Contrast Pd/Pa
Better than resting measures?

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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
- Grant/Research Support (to institution)
- Educational organizations (travel support for academic meetings but never honoraria)

Organizations (alphabetical)
- St Jude Medical (for CONTRAST study)
- Volcano/Philips (for DEFINE-FLOW study)
- 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.
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.

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

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class(^a)</th>
<th>Level(^b)</th>
<th>Ref.(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFR is recommended to identify hemodynamically relevant coronary lesion(s) when evidence of ischaemia is not available.</td>
<td>I</td>
<td>A</td>
<td>399, 401, 405</td>
</tr>
</tbody>
</table>

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

RESOLVE = Jeremias A, JACC. 2014 Apr 8;63(13):1253-61
ADVISE 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
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

Sones, 1958

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Sones, 1958

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

\[ 70 \text{ kg} \times (0.025 \text{ to } 0.25 \text{ cc/kg}) = 1.8 \text{ to } 18 \text{cc} \approx 10 \text{cc of IC contrast} \]

gave *60% increase* in flow

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 1. Effect of intracoronary injection of Renograffin 76 on mean coronary stenosis pressure gradients

<table>
<thead>
<tr>
<th>% Angiographic stenosis</th>
<th>Gradient at rest (mm Hg)</th>
<th>Gradient after Renograffin 76 (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30% LM</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30% RCA</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>60% Graft</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50% LAD</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>55% LAD</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>55% LAD</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>60% RCA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>60% LAD</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>60% LAD</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td>60% LAD</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>65% LAD</td>
<td>13</td>
<td>34</td>
</tr>
<tr>
<td>70% LAD</td>
<td>26</td>
<td>37</td>
</tr>
<tr>
<td>75% LAD</td>
<td>16</td>
<td>34</td>
</tr>
<tr>
<td>80% LAD</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>80% LAD</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td>80% LAD</td>
<td>17</td>
<td>48</td>
</tr>
<tr>
<td>80% RCA</td>
<td>25</td>
<td>44</td>
</tr>
<tr>
<td>85% CX</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>85% RCA</td>
<td>8</td>
<td>26</td>
</tr>
<tr>
<td>85% CX</td>
<td>24</td>
<td>38</td>
</tr>
<tr>
<td>85% LAD</td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>85% LAD</td>
<td>57</td>
<td>60</td>
</tr>
<tr>
<td>90% LAD</td>
<td>37</td>
<td>41</td>
</tr>
<tr>
<td>90% LAD</td>
<td>40</td>
<td>58</td>
</tr>
<tr>
<td>90% LAD</td>
<td>41</td>
<td>51</td>
</tr>
<tr>
<td>90% LAD</td>
<td>43</td>
<td>60</td>
</tr>
<tr>
<td>90% LAD</td>
<td>57</td>
<td>59</td>
</tr>
<tr>
<td>90% LAD</td>
<td>50</td>
<td>61</td>
</tr>
</tbody>
</table>

(Mean ± SE) 20 ± 4 (Mean ± SE) 33 ± 4

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 Renograffin 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
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)
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
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

80% ≈ rest physiology (Pd/Pa or iFR)
65% ≈ angiogram alone
50% = coin flip

Where does contrast fit?

Grüntzig, 1979
Sones, 1958

Concept from Pijls NH, ETP 2014 course, based on slide 26 of his April 24 lecture
CONTRAST (Can cONTrast Injection Better Approximate FFR compAre 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

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.

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)
<table>
<thead>
<tr>
<th>Country</th>
<th>Participating Centers</th>
<th>USA</th>
<th>UT-Houston (sponsor)</th>
<th>CRF (physiology core lab)</th>
</tr>
</thead>
</table>
| Belgium (Aalst)       | • B De Bruyne  
                    • E Barbato                 | • W Fearon (Palo Alto)     | • N Johnson                          | • A Jeremias              |
| France (Lyon)         | • G Rioufol                                   | • G Chrysant (OKC)         | • R Kirkeeide                        | • A Maehara               |
| Italy (Naples)        | • G Esposito                                  | • N Pijls                  | • KL Gould                           | • M Matsumura             |
| Portugal (Lisbon)     | • S Baptista                                  | • F Zimmermann             |                                      |                           |
| Scotland (Glasgow)    | • C Berry                                     |                            |                                      |                           |
| Sweden (Stockholm)    | • N Witt                                      |                            |                                      |                           |
| Korea (Seoul)         | • BK Koo (SNUH)                               |                            |                                      |                           |
|                       | • SJ Park (Asan)                              |                            |                                      |                           |
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
CONTRAST example: protocol

![Graph showing Pd/Pa ratio over time with different pressures for coronary and aortic regions.](image-url)
CONTRAST example: IC contrast #1

Time (seconds)

Pd/Pa

rest #1 = 0.94
iFR #1 = 0.92
contrast #1 = 0.84

8cc of IC contrast

aortic coronary

200 mmHg
150 mmHg
CONTRAST example: IC contrast #2

Time (seconds)
0 200 400 600 800

Pd/Pa
0 mmHg 50 mmHg 100 mmHg 150 mmHg 200 mmHg

8 cc of IC contrast
contrast #2 = 0.85

aortic

coronary
CONTRAST example: IC adeno #1

IC adenosine #1 = 0.77
80μg of IC adenosine
CONTRAST example: IC adeno #2

Pd/Pa vs Time (seconds)

IC adenosine #2 = 0.77

80μg of IC adenosine

150 mmHg

200 mmHg

coronary aortic

Pd/Pa
CONTRAST example: IV adeno #1

Time (seconds)

0 200 400 600 800

0.0 0.25 0.5 0.75 1.0

Pd/Pa

200 mmHg

150 mmHg

Pd/Pa

rest #2 = 0.95
iFR #2 = 0.93

140μg/kg/min of IV adenosine

IV adenosine #1 = 0.76

aortic

coronary
CONTRAST example: IV adeno #2

IV adenosine #2 = 0.76

140μg/kg/min of IV adenosine

Pd/Pa coronary = 0.76

Pd/Pa aortic
CONTRAST example: drift check

Drift check graph showing changes in Pd/Pa over time (seconds) with drift values at 1.02.

- Time (seconds): 0, 200, 400, 600, 800
- Pd/Pa: 0.0, 0.25, 0.5, 0.75, 1.0
- Pd/Pa values at: 0 mmHg, 50 mmHg, 100 mmHg, 150 mmHg, 200 mmHg

Graph showing pullback distal to coronary aortic with drift = 1.02.
CONTRAST example: summary

- Rest
  - $\text{Pd/Pa} = 0.94$ and $0.95$
  - $\text{iFR} = 0.92$ 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
The CONTRAST Study

Can contrast injection better approximate FFR compared to pure resting physiology?

On behalf of the CONTRAST investigators

ClinicalTrials.gov Identifier: NCT02184117

EuroPCR 2015
Late-breaking trial
May 19, 2015
Coronary physiology
“Hot line”
13:40 – 15:10
Pyramid of diagnostic accuracy

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