Evolving Progress of Cardiovascular Imaging
Redefining its Role in Biomedical Research and Clinical Practice

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The increasing power of imaging in diagnosis and management of CV disease

- Non-invasive
- High resolution
- Targeted
- Quantitative
Evolving Progress of Imaging Across the Continuum of Biomedical Research and Clinical Practice

- Translational Research
- Diagnosis and Risk Assessment
- Guide Therapy and Predict Benefit
- Treatment Monitoring
- Imaging Markers as Surrogate End Points in Clinical Trials
CMD is implicated in the pathophysiology and manifestations of a broad spectrum of CV disease

- Ischemic heart disease
- HFpEF
- Valvular heart disease
- Cardiomyopathies

Source: Chilian WM. J Nucl Cardiol 2001;8:599-605
The absence of obstructive stenosis fails to explain symptoms or risk in many patients with stable chest pain.

11,223 patients referred for coronary angiography between 1998–2009

Sources: Jespersen L et al. EHJ 2012;33:734-44; Maddox TM et al. JAMA. 2014;312(17):1754-63
We can no longer assume that a normal coronary angiogram implies a normal coronary vasculature.
Imaging based phenotyping of CMD in atherosclerosis

**atherosclerosis**

- Measures integrated hemodynamic effects of epicardial CAD, diffuse atherosclerosis and vessel remodeling, and micro-circulatory dysfunction (endothelial dysfunction, obstruction, and rarefaction) on myocardial tissue perfusion.

**microvascular dysfunction**

- **Epicardial Arteries (> 400 μm)**
- **Small Arteries (< 400 μm)**

**myocardial fibrosis**

**diastolic dysfunction**

- Image Acquisition during Inversion Recovery
- Time
- RF pulses
- TI = 40 ms, TI = 120 ms, TI = 200 ms, TI = 280 ms, TI = 360 ms
New developments about CMD in atherosclerosis

1. Definition, pathophysiology and clinical presentation
2. Diagnosis and prevalence
3. A marker of ischemia and clinical risk
4. A target for therapy?
Definition and Pathophysiology of CMD

Coronary microvascular disease is heart disease that affects the structure and function of the small coronary artery vessels.

**Structural abnormalities**
- Arteriolar remodeling (SMC thickening)
- ↓ capillary diameter and density (rarefaction)
- ↑ endothelial swelling and capillary obstruction

**Functional abnormalities**
- Vascular EC dysfunction
- SMC dysfunction
- MCV spasm

Diffuse Atherosclerosis: A common finding in patients with chest pain without obstructive stenosis

CMD - Clinical Manifestations

- Asymptomatic
- Angina pectoris
- Dyspnea
- Heart failure

Source: Crea, Camici, Bairey Merz. EHJ 2014;35: 1101–11
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Diagnosis of CMD

1. Symptoms (w/o obstructive CAD)
2. Signs of ischemia (ECG)
3. Direct measurement of coronary flow (PET, CMR, Echo)

Source: Chilian WM. J Nucl Cardiol 2001;8:599-605
High prevalence of CMD in symptomatic patients without obstructive CAD

N=1,218

Female
n=813
54% 46%
- CFR > 2.0
- CFR < 2.0

Male
n=405
51% 49%
- CFR > 2.0
- CFR < 2.0

Source: Murthy V...Di Carli M. Circulation 2014;129:2518-2527
Prevalence of CMD across the spectrum of cardiometabolic risk

Source: Osborne M...Di Carli M. JACC 2017, Dec 5;70(22):2835-37
High prevalence of CMD in obese patients

Source: Bajaj N... Di Carli M, Taqueti V. 2017, under review
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51 yo M with CAD, recent STEMI and DES to pLAD in 2/16, HTN, Type 1 DM, diabetic nephropathy s/p renal transplant in 2008, p/w several hours of chest pain and dyspnea.

Quantitative myocardial blood flow and CFR

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Stress</th>
<th>CFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>0.82</td>
<td>1.23</td>
<td>1.50</td>
</tr>
<tr>
<td>LCX</td>
<td>0.83</td>
<td>1.34</td>
<td>1.62</td>
</tr>
<tr>
<td>RCA</td>
<td>0.81</td>
<td>1.13</td>
<td>1.39</td>
</tr>
<tr>
<td>Global LV</td>
<td>0.82</td>
<td>1.23</td>
<td>1.50</td>
</tr>
</tbody>
</table>

RCA FFR=0.78
CMD affects the severity of myocardial ischemia even in the absence of epicardial stenosis


**Diagram:**
- Conductive Arteries (diameter > 500 μm)
- Prearterioles (diameter 500–100 μm)
- Arterioles (diameter <100 μm)

**Y-axis:** Coronary blood flow
- 0
- 1
- 2
- 3
- 4

**X-axis:** Coronary pressure

- MCD
- Autoregulation

Severe ischemia is only partially accounted for by the extent/severity of angiographic stenosis.

