Pd/Pa at rest, iFR, b-SRv, resting gradient
Why Can They Never Be As Good As Hyperemic Indexes

Educational Training Program ESC
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**Hyperemic indices:**

- **FFR**  
  (Pijls, De Bruyne 1992)
- **iHDPVr**  
  (Di mario, Serruys 1994)
- **hSRv**  
  (Piek, Spaan, Siebes 1997)

**Resting indices (“FFR-light”):**

- **resting transtenotic gradient**  
  (Gruentzig, 1977)
- **Pd/Pa at rest, +/- diastolic**  
  (Gould, Meier, 1981)
- **iFR**  
  (Sen, Davies 2011)
- **i-FFR**  
  (Andersson, 2013)
- **bSRv**  
  (Verhoef, Siebes 2012)

**Virtual Hyperemic Index:** **FFR$_{CT}$**  
(Min, Koo, 2009)
A collection of older and newer resting indexes derived from pressure measurement at rest: 

Pd/Pa at rest, diastolic Pd/Pa, iFR, i-FFR

which have in common that they

- all try to avoid hyperemia
- are not independently validated,
- and only have a moderate accuracy (70% -80%) compared to FFR
Why Are Resting Indices Insufficient?

- **Limited Clinical Significance**

- **Limited Physiological Meaning**
  - poor scientific background
  - no experimental validation
  - fluid-dynamic equation

- **Resting Conditions Are Very Hard to Obtain**
  - uncertainty if resting condition is present in cath lab, large variation
  - most “resting” indices vary with level of hyperemia
  - the only condition which can be reliably obtained, is maximum hyperemia
Why Are Resting Indices Insufficient?

- **Limited Clinical Significance**

In patients with Coronary Artery Disease, resting flow and gradients have little meaning....

...Angina pectoris occurs and the myocardium becomes ischemic as soon as *maximum achievable blood flow* is insufficient to match oxygen demand.

*Therefore, looking at maximum flow (as a fraction of normal maximum flow), makes most sense and is the basis of Fractional Flow Reserve (FFR)*
Why Are Resting Indices Insufficient?

- Limited Clinical Significance

- Limited Physiological Meaning
  - poor scientific background
  - no experimental validation
  - deny the fluid-dynamic equation
Similar baseline gradients can lead to large differences during hyperemia as a result of:

- geometry of the stenosis (fluid dynamics equation)
- different extent of the distal perfusion area
- age of the patient
- hemodynamic conditions like blood pressure, heart rate and contractility
\[ \Delta P = f \cdot Q + s \cdot Q^2 \]

- \( f \): friction coefficient
- \( s \): separation coefficient

Moderate gradient at rest
Moderate increment at hyperemia

Small gradient at rest
Large gradient at hyperemia

70% long prox LAD stenosis

50% ostial left main stenosis

iFR = 0.89  FFR = 0.85

iFR = 0.94  FFR = 0.57
In addition, some resting indexes have no or poor scientific basis and lack experimental validation.
iFR = Pd / Pa at rest during WFP (Sen et al, JACC 2012)

**basic assumptions:**
1. resistance during WFP at rest equals average hyperemic resistance
2. iFR is claimed to be “hyperemia-free”
Volumetric coronary blood flow

$Q_{phasic}$

$Q_{mean}$

-200 ml/min

20 sec occlusion
In the presence of constant coronary pressure

\[ R \sim \frac{1}{\text{Flow}} \]
minimal myocardial resistance during the so-called “wave-free period” is ~ 250% higher than average myocardial resistance at maximum hyperemia in all dogs and swine.
iFR = Pd / Pa during WFP  → strongly dependent on hyperemia

Colin et al, JACC 2012, in press
Johnson et al JACC 2012, in press
profound influence of hyperemia on iFR:

“iFRhyp” was already called diastolic FFR by Abe et al in Circulation, 1996)

estimated decrease of resistance during “wave-free period”

\[
\frac{(1.0 - 0.64)}{(1.0 - 0.82)} = 200\%
\]

VERIFY study, Colin et al, JACC 2012, in press
Why Are Resting Indices Insufficient?

