Coronary microvascular dysfunction in arterial hypertension

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IN DEPTH

Reappraisal of Ischemic Heart Disease
Fundamental Role of Coronary Microvascular Dysfunction in the Pathogenesis of Angina Pectoris

ABSTRACT: In recent years, it has become apparent that coronary microvascular dysfunction plays a pivotal pathogenic role in angina pectoris. Functional and structural mechanisms can affect the physiological function of the coronary microvasculature and lead to myocardial ischemia in people without coronary atheromatous disease and also in individuals with obstructive coronary artery disease. Abnormal dilatory responses of the coronary microvessels, coronary microvascular spasm, and extravascular compressive forces have been identified as pathogenic mechanisms in both chronic and acute forms of ischemic heart disease. The condition characterized by anginal symptoms and evidence of myocardial ischemia triggered by coronary microvascular dysfunction, in the absence of obstructive coronary disease, is known as microvascular angina. The
CORONARY MICROCIRCULATION

STRUCTURAL MECHANISMS
- Adverse arteriolar remodeling
  - Increased medial wall thickness
  - Intimal thickening
  - Reduced wall/lumen ratio
- Intravascular plugging
- Perivascular fibrosis
- Capillary rarefaction

FUNCTIONAL MECHANISMS
- Microvascular spasm
- Abnormal vasodilation
- Endothelial dysfunction and/or VSMC dysfunction

MYOCARDIAL FACTORS AFFECTING MICROVASCULAR FUNCTION
- Left ventricular hypertrophy
- Reduced diastolic time
- Calcium overload
- Amyloidosis
- Increased intramyocardial pressure
- Increased intracavitary pressure
- Tissue edema

Occlusive CAD
Coronary spasm
Coronary ATS and Myocardial Ischemia

**Coronary Vasodilator Reserve**

\[ Y = 6.73 - 0.13x + 7.8x^2 \]

\[ r = 0.77 \quad (N = 35) \]

**Percent diameter stenosis**

- Patients with CAD
- Normal subjects

**ATS: Coronary stenosis**

**In vivo anatomy**

**CFR reduction with stenosis severity**

- Normal subjects
- Patients with CAD

**Regional perfusion abnormality**

**Stress MPI**

**Rest MPI**

Low Diagnostic Yield of Elective Coronary Angiography

Manesh R. Patel, M.D., Eric D. Peterson, M.D., M.P.H., David Dai, M.S.,
J. Matthew Brennan, M.D., Rita F. Redberg, M.D., H. Vernon Anderson, M.D.,
Ralph G. Brindis, M.D., and Pamela S. Douglas, M.D.

RESULTS
A total of 398,978 patients were included in the study. The median age was 61 years;
52.7% of the patients were men, 26.0% had diabetes, and 69.6% had hypertension.
Noninvasive testing was performed in 83.9% of the patients. At catheterization,
149,739 patients (37.6%) had obstructive coronary artery disease. No coronary artery
disease (defined as <20% stenosis in all vessels) was reported in 39.2% of the pa-
tients. Independent predictors of obstructive coronary artery disease included male
sex (odds ratio, 2.70; 95% confidence interval [CI], 2.64 to 2.76), older age (odds
ratio per 5-year increment, 1.29; 95% CI, 1.28 to 1.30), presence of insulin-dependent
diabetes (odds ratio, 2.14; 95% CI, 2.07 to 2.21), and presence of dyslipidemia (odds
ratio, 1.62; 95% CI, 1.57 to 1.67). Patients with a positive result on a noninvasive test
were moderately more likely to have obstructive coronary artery disease than those
who did not undergo any testing (41.0% vs. 35.0%; P<0.001; adjusted odds ratio,
1.28; 95% CI, 1.19 to 1.37).
Table 1. Baseline Characteristics of the Patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N= 397,954)</th>
<th>Obstructive Coronary Artery Disease (N= 149,739)</th>
<th>No Obstructive Coronary Artery Disease (N= 248,215)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>61</td>
<td>66</td>
<td>58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>52–70</td>
<td>58–74</td>
<td>50–68</td>
<td></td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>47.3</td>
<td>33.9</td>
<td>55.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinical presentation (%)</td>
<td></td>
<td></td>
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<tr>
<td>No symptoms, including no angina</td>
<td>30.0</td>
<td>31.5</td>
<td>29.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atypical symptoms</td>
<td>36.8</td>
<td>24.6</td>
<td>44.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stable angina</td>
<td>33.2</td>
<td>43.9</td>
<td>26.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NONINVASIVE TESTING

