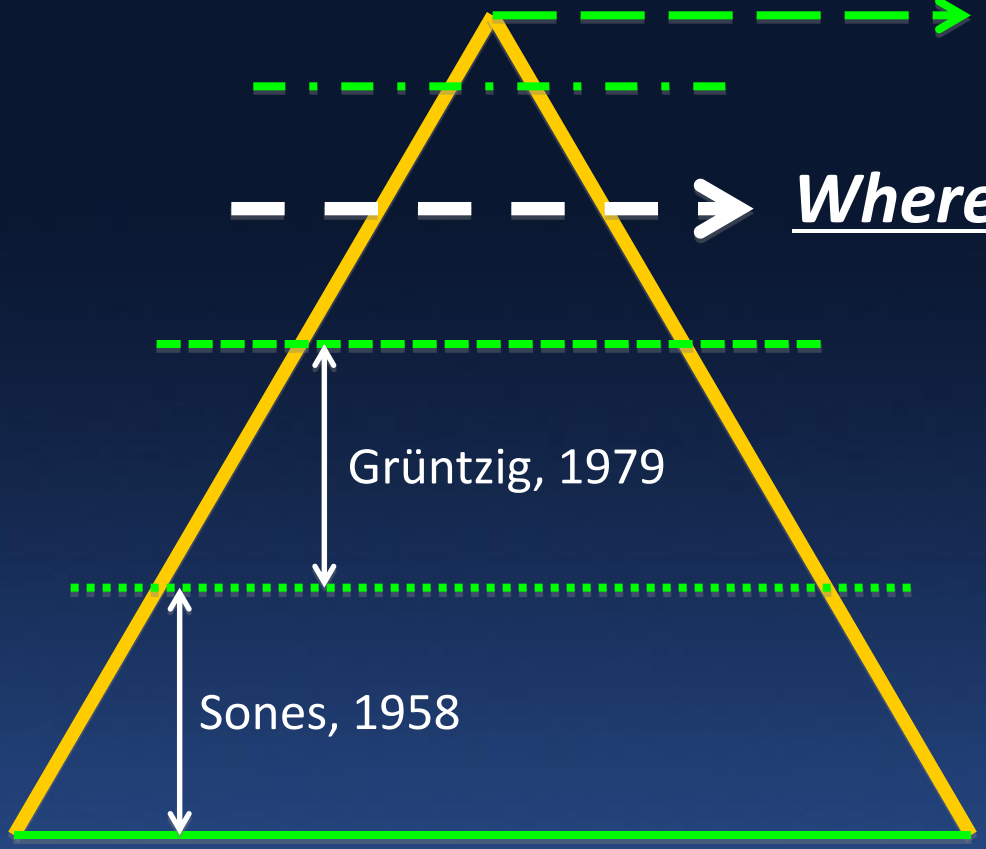
May 19, 2015

Coronary physiology

"Hot line"

13:40 – 15:10

Pyramid of diagnostic accuracy



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