Resting measures, Pd/Pa and iFR

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Italy
Flavio Ribichini,

I have no conflict of interest related to this talk.

I was ESC Research Fellow in Aalst 1997-1998.

I use of FFR since 1999 in Italy.

I am an FFR believer.
Under the High Patronage of his Excellency the President of The Republic of Tunisia Zine El Abidine Ben Ali and the Auspices of the Tunisian Society of Cardiology and Cardio-Vascular Surgery

Sixth Panafrican Course on Interventional Cardiology

September 29th, to October 1st, 2005
Monastir-Tunisia
65 yo male, effort chest pain
Myocardial perfusion scintigraphy with adenosine 99mTc SPECT
FFR Diagonal = 0.81

Allarmi Off

155/75  m 108

130/65  m 88
FFR LAD = 0.82
I got news of this patient for more than 5 years (2010) and He had no recurrences of ischemia.

Then, He lost me at follow-up.
At TCT 2011 formal presentation of the iFR concept.

In 2012 publication of the ADVISE Study.

instant wave-Free Ratio
Using Pressure to Get Flow

- Coronary pressure is simple to measure
- Flow velocity is more challenging

Fundamental Equation for relating Pressure and Flow:

\[ P = Q \times R \]

Pressure = Flow \times Resistance

or

\[ \Delta P \approx \Delta Q \times R \]

Change in Pressure = Change in Flow \times Constant Resistance

When Resistance is Constant, changes in Pressure are proportional to changes in Flow

Derived from Poiseuille’s Law for Fluid Dynamics
Resistance is Constant in the Wave-Free Period

*Phasic resistance during the cardiac cycle*

Davies J. PRIMARY Results of ADVISE. TCT 2011.
Resistance is Constant in the Wave-Free Period

Phasic resistance during the cardiac cycle

Davies J. PRIMARY Results of ADVISE. TCT 2011.
**Definition:** Instantaneous pressure ratio, across a stenosis during the wave-free period, when *resistance is more constant* and minimized in the cardiac cycle.

Escaned J. ADVISE II: A Prospective, Registry Evaluation of iFR vs. FFR. TCT 2013.
iFR Window Maximizes Flow Velocity

- iFR Flow is ~30% higher which amplifies the signal vs. Pd/Pa alone

- Increasing Flow Velocity exaggerates the pressure drop across a stenosis

- Bigger pressure drop allows for better classification of stenosis severity
Consistent iFR Cut Off

Best iFR cut off compared with FFR≤ 0.80

ADVISE-Registry (n=339) 0.89
South Korean Study (n=238) 0.90
RESOLVE (n=1593) 0.90
ADVISE-in Practice (n=392) 0.90
ADVISE 2 (n=689) 0.89
The Hybrid iFR/FFR Approach

- 94.0% match to FFR\(^1\)
- 65.1% of patients were free from hyperemic agents\(^2\)

1. Using the iFR cut points of 0.85 and 0.94 matches best with an FFR ischemic cut-point of 0.80 with a specificity of 90.7% and sensitivity of 96.2%.

2. The ADVISE II study illustrated a 5.8%, i.e. \((17+23)/690\), classification discordance between the iFR Hybrid Approach and FFR. Among 477 lesions that would be assessed without hyperemia by the iFR Hybrid Approach, 40 \((17+23)\) were due to classification discordance.

3. An iFR cut-point of 0.89 matches best with an FFR ischemic cut-point of 0.80 with a specificity of 87.8% and sensitivity of 73.0%. (iFR Operator’s Manual 505-0101.23)
Providing Choice

An iFR of 0.89 approximates an FFR of 0.80

Fractional Flow Reserve
• Clinically proven for ischemia detection
• Supported by guidelines worldwide
• However, use of FFR is still very low

The iFR Modality
• Volcano’s proprietary instantaneous, trans-lesional pressure ratio measured during the wave-free period
• Prospectively tested in the ADVISE II Study and in the ongoing RCT FLAIR

