Index of Microcirculatory Resistance: The Basics

William F. Fearon, MD
Associate Professor of Medicine
Director, Interventional Cardiology
Stanford University Medical Center
Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

**Affiliation/Financial Relationship**
- Grant/Research Support
- Consulting Fees/Honoraria
- Major Stock Shareholder/Equity
- Royalty Income
- Ownership/Founder
- Intellectual Property Rights
- Other Financial Benefit

**Company**
- St. Jude Medical, Medtronic, NHLBI
- Medtronic
- Minor stock options: HeartFlow
Assessment of the Microvasculature

Diagnostic Challenge

Assessment of the Microvasculature

Diagnostic Challenge

A

Epicardial vessel

Prearterioles

Arterioles

Epicardium

Endocardium

B

Conduit vessels

Flow distribution

Metabolic flow control

Epicardium

Endocardium

Epicardial CAD

Microvascular Dysfunction

Assessment of the Microvasculature

- Extremely challenging diagnosis
  - Heterogeneous patient population
  - Variety of pathogenetic mechanisms
  - Poor anatomic resolution
  - Potentially patchy nature of the disease

- Therefore, assessment of the microvasculature is primarily *functional* and not *anatomic*
Evaluating the Microcirculation...
...in the Cath Lab

TIMI Myocardial Perfusion Grade:
Evaluating the Microcirculation…

...in the Cath Lab

TIMI Myocardial Perfusion Grade:
- Easy to obtain
- Specific for microvasculature
- Predictive of outcomes in large studies

Drawbacks:
- Qualitative
- Interobserver variability
- Not as useful in smaller studies
Doppler Wire Coronary Flow Reserve

\[ CFR = \frac{\text{Hyperemic Flow}}{\text{Resting Flow}} \]
Coronary Wire-Based Assessment

**Coronary Flow Reserve**

- Not microvascular specific
- No clearly defined normal value
- Affected by resting hemodynamics

---

Pijls NHJ and De Bruyne B, Coronary Pressure
Index of Microcirculatory Resistance

Epicardial Vessel

FFR

IMR

Microvasculature
Index of Microcirculatory Resistance

**Potential Advantages:**

- Readily available in the cath lab
- Specific for the microvasculature
- Quantitative and reproducible
- Predictive of outcomes
Estimation of Coronary Flow

Calculation of mean transit time

Resistance = $\Delta$ Pressure / Flow

$\Delta$ Pressure = $P_d - P_v$  Flow $\approx 1 / T_{mn}$

IMR = $P_d - P_v / (1 / T_{mn})$

IMR = $P_d \times T_{mn}$ at maximal hyperemia…

Practical Measurement of IMR

$$IMR = P_d \times Hyperemic T_{mn}$$

$$= 89 \times 0.37$$

$$= 33$$
IMR Case Example

Cardiac transplant recipient enrolled in study evaluating ACE inhibition
IMR Case Example

Cardiac transplant recipient enrolled in study evaluating ACE inhibition
Accessing IMR
Flushing the System
Resting $T_{mn}$ Measurements
Hyperemic $T_{mn}$ Measurements
Calculating IMR

IMR = \( P_d \times \text{Hyp} \times T_{mn} \)
IMR = 59 \times 0.39
IMR = 23
Animal Validation of IMR

Animal Validation of IMR

- Normal Microcirculation
- Abnormal Microcirculation

p = 0.002

Circulation 2003;107:3129-3132
Animal Validation of IMR

Circulation 2003;107:3129-3132
Animal Validation of IMR

- IMR
- TMR

% Change after Disruption of the Microcirculation

Total Group
Stenosis Absent
Stenosis Present

p = NS

## Reproducibility of IMR

### Effect of Pacing on FFR/CFR/IMR

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>RV Pacing at 110 bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFR</td>
<td>$3.1 \pm 1.1$</td>
<td>$2.3 \pm 1.2^\dagger$</td>
</tr>
<tr>
<td>IMR, U</td>
<td>$21.8 \pm 6.5$</td>
<td>$22.9 \pm 6.9$</td>
</tr>
<tr>
<td>FFR</td>
<td>$0.88 \pm 0.07$</td>
<td>$0.87 \pm 0.07$</td>
</tr>
</tbody>
</table>