Source: Christensen T...Di Carli M. 2017, under review
Adjusted cardiac mortality by severity of CFR impairment

N= 2,783
CD= 137

Lower Tertile vs. Upper: HR 5.6 [2.5-12.4] p<0.0001
Middle Tertile vs. Upper: HR 3.4 [1.5-7.7] p=0.003

CFR Reclassifies Risk of Cardiac Death in Diabetics

*Adjusted for Duke score, ischemia + scar, rest LVEF and early revascularization

Source: Murthy VL...Di Carli M. Circulation. 2012;126:1858-1868
CMD and risk stratification across the spectrum of cardiometabolic risk

Source: Osborne M...Di Carli M. JACC 2017, Dec 5;70(22):2835-37
Proposed pathophysiologic link between CMD and clinical outcomes and role of imaging and serum biomarkers

- Obesity,
- Hypertension,
- Diabetes Mellitus,
- CKD, CAD

> Inflammation

Risk Factors → CMD → Structural changes → Myoc Injury/fibrosis → MCV Ischemia → (PET, SPECT, CMR, CTA)

Symptoms → (CPET)

- (Echo, BNP)

- (CMR, hs-Tn)
Association between CMD, myocyte injury, and outcomes in patients w/o obstructive CAD

Annualized event rates adjusted for pretest clinical score, LVEF, and estimated glomerular filtration rate <60 mL.min\(^{-1}\).1.73 m\(^{-2}\).

**Table 2. Association Between CFR and Positive Troponin**

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Univariable Model</th>
<th>Multivariable Model*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>CFR(_{\text{mean}})†</td>
<td>2.45 (1.57–3.82)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CFR(_{\text{continuous}})†</td>
<td>1.80 (1.34–2.43)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*Adjusted for pretest clinical score, left ventricular ejection fraction, estimated glomerular filtration rate <60 mL.min\(^{-1}\).1.73 m\(^{-2}\), history of atrial fibrillation, and use of aspirin, \(\beta\)-blocker, statin, or angiotensin inhibitor.

Source: Taqueti VR...Di Carli M. Circulation. 2015 Feb 10;131(6):528-35
Reduced coronary microvascular density associates with fibrosis in HFpEF
Interstitial fibrosis and LV diastolic dysfunction

CMD, diastolic dysfunction, and HF hospitalizations

CFR and markers of diastolic dysfunction

A. Unadjusted

B. Adjusted

Freedom from Hospitalization for HF by CFR and E/e'

Freedom from Event (%)

Days

N = 101

p < 0.001

Adapted Annualized Rate of HF Hospitalization (%)

E/e’ refers to E/e’ skeletal

Adjusted for pretest clinical score and detectable troponin

Source: Taqueti VR...Di Carli M. EHJ 2017, in press
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# Medical management of MCD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline CFR &lt; 2.5</th>
<th>No CAD ≥50% Stenosis</th>
<th>Mode of Assessing CFR or MPR</th>
<th>Patients (n)</th>
<th>Findings</th>
<th>First Author, Year (Ref. #)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renin/angiotensin/aldosterone inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Eplerenone 25 mg</td>
<td>No</td>
<td>Yes</td>
<td>IC Doppler</td>
<td>25</td>
<td>Angina ↑, CFR ↑</td>
<td>Bavry et al., 2014 (44)</td>
</tr>
<tr>
<td>Candesartan 4-8 mg</td>
<td>NA</td>
<td>No</td>
<td>IC Doppler</td>
<td>14</td>
<td>CFR ↑</td>
<td>Iino et al., 2012 (74)</td>
</tr>
<tr>
<td>Enalapril 5 mg 2× daily</td>
<td>No</td>
<td>Yes</td>
<td>IC Doppler</td>
<td>10</td>
<td>Angina ↑, CFR ↑</td>
<td>Chen et al., 2002 (75)</td>
</tr>
<tr>
<td>Enalapril 10-20 mg/day</td>
<td>No</td>
<td>Yes</td>
<td>Argon dilution</td>
<td>15</td>
<td>Symptoms ↑, CFR ↑</td>
<td>Motz et al., 1996 (43)</td>
</tr>
<tr>
<td>Enalapril 5-10 mg 2× daily</td>
<td>No</td>
<td>Yes</td>
<td>PET</td>
<td>10</td>
<td>Exercise capacity ↑</td>
<td>Kasdi et al., 1994 (42)</td>
</tr>
</tbody>
</table>