1. An iFR cut-point of 0.89 matches best with an FFR ischemic cut-point of 0.80 with a specificity of 87.8% and sensitivity of 73.0%. (iFR Operator’s Manual 505-0101.23)
Example of positive resting gradient in intermediate-severe lesion

Measurement of any gradient is better than no proof of ischemia before PCI
Measurement of any gradient is better than no proof of ischemia before PCI

Example of negative resting gradient in intermediate-mild lesion
Example of wrong resting gradient in intermediate-mild lesion
Case presentation to remind the “good physiologic Practice”

35 years old male

Heart transplant at the age of 28

Intensive life with regular exercise

Routine coronary angiogram in October 2014 for CAV stratification
Advanced CAV with severe LM stenosis.

Scheduled for elective PCI of the LM after Heart Team discussion.

No symptoms or signs of ischemia...
Pre-PCI angiogram confirms the LM stenosis in advanced CAV
Resting gradients confirm the stenosis severity.

But, after infusion of nitrates and ADN...
At 8 months follow-up the patient remains asymptomatic.
But there are opinions against the reliability of iFR

- iFR correlates weakly with FFR and is not independent of hyperemia.
- iFR cannot be recommended for clinical decision making in patients with coronary heart disease.
Objections of the iFR authors to VERIFY

VERIFY paper’s primary conclusion was based on the assumption that an iFR of 0.80 is equivalent to an FFR 0.80, which is incorrect. The proper cut-point in the FDA labeling is iFR of 0.89 equivalent to an FFR of 0.80.

“The best cut-off value was not published in this paper.”

VERIFY Investigators pointed out that the iFR window is not ‘independent’ of hyperemia.”

iFR does not intend to show independence from adenosine, but rather that adenosine may not be needed to measure lesion severity.

Results

The clinical characteristics of the patients in the prospective study are shown in Table 1. The relationships between FFR and iFR are shown in Figure 2. Compared to the commonly used FFR cut-off value of ≤0.80, the diagnostic performance of iFR of ≤0.80 is shown in Table 2. Overall accuracy was 60% (95% CI: 53% to 67%) for all vessels studied and 51% (95% CI: 43% to 59%) for those with FFR in the range of 0.60 to 0.90. Sen et al. (14) proposed that iFR of ≤0.83 has diagnostic performance equivalent to an FFR of ≤0.80. The diagnostic performance of iFR at ≤0.83 in our prospectively acquired dataset is shown in Table 3. Overall accuracy was 68% (95% CI: 61% to 75%) for all vessels studied and 68% (95% CI: 53% to 78%) for those with FFR in the range of 0.60 to 0.90.

Refer to the graphs in Figures 3 and 4 for additional data and analysis.
Conclusions

Hyperaemic and non-hyperaemic intracoronary indeces have an equivalent diagnostic performance in comparison to PET MBF for the assessment of intermediate coronary artery stenoses.
I am an FFR believer,

I am a clinician and a researcher

I work in a University Hospital

When we introduce a new technology we VERIFY it...

because “I trust what I see”
and “I do what I trust”

Let’s do an independent validation study of iFR versus FFR...
iFR-FFR comparison in daily practice: a single-center, prospective, online assessment

Table 1  Clinical and angiographic characteristics of the entire population

<table>
<thead>
<tr>
<th>Patient demographic data (54 patients)</th>
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</thead>
<tbody>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>Stable angina (CCS I-II)</td>
</tr>
<tr>
<td>Unstable angina</td>
</tr>
<tr>
<td>NSTEMI</td>
</tr>
<tr>
<td>NYHA class I-II</td>
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</table>