### Effect of Blood Pressure on FFR/CFR/IMR

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Nitroprusside</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFR</td>
<td>$2.9 \pm 0.9$</td>
<td>$2.5 \pm 1.2$</td>
</tr>
<tr>
<td>IMR, U</td>
<td>$23.85 \pm 6.1$</td>
<td>$24.00 \pm 7.9$</td>
</tr>
<tr>
<td>FFR</td>
<td>$0.88 \pm 0.04$</td>
<td>$0.87 \pm 0.05$</td>
</tr>
</tbody>
</table>

### Change in LV Contractility and FFR/CFR/IMR

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFR</td>
<td>$3.0 \pm 1.0$</td>
<td>$1.7 \pm 0.6^\dagger$</td>
</tr>
<tr>
<td>IMR, U</td>
<td>$22.2 \pm 6.0$</td>
<td>$23.6 \pm 8.2$</td>
</tr>
<tr>
<td>FFR</td>
<td>$0.88 \pm 0.06$</td>
<td>$0.87 \pm 0.06$</td>
</tr>
</tbody>
</table>

Reproducibility of IMR

Mean correlation coefficients of IMR, CFR and FFR values comparing baseline measurement with each hemodynamic intervention

\[ P < 0.05 \]

Reproducibility of IMR

Coefficient of variation between pairs of baseline values of IMR and CFR

P < 0.01

Reproducibility of IMR

Repeated IMR measurements obtained by 4 different operators in 12 STEMI patients were highly correlated \((r=0.99, \ P<0.001)\), with a mean difference between IMR measurements of 0.01 (mean standard error 1.59 [95% CI −3.52 to 3.54], \(P=0.48\)).

An IMR $\leq 25$ is considered normal

- The mean IMR measured in 15 subjects (22 arteries) without any evidence of atherosclerosis and no/minimal risk factors was $19\pm5$.

- The mean IMR measured in 18 subjects with normal stress tests and normal coronary angiography was $18.9\pm5.6$. 

Luo, et al. Circ Cardiovasc Interv 2014;7:
IMR and Epicardial Stenosis

Role of collaterals when measuring IMR in patients with significant epicardial stenosis

- Resistance = \( \frac{\text{Pressure}}{Q_{\text{myo}}} \)
- \( Q_{\text{myo}} = Q_{\text{cor}} + Q_{\text{coll}} \)
- Simplified IMR = \( P_d \times T_{mn} \)
- But \( T_{mn} \) is inversely proportional to coronary flow

Importance of Collaterals when Measuring IMR

\[
\begin{align*}
Q_{\text{cor}} & \quad Q_{\text{coll}} & \quad P_d & \quad R_{\text{myo}} \\
\uparrow & \quad \uparrow & \quad \uparrow & \quad \uparrow \\
\uparrow & \quad \uparrow & \quad \uparrow & \quad \uparrow \\
\uparrow & \quad \uparrow & \quad \uparrow & \quad \uparrow
\end{align*}
\]

Importance of Collaterals when Measuring IMR

To measure true IMR, must measure coronary wedge pressure to incorporate collateral flow

\[ \text{IMR} = P_d \times T_{mn} \times \left( \frac{\text{FFR}_{\text{cor}}}{\text{FFR}_{\text{myo}}} \right) \]

Flow ↓’s more than it should, T_{mn} ↑’s and IMR_{app} = P_d \times T_{mn} ↑’s

*To measure true IMR, must measure coronary wedge pressure to incorporate collateral flow*
IMR is not affected by epicardial stenosis severity:

**Animal Validation**

![Graph showing IMR values across different stenosis severities.](image)

IMR<sub>app</sub>

p < 0.001

IMR

p = 0.30

Circulation 2004;109:2269-2272
IMR is not affected by epicardial stenosis severity:

**Human Validation**

<table>
<thead>
<tr>
<th>Stenosis</th>
<th>FFR ± SD</th>
<th>IMR ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% AS</td>
<td>0.53 ± 0.19</td>
<td>22 ± 15</td>
</tr>
<tr>
<td>50% AS</td>
<td>0.90 ± 0.12</td>
<td>22 ± 15</td>
</tr>
<tr>
<td>75% AS</td>
<td>0.84 ± 0.08</td>
<td>23 ± 14</td>
</tr>
</tbody>
</table>