| Statins | | | | | | |
| Fluvastatin 40 mg | Yes | Yes | TTDE | 23 | Angina ↑, CFR ↑ | Zhang et al., 2014 (50) |
| Atorvastatin 80 mg | No | No | IC Doppler | 20 | CFR ↑ | Eshleman et al., 2012 (51) |
| Atorvastatin 20 mg | Yes | Yes | TTDE | 20 | CFR ↑ | Galis et al., 2007 (52) |

| Nitric oxide modulators | | | | | | |
| L-arginine 1-time infusion | No | Yes | IC Doppler | 11 | CBF ↓ | Gellman et al., 2004 (58) |
| Tetrahydrobiopterin 1-time infusion | No | No | IC Doppler | 23 | CBF ↑ | Setoguchi et al., 2001 (76) |
| L-arginine infusion 3 g 3× daily | No | No | IC Doppler | 13 | Angina ↑, CFR ↑ | Lerman et al., 1998 (59) |
| L-arginine 1-time infusion | No | No | IC Doppler | 8 | CBF ↑ | Egashira et al., 1996 (57) |

| Calcium-channel blockers | | | | | | |
| Diltiazem 90 mg | No | Yes | TTDE | 23 | Angina ↑, CPR ↑ | Zhang et al., 2014 (50) |
| Lidoflazine 240-360 mg | No | Yes | Thermodilution | 11 | Angina ↑, MFR ↑, Arrhythmias* | Cannon et al., 1990 (48) |
| Verapamil 80 mg 4× daily | No | Yes | Thermodilution | 17 | Angina ↑ | Cannon et al., 1985 (47) |
| Nifedipine 10 mg 4× daily | No | Yes | Thermodilution | 9 | Angina ↑ | Cannon et al., 1985 (47) |

| Alpha-blockers | | | | | | |
| Doxazosin 2 mg | No | Yes | PET scan | 11 | Angina ↑, CBF ↓ | Rosen et al., 1999 (63) |

| Antianginal agents and nitrates | | | | | | |
| Ivabradine 5 mg | Yes | Yes | TTDE | 29 | Stress testing ↑ | Villano et al., 2013 (68) |
| Isosorbide dinitrate 5 mg (SL) | NA | Yes | TTDE | 29 | Stress testing ↑ | Russo et al., 2013 (69) |
| Ranolazine 500-1,000 mg | No | Yes | CMR | 20 | Angina ↑, CFR ↑ | Mehta et al., 2011 (67) |
| Isosorbide dinitrate 10 mg (SL), 2 mg (IV) | NA | Yes | Thermmodilution | 11 | Angina ↑, CBF ↓ | Bugiardini et al., 1993 (70) |

| Estrogens | | | | | | |
| 17β-estradiol 1 mg + drospirenone 2 mg | No | NA | PET | 27 | MFR ↑ | Knutti et al., 2007 (63) |

| Devices | | | | | | |
| EECP | Yes | Yes | TTDE | 24 | Angina ↑, CFR ↑ | Luo et al., 2012 (65) |
| TENS | NA | Yes | IC Doppler | 13 | CBF ↓ | Sanderson et al., 1996 (66) |

| Other | | | | | | |
| Bariatric surgery | Yes | NA | TTDE | 50 | CBF ↑ | Nerla et al., 2012 (72) |
| Cogniac | No | NA | TTDE | 18 | CFR ↑ | Kiviniemi et al., 2008 (77) |
| Vitamin C 3 g infusion | No | NA | PET | 19 | CFR ↑ in asymptomatic smokers | Kaufmann et al., 2000 (78) |
| Exercise training | No | No | PET | 13 | CFR ↑ | Czernin et al., 1995 (71) |
Potential role of novel therapies

- Inflammation reduction (CIRT-CFR)
- Lipid management
- Metabolic modulators
- Neurohormonal inhibition
- MR receptor antagonists (SPIN-D)
- Rho kinase inhibition (ANOCA)
CIRT-CFR trial

• Does reduction in systemic inflammation improve CFR?
• Is the improvement in CFR associated with improved LV function?

NHLBI-funded multicenter RCT allocating 7,000 pts with prior MI and T2DM or MS to LDM vs. placebo, primary outcome MACE (CD, MI, stroke) target follow-up 3 yrs

NCT02786134
Summary

• We have seen fantastic progress
• Quantitative imaging is helping us advance:
  – Mechanisms of disease
  – Early diagnosis
  – Drug discovery
  – Improving clinical trials
    • Enrich cohorts
    • Mechanistic insights into how drugs work