<table>
<thead>
<tr>
<th>Angiographic characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of assessed stenosis</td>
</tr>
<tr>
<td>Left anterior descending</td>
</tr>
<tr>
<td>Left circumflex</td>
</tr>
<tr>
<td>Right coronary artery</td>
</tr>
<tr>
<td>Mean % diameter stenosis</td>
</tr>
<tr>
<td>Mean lesion length</td>
</tr>
<tr>
<td>Mean reference vessel diameter</td>
</tr>
<tr>
<td>Mean minimum lumen diameter</td>
</tr>
<tr>
<td>Mean iFR ratio</td>
</tr>
<tr>
<td>Mean FFR ratio</td>
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Correlation between iFR and FFR values of the 68 lesions analyzed, with the respective cut-off values indicated, which, apart from a correlation value of 0.83, highlight the low number of false-positive and false-negative values when the two methods are compared. FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; NSTEMI, non-ST-segment elevation myocardial infarction; NYHA, New York Heart Association.
**iFR-FFR comparison in daily practice: a single-center, prospective, online assessment**

iFR FFR 100% agreement in 45% of cases (ADN not needed)

Gray zone (iFR 0.86-0.93) 55%, of these, 70% were both negative

iFR identified positive values in 15% of FFR >0.80.

In conclusion, in our experience, iFR identified correctly all FFR negative lesions and would induce 15% more PCI in lesions with an FFR value >0.80 <0.85.
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I am a clinician and a researcher
I work in a University Hospital
When we introduce a new technology we VERIFY it...
Let’s do a validation study of iFR versus FFR...
Following our validation study, we were invited to participate in DEFINE FLAIR
Intermediate lesion requiring physiological assessment
In ACS: intermediate *non-culprit* lesion

N=2500, 1:1 Randomisation

**DEFINE FLAIR**

*Functional lesion assessment of intermediate stenosis to guide revascularisation*

**FFR** guided PCI

- **FFR > 0.8**
  - Defer PCI

- **FFR ≤ 0.8**
  - Perform PCI

**iFR** guided PCI

- **iFR ≥ 0.9**
  - Defer PCI

- **iFR < 0.9**
  - Perform PCI

30 day, 1, 2 and 5yr follow-up
Example of a DEFINE FLAIR PATIENT RANDOMIZED IN VERONA.

54 y.o male
ACS presentation
Proximal LAD culprit
Distal LAD significant

PCI on LAD
Significant lesions on ostial RI and LCx
PCI on LAD

Significant lesions on ostial RI and LCx and the RCA
Pre-discharge functional assessment of the RI and LCx

Enrolled
DEFINE
FLAIR
TRIAL

April 4 2014
Pre-discharge functional assessment of the RI and LCx
Pre-discharge functional assessment of the RCA

Enrolled DEFINE FLAIR TRIAL April 4 2014
This patient has completed one-year follow-up

- No clinical events
- No angina

- So far 36 patients enrolled (21 to FFR and 15 to iFR)
- Of 51 lesions, 13 treated and 38 lesions deferred
- None has been re-admitted for recurrence of ischemia.
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I am a clinician and a researcher

I work in a University Hospital

When we introduce a new technology we VERIFY it...

Let’s do a validation study of iFR versus FFR...

Following our validation study, we were invited to participate in DEFINE FLAIR.

... and my friend Emanuele Barbato from Aalst got very jealous and asked us to participate in GRAFFITI
GRAft Patency After FFR-guided versus Angio-guided CABG: a randomized clinical trial (GRAFFITI)
Patient with
- Significant LAD / LM lesion AND
- At least one more lesion

~ 200 pts
- proved by FFR (<0.80) / Angio (>69%)
- angiographically intermediate (30-90%)

DS 30 - 90%

FFR measurement

FFR blinded HEART TEAM consultation
(Surgeons will be asked to identify by visual estimation the target vessels to be revascularized, number of anastomosis and grafts)

PATIENT 1:1 RANDOMIZATION

FFR-GUIDED GROUP
INFORM surgeons about FFR-values

GRAFT ONLY THE FUNCTIONALLY SIGNIFICANT LESIONS

12 ± 2M FOLLOW-UP

ANGIO-GUIDED GROUP
Let surgeons BLINDED for FFR-values

GRAFT ALL THE ANGIOGRAPHICALLY SIGNIFICANT LESIONS

GRAFT PATENCY CONTROLLED BY CCTA and/or CA
<table>
<thead>
<tr>
<th>Preliminary Surgical Strategy</th>
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<tbody>
<tr>
<td>Date</td>
<td></td>
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<td>Please use this format: 2014-01-22</td>
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</tbody>
</table>