• Limited Clinical Significance

• Limited Physiological Meaning
  - poor scientific background
  - no experimental validation
  - fluid-dynamic equation

• Resting Conditions Are Very Hard to Obtain
  - uncertainty if resting condition is present in cath lab ➔ large fluctuations
  - most “resting” indices vary considerably
  - in fact, the only condition which can be reliably obtained in the cathlab, is maximum hyperemia
Mr M, born 26-03-1937, long mild/moderate proximal LAD lesion
long moderate proximal LAD lesion; equalization (PW at tip of guiding catheter)
PW in distal LAD; patient “asleep” (relaxed)

distal LAD; “resting” pressures
PW in distal LAD; patient “awake”
distal LAD; “resting” pressures

prior to adenosine: explanation to patient what is going to happen
advancing the wire 2 cm and pulling it back again
Measurement of FFR

- distal LAD; maximum hyperemia
- adenosine i.v. infusion
After waiting for 5 minutes, not touching anything
PW back to tip of guiding catheter

verification of equal pressures and absence of drift
what is “resting”?

nothing is so variable in the cathlab as “resting”
obtaining true resting conditions in a conscious patient in the catheterization room, is often an illusion.
and as a consequence, large variation in cut-off values for resting indices are found

**Traditional CFR:** $1.7 - 2.0 - 2.5 - 3.5$

\[
CFR = \frac{4.0}{1.0} = 4, \text{ but: } \frac{4.0}{1.5} = 2.7
\]

**iFR:**
- $0.83$ (Advise study, Sen et al)
- $0.88$ (Koo et al)
- $0.90$ (Jeremias et al, resolve registry)

Similar for all indexes which rely upon resting value of flow
Resting flow in the cath lab is an illusion:

Influence of the “Resting Flow” on CFR

RR = 115/76 (mean 90) asleep 
48 cm.s⁻¹ CFR = 4.8

RR = 129/84 (mean 101) awake 
56 cm.s⁻¹

RR = 129/84 (mean 101)
56 cm.s⁻¹

10 cm.s⁻¹
CFR = 2.8
Resting flow in the cath lab is an illusion:

FFR IS NOT AFFECTED!

JJongen Egidius

RR = 115/76 (mean 90)  RR = 129/84 (mean 101)

CFR = 4.8  CFR = 2.8
Cut-off = 0.83

ADVISE STUDY (N = 131)

From: Sen, Davies, et al JACC 2011
Retrospective analysis
IFR versus FFR in 500 patients
(VERIFY study, Berry et al, JACC 2013)

Prospective analysis
IFR versus FFR in 205 patients
(VERIFY study, Berry et al, JACC 2013)

\[ R^2 = 0.67 \]
Diagn accuracy = 66%

\[ R^2 = 0.70 \]
Diagn accuracy = 67%
~ $\text{FFR}_{\text{diast}}$
defined by Abe,
_Circulation_ 2000
_threshold 0.76

<table>
<thead>
<tr>
<th>Method</th>
<th>AUC</th>
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<tbody>
<tr>
<td>iFR</td>
<td>0.871</td>
</tr>
<tr>
<td>Rest grad.</td>
<td>0.875</td>
</tr>
<tr>
<td>Pd / Pa</td>
<td>0.880</td>
</tr>
<tr>
<td>iFRhyp</td>
<td>0.988</td>
</tr>
</tbody>
</table>

Reproducibility of FFR and iFR

From VERIFY study, Berry et al, JACC 2013
CALCULATION OF iFR: VOLCANO BOX vs MATLAB

DOES IT MATTER?

VERIFY STUDY: 705 resting and hyperemic tracings

Calculation by Mathlab (free available computer program) blinded for results by the Volcano algorithm (University of Technology, BME dept)

Calculation by the Volcano algorithm blinded for the results by Mathlab (CRF, New York)
From: VERIFY
N=705

Berry et al
JACC 2013;
# Data Contribution

<table>
<thead>
<tr>
<th>Registry</th>
<th>Patients</th>
<th>Lesions</th>
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<td>ADVISE/ADVISE Registry</td>
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<td>VERIFY Prospective Cohort</td>
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<td>VERIFY Retrospective Cohort</td>
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<td>Seoul National University</td>
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<td>UT Houston</td>
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<td>Stony Brook University</td>
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<td>200</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>1802</strong></td>
<td><strong>1850</strong></td>
</tr>
</tbody>
</table>
Correlation FFR and iFR

$R^2 = 65\%$

24.3% of Population

0.82
ROC Curve iFR and Pd/Pa Based on FFR 0.80

- **IFR**
- **Resting Pd/Pa**

**AUC (95% CI)**
- **IFR**: 0.875 (0.858 - 0.892)
- **Resting Pd/Pa**: 0.876 (0.859 - 0.893)

**P = 0.84**
necessity of hyperemia

• If Pd/Pa at rest (or comparable indices) is < 0.80, as a matter of fact FFR will also be < 0.80 and hyperemia in itself is not strictly mandatory to decide upon inducible ischemia

• But without hyperemia and FRR, you cannot judge how much a patient improved by stenting: "did FFR go from 0.78 to 0.91 or from 0.65 to 0.91?"