Noninvasive testing (resting electrocardiography, echocardiography, computed tomography [CT], or a stress test) was performed in 83.9% of the patients before invasive angiography. A positive test result was recorded in the case of 68.6% of all the patients in the cohort. A noninvasive test was not
Angina is frequent after PCI

% of patients with angina at baseline versus 1 year post-PCI

- NHLBI, n=1755
- COURAGE, n=2287
- SYNTAX, n=1800
- BARI-2D, n=1434

Increasing with comorbidities

Case report

• Female, DoB 25/06/1964
• Family history for hypertension
• Never smoked
• Menopause since 7 years
• Hypertension diagnosed during pregnancy

• Since 4-5 years she complains of retrosternal pain with radiation to the left arm that occur both during exercise and at rest. During the episode sometimes she also experiences dyspnea.

• Recently she was admitted to hospital (ECG shows ST depression) for a prolonged episode of chest (no troponin). Coronary angiography shows normal smooth epicardial coronary arteries.
Baseline ECG

<table>
<thead>
<tr>
<th>Freq.</th>
<th>59</th>
<th>Ritmo sinusal.</th>
<th>asse P normale, freq. V 50-99</th>
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</thead>
<tbody>
<tr>
<td>RR</td>
<td>1028</td>
<td>Alterazioni T ai limiti, der. laterali.</td>
<td>T piatta/neg., I aVL V5 V6</td>
</tr>
<tr>
<td>PR</td>
<td>146</td>
<td>Instabilità linea di base in deriv. V5,V6</td>
<td></td>
</tr>
<tr>
<td>QRS</td>
<td>101</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QT</td>
<td>42A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTCb</td>
<td>421</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTCfma</td>
<td>423</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>69</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

12 deriv.; posizionamento standard

Unconfirmed Diagnosis
ECG during chest pain
**BOX 5.1 Key Points 1**

- Intramyocardial arterioles below 500 μm in diameter that are the main site of myocardial perfusion regulation make up the coronary microcirculation.
- Coronary microvascular dysfunction is an additional mechanism of myocardial ischemia.
- Dysfunction of the coronary microcirculation is caused by functional and/or structural alterations of the intramyocardial arterioles as well as by increased extravascular compression.
- No technique allows direct visualization of the anatomy of the coronary microcirculation in vivo in humans.
The emerging concept of coronary “microvascular disease”

The tip of the iceberg - Resolution >500μm

Resolution <500mm

Courtesy of M Gibson MD

Mechanisms of myocardial ischaemia

Epicardial coronary arteries

Atherosclerotic disease
- Stable plaque
  - Reduction in CFR
  - Demand ischaemia ± angina
- Vulnerable plaque
  - Plaque rupture
  - Thrombosis
  - Acute coronary syndromes/infarction

Vasospastic disease
- Focal/transient vasospasm
- Persistent vasospasm
- Prinzmetal angina
- Myocardial infarction

Coronary microcirculation

Microvascular dysfunction
- Impairs coronary physiology and myocardial blood flow in subjects with risk factors
  - Contributes to myocardial ischaemia in CAD and CMP
  - Induces severe acute ischaemia ‘Takotsubo’

These three mechanisms can overlap

Crea F, Camici PG, Bairey Merz CN Eur Heart J. 2014 May;35(17):1101-11
Microvascular dysfunction and MACE at follow up

Data adjusted for the modified Duke clinical risk score and rest LVEF
Patients with microvascular angina are more likely to develop HFpEF

* Cardiovascular death or hospitalization for myocardial infarction or heart failure
** Adjusted for pretest clinical score, history of AFib, estimated glomerular filtration rate <60 ml·min⁻¹·1.73m⁻², detectable troponin, left ventricular ejection fractions and E/e₉-septal >15

Signs and/or symptoms of angina

Objective evidence of myocardial ischemia

Absence of obstructive CAD (or coronary stenoses not responsible for ischemia)

Coronary microvascular dysfunction (i.e. CFR <2.5 or microvascular spasm)

Abbreviations: CAD, coronary artery disease; CFR, coronary flow reserve
In normal subjects myocardial blood flow (MBF) increases 3- to 5-fold during near-maximal pharmacologically induced vasodilatation (i.v. adenosine).

There is no *in vivo* technique for imaging the coronary microcirculation; Maximum myocardial blood flow is an index of microvascular function.

In the absence of coronary stenosis, maximum MBF reflects microvascular function.