- **Lesion #1**
  - **Segment**
    - 3 - Dist RCA
  - **Graft #1**
    - 1 - Prox RCA
  - **Type of graft**
    - LIMA

- **Type of Surgery**
  - **On-Pump/Off-pump**
    - Off-Pump

- **Comment**

- **First case enrolled February 24° 2014**
- **Total cases enrolled in Verona: 20**
- **Complete follow-up obtained in the first 5 cases**
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Following our validation study, we were invited to participate in DEFINE FLAIR

... and my friend Emanuele Barbato got very jealous and asked us to participate in GRAFFITI

... and we still like doing new clinical studies...
CART STUDY
Cardiac Allograft Reparative Therapy

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

1 study found for: CART Verona
Modify this search | How to Use Search Results

Safety and Efficacy of Everolimus - Eluting Bioresorbable Vascular Scaffold for Cardiac Allograft Vasculopathy
Condition: Cardiac Allograft Vasculopathy
Intervention: Device: Everolimus-Eluting Bioresorbable Vascular Scaffold (ABSORB)
CART STUDY
Cardiac Allograft Reparative Therapy

MULTI-MODALITY DIAGNOSIS IN CAV, INCLUDING FFR IN TRANSPLANTED HEART.

RESTENOSIS AFTER BVS IMPLANTATION IN CAV

CLINICALTRIAL.GOV IDENTIFIER.

PARTICIPATING CENTERS: VERONA, ROME, MILANO, PADOVA, PAVIA

SO FAR 8 PATIENTS ENROLLED
Case Presentation

40 years old male

Heart transplant at the age of 30
Intensive life with regular exercise
Since November 2012, typical effort angina
Admitted for coronary angiogram in March 2013
Result after implantation of a 3.0x18mm BVS
RCA: mild proximal stenosis
Uneventful hospital course
Discharged 48 hours later

Medical therapy:
DAPT x 12m
Atorvastatin 80mg
Nitrates
Beta blocker
Prednisonc 5mg and Everolimus 10mg day
Case follow-up

After 6 months of total well being, the patient complains rapidly worsening effort angina from CCS class I to III in a few weeks.

He came back to our Center for a control angio.
Follow-up angiogram of the left coronary artery
Right coronary artery at follow-up with IVUS and VH of the proximal segment (September 2013)
Follow-up at 2 years is OK.

CAV represents a very aggressive form of ATH.

In this case, a non-significant lesion (FFR -) became sub-occlusive in less than 6 months.

The value of FFR in CAV needs validation.
My personal opinion on the hyperaemia-free method:

• Will facilitate penetration of physiology in the cath lab.
• Speeds the procedures and reduces cost of adenosine.
• May cause a slight increment (10%) in the number of treated lesions compared to FFR.
• May yield similar clinical outcomes compared to FFR.

Thank you
iFR-FFR comparison in daily practice: a single-center, prospective, online assessment

Impact on the numerical correlation of different values with the same meaning.
Algorithm is Critical for Accurate iFR® Calculation

iFR Calculated with Incorrect Algorithm & 0.80 cutpoint (instead of 0.89)

1. An iFR cut-point of 0.89 matches best with an FFR ischemic cut-point of 0.80 with a specificity of 87.8% and sensitivity of 73.0%. (iFR Operator’s Manual 505-0101.23)
Objections of the iFR authors to VERIFY

VERIFY used an offline analysis tool that did not have the ECG trigger that iFR uses, and had a window that does not seem constant with the iFR window. In the published diagram the two waveforms are out of phase, and the wave-free window seems to creep into the upswing of the systolic portion of the next heartbeat. The possible consequences of this disagreement are unknown.”