• And without hyperemia, you cannot make a meaningful pull-back recording and you are losing a lot of valuable information
“hyperemic pull back recording”

in case of diffuse disease or multiple lesions: *how would you believe to get this information without hyperemia?*
AVOIDING HYPEREMIA IS PROHIBITIVE FOR STENT EVALUATION

After stenting, in the majority of patients no resting conditions are obtained anymore and “semi-hyperemic” status persists, with a lot of inter-individual variation.

It often takes > 30 minutes to achieve “baseline” again.

As a consequence, “resting” Pd/Pa (and iFR) are often lower after stenting than before (“paradoxical deterioration of iFR or resting Pd/Pa”).

To evaluate improvement by stenting, you need to compare FFR after and before stenting.
Correct Classification of Ischemic Stenosis

100 % certainty (holy grail)

95 %

80 %

70 %

angio

the piramid of diagnostic accuracy

FFR

resting Pd/Pa, iFR, bSVr ("FFR-light")

hyperemia

resting indexes
CONCLUSIONS

• the physiologic basis for using resting indices is flawed and based upon unproven assumptions

• the experimental validation is lacking and experiments in dogs and swine in fact reject those assumptions

• none of these resting indexes has been independently validated

• the accuracy of all of these resting indices (whether $\Delta p$, $P_{d}/P_{a}$ at rest, or iFR) in clinical studies is similar for all of them and $\sim < 80\%$ only when compared to FFR

• It is questionable if you should accept 80% certainty in your patients if you can get 95%
CONCLUSIONS

• using resting indices is like testing in a wind tunnel without wind

• the physiologic basis for using resting indices is flawed and based upon unproven assumptions

• the experimental validation is completely absent and in fact experiments in dogs and swine reject their validity incontrovertably

• the accuracy of all resting indices (whether $\Delta P$, Pd/Pa at rest, or iFR) in clinical studies is similar and $\sim 80\%$ only, versus $95\%$ for (hyperemic) FFR

→ relying upon resting indexes only, means a wrong decision in 1 out of every 5 patients
“The resting gradient is far from enough but unfortunately it’s all I have now.”
“The resting gradient is far from enough but unfortunately it’s all I have now”.

why guessing if you can have certainty?
Neem als basis
TCT 2012 (soortgelijke voordracht)
Budapest (soortgelijke voordracht)

Latere data:
Dia’s met reprod heid
Inaccuracy van 80% en van 70% tov die 80%
(lijn met intervallen)
Ook Nils Johnson
**Hocus-pocus with statistics (1)**

true value = 100

measuring methodology #1 : accuracy = 80 %

measured value between 80 and 120
measuring methodology #1: accuracy = 80%

Range of uncertainty between 70 and 130 (and not between 90 and 110)

measuring methodology #2: accuracy = 90% compared to methodology #1
Accuracy of method #1 = 90 % compared to gold standard

Accuracy of method #2 = 80 % compared to method #1

What is the accuracy of method #2 compared to gold standard?

$\text{(0.8 x 0.9)} = 0.72$ (or 72 %)

And NOT: $(0.8 : 0.9) = 0.89$ (or 89 %)
Hocus-pocus with statistics (3)
About reproducibility and “wrong decisions”

Or: confusing a-priori and a-posteriori knowledge

• In Catharina Hospital, 7000 invasive procedures (diagnostics and PCI) are performed annually

• Prior to a procedure, kidney function is checked

• If GFR < 60 ml/min → prehydration

• Accuracy of GFR measurement is ≤ 3ml/min (rather good!, you don’t think so?)
Hocus-pocus with statistics (3)
About reproducibility and “wrong decisions”

Or: confusing a-priori and a-posteriori knowledge

• In the year 2012, out of the 7000 patients GFR was between 57 and 63 ml/min in 387 of them.

• In ~50% of these 387 patients, a second measurement would have switched them from above 60 ml to below or vice versa.

• Does this mean that you could better not determine renal function prior to PCI/ CAG, because “it is wrong in the group of patients where it matters”???
What is fundamentally wrong in this reasoning?

