How to Evaluate Microvascular Function and Angina

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Angina without Coronary Artery Disease (CAD)

- Prevalence: 20-30% going cangiography, with a higher prevalence (almost 50%) in women.

- The 5-year rate of MACE outcomes were 3-fold higher in symptomatic women with normal coronary arteries and approximately 8-fold higher in symptomatic women with nonobstructive CAD compared with asymptomatic women without CAD.

Angina Pectoris and Myocardial Ischemia Without Obstructive CAD

- Cardiac syndrome X (CSX)
  1) Typical exercise-induced angina
  2) Documented stress-induced myocardial ischemia
  3) Absence of obstructive atherosclerotic CAD
  4) Absence of vasospastic angina
     - Female predominance: 70% of CSX
     - In WISE study, almost half of the women with no obstructive CAD showed abnormal CFR consistent with coronary microvascular dysfunction (CMD)
Angina Pectoris and Myocardial Ischemia in the Absence of Obstructive CAD

- **Microvascular angina**
  - 1)+2)+3)+4)+5) Active demonstration of CMD (positive acetylcholine and/or adenosine test results)
  - As many as 50% to 65% of angina patients without obstructive CAD are believed to have CMD, also known as microvascular angina.
Coronary Microvascular Circulation

- Current cardiovascular imaging technologies are unable to image the vessels that are smaller than 500 μm in diameter.
Assessment of Coronary Microvascular Function

- Study of the coronary microcirculation is indirect parameters, such as coronary blood flow and coronary flow reserve (CFR), which reflect its functional status.
- Lack of uniform diagnostic criteria.
- Relative contributions of CMD to pathologic microvascular angina are poorly understood yet.
Prognosis of CMD or Microvascular Angina

- 20% higher rate of cardiovascular events (death, acute coronary syndromes, stroke, and need for revascularization) at 46-month follow-up.
  

- Microvascular dysfunction was associated with a 3.3-fold increase in the risk of cardiac death at 12 years (36.9%) compared with subjects having a normal endothelial function.

F/45, exertional chest pain and dyspnea for 2 years
CFR measured by Flow Wire
Non-Invasive Methods to Assess the Microvascular Function

- Exercise stress test, exercise treadmill test (ETT): low accuracy, in-sensitive
- Traditional stress imaging; stress imaging techniques (stress echocardiography, nuclear perfusion stress testing) remain insensitive in diagnosing CMD.
  - Standard noninvasive imaging (stress echo and myocardial perfusion SPECT) is often normal in CMD.

Camici PG et al. Circulation 992;86:179-86
Non-Invasive Assessment of Coronary Microcirculation

- PET (positron emission tomography) scan:
  - Most established non-invasive technique for the assessment of CBF, regional MBF and reserve
Why PET?
- Comparison of PET and SPECT Perfusion Imaging
### Diagnostic Accuracy of PET Myocardial Perfusion Imaging

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Flow Quantification by PET

A

Stress

SA

VLA

HLA

Rest

B

Stress

SA

VLA

HLA

Rest

Qualitative Perfusion

Quantitative Flow Polarmaps

LV Average

Flow Reserve: 3.3

2.3 ml/min/g

0.7 ml/min/g

1.2 ml/min/g

Flow Reserve: 1.2

1.0 ml/min/g
Myocardial Blood Flow And Reserve by PET

- Provides insight into early and subclinical abnormalities in coronary arterial vascular function and/or structure, non-invasively
- Predict Prognosis

Non-Invasive Assessment of Coronary Microcirculation

- MRI
  - Can also be used for quantification of myocardial blood flow
Phase-Contrast Cine MRI

- RPP (mm Hg/min) = Systolic blood pressure (mm Hg) \times Heart rate (beats/min)
- Corrected coronary sinus flow (mL/min) = coronary sinus flow (mL/min) / RPP (mm Hg/min) \times 7500
- The CFR were calculated as: CFR = Corrected coronary sinus flow during ATP infusion (mL/min)/Corrected coronary sinus flow at rest (mL/min)

Invasive Assessment of CMD

- TIMI Frame Count and TIMI Frame Count Reserve
- TIMI Myocardial Perfusion Grade
- Coronary Reactivity Test
  - Coronary blood flow reserve (CFR)
  - Index of microvascular index (IMR)
  - Hyperemic microvascular resistance index
Coronary Reactivity Test

• Assessment of endothelium-dependent CFR by acetylcholine
• Assessment of endothelium-independent CFR by adenosine
• A >50% increase in CBF above baseline in response to acetylcholine and a CFR >2.5 in response to adenosine is considered normal.
Normal Flow in the Absence of MI: 21.0 ± 3.1 Frames

**First Frame Definition**

- **Frame 0**: Dye Touches One or No Borders
- **Frame 1**: Dye Touches Both Borders & Moves Forward

**Last Frame Definition**

**Distal Landmark**

- **RCA**: 1st branch off posterolateral
- **LCX**: Last branch off most distal OM
- **LAD**: “Whale’s tail” or “pitchfork” or most distal branch LAD at apex

Myocardial Blush

- Following contrast injection into the coronary arteries, there is late filling of the distal capillaries.
- In order to visualize myocardial blush, it is important to remain on the cine pedal for an extended period.
TIMI Myocardial Perfusion Grade (TMPG)

- **TMPG 0**
  No appearance of blush or opacification of the myocardium

- **TMPG 1**
  Presence of blush but no clearance of contrast (stain is present on the next injection)

- **TMPG 2**
  Blush clears slowly – clears minimally or not at all during three cardiac cycles

- **TMPG 3**
  Blush begins to washout and is only minimally persistent after three cardiac cycles
TIMI Myocardial Perfusion (TMP) Grades

TMP Grade 3
Normal ground-glass appearance of blush. Dye mildly persistent at end of washout.