**Diagram:**
- **MBF**
- **Normal subjects**
- **Patients with impaired microvascular function**
- **Flow deficit**
**PET: the gold standard for the non-invasive measurement of myocardial blood flow**

*PET with \( \text{H}_2^{15}\text{O} \) or \( ^{13}\text{NH}_3 \) allows accurate, reproducible and non-invasive measurement of absolute (ml/min/g) myocardial blood flow in man*

**Accuracy of PET MBF measurement**

\[ y = 0.15 + 0.97x, \quad r = 0.87, \quad r^2 = 0.76 \]

**Reproducibility of PET MBF measurement**

- **Baseline**
- **Adenosine**

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In the absence of obstructive CAD a reduced CFR suggests microvascular dysfunction.
Symptoms associated with Coronary Microvascular Dysfunction

Symptoms of myocardial ischemia

a. Predominantly effort angina (±rest)
b. Angina equivalents (i.e. shortness of breath)
c. Predominantly rest angina
Typically diffuse reduction of CFR
Microvascular Angina in Hypertension

- Angina and/or ischemic signs on ECG are common in patients with primary or secondary LVH

- Maximum myocardial blood flow and CFR are reduced despite angiographically normal coronary arteries

Rimoldi O & Camici PG. J Hypert 2014
Mechanisms of Coronary Microvascular Dysfunction “Vascular”

Structural changes

Remodelling of coronary arterioles

Normal Epicardial Coronary Arteries

Microcirculation

Normal heart

Hypertension

- Peri-myocitic fibrosis
- Thickening of the wall of intramural arterioles
- Increased wall/lumen ratio

Coronary arteriolar remodelling precedes onset of hypertension in the SHR model.
Fibrosis in primary and secondary LVH

<table>
<thead>
<tr>
<th>LGE: frequency</th>
<th>LGE: patterns</th>
<th>representative images</th>
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</thead>
<tbody>
<tr>
<td><strong>AH</strong></td>
<td></td>
<td></td>
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<tr>
<td><img src="image1.png" alt="Pie Chart" /></td>
<td><img src="image2.png" alt="Circle Diagram" /></td>
<td><img src="image3.png" alt="Image" /></td>
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<td><strong>HCM</strong></td>
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<td><img src="image4.png" alt="Pie Chart" /></td>
<td><img src="image5.png" alt="Circle Diagram" /></td>
<td><img src="image6.png" alt="Image" /></td>
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</tbody>
</table>

In HCM the late enhancement was predominantly antero–septal and infero–septal whilst in AH no specific pattern of fibrosis could be identified.

The pathway from hypertension to HF
“Role of microvascular ischemia”

Adapted from Drazner et al, Circulation, 2011
Can we treat microvascular remodelling in LVH?

Thickened small intramural vessel with luminal narrowing

(Bar indicates 20 μm)

Kanzaki Y et al. Circulation 2012;125:738-739
Pro- and anti-growth stimuli

The homogeneity of cardiac tissue is achieved through a balanced equilibrium between stimulator and inhibitor signals of cell growth.

**Stimulators**
- angiotensin II
- aldosterone
- deoxycorticost.
- endothelin
- catecholamine

**Inhibitors**
- nitric oxide
- bradykinin
- prostaglandin
- ANP
- glucocort.
Effects of perindopril/indapamide on blood pressure and LVH

Blood pressure

Left ventricular mass (MRI)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>After 6 months’ treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td>150 ± 10</td>
<td>125 ± 5</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>100 ± 5</td>
<td>75 ± 3</td>
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</tbody>
</table>

n=20 *P<0.01

Myocardial blood flow in patients after 6 months treatment with perindopril/indapamide


*P < 0.05, **P < 0.01 M0 vs M6
Coronary flow in SHR

Coronary flow (ml/min/g)

Baseline

Placebo

Per + Ind

Hyperaemia

Placebo

Per + Ind

Baseline

Placebo

Per + Ind

Minimal (hyperaemic)

Placebo

Per + Ind

**P < 0.01 placebo vs perindopril/indapamide

Correlation between microvascular remodelling and coronary flow

Placebo

Perindopril/indapamide

Medial area (μm²)

Placebo

Per/ind

**P < 0.001

Peak/baseline coronary flow

Placebo

Per/ind

Perindopril promotes Bradykinin and NO production

Effect of different drug classes on reverse remodeling of intramural coronary arterioles in the spontaneously hypertensive rat

Massimiliano Mancini, Angela Scavone, Carmelo Luiza Sartorio, Rocco Baccaro, Christina Kleinert, Angelina Pernazza, Veronica Bula, Martina Leopizzi, Giulia d’Amati, Paolo G. Camici