- confusing *a-priori* and *a-posteriori* knowledge

- You do not know *beforehand* who is close to the “cut-off” value (if you would know that, there would be no need to measure at all)

- Of the total population you need to examine, only a small percentage is close to the cut-off value and might “cross the border” (387/7000 = 6 % in case of GFR & hydration)
Reproducibility of FFR

VERIFY study, Berry et al, JACC 2013 (published februari 2013)

There is not any other index in physiology so reproducible as FFR
There is not any other index in physiology so reproducible as FFR.

VERIFY study, Berry et al, JACC 2013 (published februari 2013)
At 1200 consecutive in-duplo measurements of FFR, there was NOT ANY cross-over across the gray zone.

FFR

- non-signif.
- stenosis significant

1.0 0.80 0.75 0

3% 2% 0%
Reproducibility iFR using matlab

Data from Verify Study
Bland-Altman Reproducibility iFR

Mean difference (std): -0.007 ± 0.037
Measurements compared
\(iFR_{\text{matlab}}\) vs \(iFR_{\text{volcano}}\)

Absolute difference 2 measurements > 0.3 (axes Bland-Altman are truncated)

All 705 measurements
Bland-Altman iFR

Mean difference (std): -0.005 ± 0.034
Measurements compared

\( iFR_{\text{matlab}} \) vs \( iFR_{\text{volcano}} \)

Difference of 18 measurements \( \leq 0.1 \)

\( iFR_{\text{volcano}} < iFR_{\text{matlab}} \)

Difference of 2 measurements \( \geq 0.1 \)

\( iFR_{\text{volcano}} > iFR_{\text{matlab}} \)

Remain 685 measurements
iFR comparison

iFR_matlab

iFR_Resolve
Bland-Altman iFR

Mean difference (std): \(-0.003 \pm 0.020\)
Summary

705 measurements

Mean difference (std): -0.005 ± 0.034

685 measurements

Mean difference (std): -0.003 ± 0.020

Reproducibility; difference between two iFR measurements (Verify)

Mean difference (std): -0.007 ± 0.037
Cut-off = 0.83

From: Sen, Davies, et al JACC 2011
ADVISE STUDY (N=131)

From: Sen, Davies, et al JACC 2011
ADVISE STUDY (N= 131)

From: Sen, Davies, et al JACC 2011

Figure 5:

FFR 0.34  FFR 0.87
Retrospective analysis IFR versus FFR in retrospective analysis in 500 patients in Aalst and Eindhoven.

A) all data: $R^2 = 0.67$
diagn accuracy = 66%

B) FFR range 0.6-0.9: $R^2 = 0.39$
diagn accuracy = 59%
Correlation between iFR and FFR (N=206)

\[ y = 0.98x + 0.1 \]
\[ r^2 = 0.70 \]

FFR range 0.6 - 0.9:
\[ y = 0.66x + 0.36 \]
\[ r^2 = 0.33 \]

diagn accuracy = 67 %

(diagnostic accuracy of flipping a coin = 50 %)

diagn accuracy = 58 %
ADVISE STUDY (N=131)

From: Sen, Davies, et al JACC 2011
Berry et al.
JACC 2013;
Bland-Altman iFR

Mean difference (std): -0.003 ± 0.020
## Overall Precision

**Proportion of Patients with 90% Precision**

<table>
<thead>
<tr>
<th></th>
<th>PPV</th>
<th>NPV</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>iFR</td>
<td>44.2%</td>
<td>12.9%</td>
<td>57.1%</td>
</tr>
<tr>
<td>Pd/Pa</td>
<td>43.1%</td>
<td>--</td>
<td>43.1%</td>
</tr>
</tbody>
</table>

**Proportion of Patients with 95% Precision**

<table>
<thead>
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<th>PPV</th>
<th>NPV</th>
<th>Total</th>
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<tbody>
<tr>
<td>iFR</td>
<td>24.3%</td>
<td>--</td>
<td>24.3%</td>
</tr>
<tr>
<td>Pd/Pa</td>
<td>33.4%</td>
<td>--</td>
<td>33.4%</td>
</tr>
</tbody>
</table>
Figure 5:

- Scatter plot showing correlation between iFR and FFR.
- The equation $y = 0.98x + 0.1$ with $r^2 = 0.70$ indicates a strong linear relationship.
- FFR value of 0.55 is marked on the graph.