TMP Grade 2
Dye strongly persistent at end of washout. Gone by next injection.

TMP Grade 1
Stain present. Blush persists on next injection.

TMP Grade 0
No or minimal blush.

TMPG

- Simple, however, several limitations
  - Inter- and intraobserver variability
  - Semi-quantitative, subjective

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<td>Intraobserver variability</td>
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<td>Interobserver variability</td>
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CFR by Intracoronary Doppler

- \( \text{CFR}_{doppler} = \frac{\text{hAPV}/2 \times \text{CSA}}{\text{bAPV}/2 \times \text{CSA}} \)
- \( = \frac{\text{hAPV}}{\text{bAPV}} \)
CFR by Pressure Wire (Thermodilusion Method)

- CFR thermo = mean bTMN / mean hTMN
CMD in Women Without or Non-Obstructive CAD

**All Women**

- % Event-Free Survival
- Years Follow-Up
- CVR ≥2.32 (n=115)
- CVR <2.32 (n=74)
- p=0.003 (Log Rank)

**Women without CAD**

- % Event-Free Survival
- Years Follow-Up
- CVR ≥2.32 (n=97)
- CVR <2.32 (n=56)
- p=0.004 (Log Rank)

CFR After Primary PCI for AMI in Predicting Long-Term MACE

Takahashi T, et al. Am J Cardiol 2007;100:806

BCV: 1.3
Sensitivity: 86%
Specificity: 70%
AUC: 0.80

p < 0.0001
Advantages and Limitations of CFR

- Advantages
  - Concrete Data for microvascular angina
  - Abnormal value between 2.0-2.5

- Another factors affecting CFR
  - LVH, LVEDP, HR, Age, Hemodynamic conditions
IMR
(Index of Microvascular Resistance)

- Resistance = $\Delta$ Pressure / Flow
- $1 / T_{mn} \simeq$ Flow
- $IMR = (P_d - P_v) / (1 / T_{mn})$
- $IMR = P_d \times T_{mn}$

*at maximal hyperemia*
Measurement of IMR

IMR = 15 U
Case 1 : IMR

M/64 STEMI (ant.)  IMR : 11.7 U
Case 1: FDG PET

Myocardial viability with FDG PET

FDG Uptake = 70.7%
Case 2: IMR

M/60 STEMI (ant.)

IMR: 72.3 U

Pa mean: 1.06
Pd mean: 0.94
FFR: 1.7
CFR: 4.98

Baseline (1.24): 1.33, 1.23, 1.17
Hypotension (0.73): 0.46, 0.82, 0.90

dT: -0.10

Reset button
Case 2 : FDG PET

Myocardial viability with FDG PET

FDG Uptake = 37.4%
Prognostic Value of the IMR

- The Kaplan–Meier curves between IMR >40 and survival free of death or rehospitalization for heart failure.

![Graph showing Kaplan–Meier curves between IMR >40 and survival free of death or rehospitalization for heart failure.](image)

*P = 0.030

Combined Index (IMR and CFR) in AMI

Ahn SG et al. J Am Coll Cardiol Intv 2016;--:---
Advantage of IMR

Correlation between IMR and TMR at 24 different combinations of myocardial resistance and epicardial stenosis severity

Advantage of IMR

Mean correlation coefficients of IMR, CFR, FFR values comparing baseline measurements with each hemodynamic intervention.

Repeat baseline / RV pacing at 110 bpm
Nitroprusside infusion / dobutamine infusion

Correlation with base line

IMR  CFR  FFR

Martin et al. Circulation 2006;113;2054-2061
Limitations of IMR

• Invasive
• Interpatient variability?
  – Sensor distance (in the distal 2/3 of the vessel)
• Normal value?
• No clinical data in patients with angina and non-obstructive CAD
• Independent of epicardial stenosis
  – Coronary wedge pressure
Hyperemic Microvascular Resistance Index (hMVRI) vs. IMR

- hMVRI (mmHg cm sec\(^{-1}\)) = \(\frac{Pd}{hAPV}\) (by Combo Wire)

- IMR = \(Pd \times Tmn\) (by Radi Wire)
ComboMap®:
Pressure and Flow System, Software
Version 2.1

3mm

Doppler Velocity Transducer
Pressure Sensor
Measurement of hMVRI by Combo Wire

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✓ hMVRI (mmHg⋅cm⋅sec⁻¹) = Pd/hAPV

= 91/27 = 3.37 mmHg⋅cm⋅sec⁻¹
hMVRI and LV-WMA

\[ r = 0.443, \ p = 0.002 \]

Kaplan-Meier event free survival analysis for MACE

Why Should We Measure the Coronary Microvascular Function?

• Microvascular function is an important prognostic factor in a wide range of disease.

• In recent years, evidence has shown that CMD is a true clinical entity rather than a mystery or an academic curiosity.

• Measurement of CMD and identifying the mechanisms of angina is important to provide a rational treatment strategy and improving the quality of life and long-term prognosis.
Thank You for Your Attention