IMR is not affected by epicardial stenosis severity:

Estimating True IMR without Wedge

- IMR = P_d x T_{mn} x (\text{FFR}_{\text{cor}} / \text{FFR}_{\text{myo}})
- IMR = P_d x T_{mn} x ((P_d-P_w)/(P_a-P_w) / (P_d/P_a))

If there is a relationship between FFR_{cor} and FFR_{myo}, perhaps we can estimate FFR_{cor} without having to measure the coronary wedge pressure.

In a derivation cohort of 50 patients, a strong linear relationship was found between $\text{FFR}_{\text{cor}}$ and $\text{FFR}_{\text{myo}}$.
Estimating True IMR without Wedge

In a validation cohort of 72 patients, there was no significant difference in IMR with estimate $\text{FFR}_{\text{cor}}$ or measured $\text{FFR}_{\text{cor}}$.

Estimating True IMR without Wedge

In a validation cohort of 72 patients, there was no significant difference in IMR with estimate $FFR_{cor}$ or measured $FFR_{cor}$.

Clinical Application of IMR

59 year old man with HTN, dyslipidemia and chest pain with emotional stress and septal ischemia on Nuclear Scan
IMR = 76 \times 0.70 = 53
Chest Pain and “Normal Coronaries”

- 139 patients referred for coronary angiography because of symptoms and/or abnormal stress test and found to have “normal” appearing coronaries

- FFR, IMR, CFR, IVUS and acetylcholine challenge were performed down the LAD

## Chest Pain and “Normal Coronaries”

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>n=139</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54 ±11</td>
</tr>
<tr>
<td>Female</td>
<td>77%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>53%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>23%</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>63%</td>
</tr>
<tr>
<td>Tobacco Use</td>
<td>8%</td>
</tr>
</tbody>
</table>

Chest Pain and “Normal Coronaries”

- The mean IMR was 19.6 ±9.1
- Microvascular dysfunction was present in 21% (defined as IMR ≥ 25)
- Predictors of microvascular dysfunction were age, diabetes, HTN, and BMI

Chest Pain and “Normal Coronaries”

- 5% of patients had an FFR of the LAD ≤ 0.80
- 44% had epicardial endothelial dysfunction
- 58% had a myocardial bridge
- 24% had nonischemic FFR, normal IMR, no endothelial dysfunction and no “bridge”

**IMR Before PCI in Stable Patients**

*IMR measured before PCI in 50 stable patients undergoing LAD PCI*

Predictive Value of IMR after PCI for STEMI

**IMR predicts peak CK in patients with STEMI**

![Graph showing IMR predicts peak CK in patients with STEMI](graph.png)

- **IMR ≤32**: 1201 ± 911
- **IMR >32**: 3128 ± 1634

*J Am Coll Cardiol 2008;51:560-5*
IMR and Outcomes post STEMI

Multicenter study evaluating relationship between IMR and longer-term outcomes in 253 STEMI patients

*Circulation 2013; 127:2436-2441.*
IMR post Stem Cell Therapy

IMR measured in 15 patients with ischemic cardiomyopathy before and 6 months after intracoronary stem cell delivery

IMR post Statin Therapy

*IMR measured after PCI in 80 patients randomized to either 1 month pretreatment with pravastatin or placebo*
IMR post ACE Inhibitor Therapy

40 patients randomized to IC enalaprilat or placebo prior to PCI

Limitations of IMR

- Invasive

- Interpatient and intervessel variability?
  - Sensor distance

- Independent of epicardial stenosis
  - Coronary wedge pressure
Conclusion

Take Home Messages:

- The microvasculature is a complex entity, which is challenging to investigate.

- Measurement of IMR is easy, specific for the microvasculature, quantitative, reproducible, and independent of hemodynamic changes.

- Measurement of IMR may help guide treatment in patients with “normal coronaries” and chest pain. IMR predicts outcomes in acute MI; emerging data suggest its utility in stable PCI patients, as well.