Hyperemic Coronary Flow

- SHR Placebo
- WKY
- Ramipril
- Perindopril
- Candesartan
- Atenolol
- Indapamide
- Amlodipine
- HMR1766

Medial Area

Lumen Area / Vessel Area

Lumen diameter

Vessel diameter

Hyperemic coronary flow (ml/min/g)

SHR
WKY
Ramipril
Perindopril
Candesartan
Atenolol
Indapamide
Amlodipine
HMR1766

***
***
*

Histological images:
- SHR
- WKY
- RAM
- PER
- CAN
- ATE
- IND
- AML
- HMR
Symptoms associated with Coronary Microvascular Dysfunction

Symptoms of myocardial ischemia

a. Effort and rest angina
b. Angina equivalents (i.e. shortness of breath)
c. Predominantly rest angina
Mechanisms of Coronary Microvascular Dysfunction “Vascular”

Functional changes
<table>
<thead>
<tr>
<th>Segmenti</th>
<th>Flusso STRESS</th>
<th>Flusso REST*</th>
<th>Riserva Coronarica</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ml/min/g</td>
<td>ml/min/g</td>
<td>S/R</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>SD</td>
<td></td>
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<td><strong>Territorio LDA</strong></td>
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<tr>
<td>1. Basale Anteriore</td>
<td>2,162</td>
<td>0,689</td>
<td>3,137</td>
</tr>
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<td>2. Basale Antero-Settale</td>
<td>2,691</td>
<td>0,723</td>
<td>3,722</td>
</tr>
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<td>7. Medio Anteriore</td>
<td>2,425</td>
<td>0,683</td>
<td>3,550</td>
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<tr>
<td>8. Medio Antero-Settale</td>
<td>2,852</td>
<td>0,721</td>
<td>3,954</td>
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<tr>
<td>13. Apicale Anteriore</td>
<td>2,400</td>
<td>0,700</td>
<td>3,428</td>
</tr>
<tr>
<td>14. Apicale Settale</td>
<td>2,798</td>
<td>0,705</td>
<td>3,967</td>
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<tr>
<td>17. Apice</td>
<td>1,937</td>
<td>0,683</td>
<td>2,837</td>
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<td><strong>Territorio LCX</strong></td>
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<tr>
<td>5. Basale Infero-Laterale</td>
<td>2,399</td>
<td>0,839</td>
<td>2,859</td>
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<td>6. Basale Antero-Laterale</td>
<td>2,430</td>
<td>0,751</td>
<td>3,234</td>
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<tr>
<td>11. Medio Infero-Laterale</td>
<td>2,203</td>
<td>0,754</td>
<td>2,921</td>
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<td>2,322</td>
<td>0,756</td>
<td>3,072</td>
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<tr>
<td>16. Apicale Laterale</td>
<td>2,093</td>
<td>0,680</td>
<td>3,079</td>
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<td><strong>Territorio RCA</strong></td>
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<td>3. Basale Infero-Settale</td>
<td>2,575</td>
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<td>4. Basale Inferiore</td>
<td>2,487</td>
<td>0,706</td>
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<td>9. Medio Infero-Settale</td>
<td>2,902</td>
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<td>2,152</td>
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<td>15. Apicale Inferiore</td>
<td>1,967</td>
<td>0,693</td>
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<tr>
<td><strong>GLOBALE</strong></td>
<td>2,412</td>
<td>0,724</td>
<td>3,331</td>
</tr>
</tbody>
</table>
Baseline
ACH – 20µg

No symptoms
No ECG changes
ACH – 100µg

Typical chest pain
Flat T waves
ACH – 200µg

Microvascular Spasm

Typical chest pain
ST depression
Anginal symptoms and documented myocardial ischemia*

Previous coronary angiogram showing normal coronary arteries or non-obstructive coronary artery disease

Assess CFR non-invasively (PET, ECHO, CMRI)

- CFR<2.5: Microvascular angina
  - No or <90% diameter reduction
  - No angina
  - No ischemic ECG changes

- CFR≥2.5: Acetylcholine test
  - No or <90% diameter reduction
  - + angina
  - + ischemic ECG changes

- ≥90% diameter reduction
  - + angina
  - + ischemic ECG changes

Adenosine test

- CFR>2.5 IMR<25: Investigate abnormal nociception
- CFR<2.5 IMR ≥25: Microvascular angina Endothelium independent dysfunction

Likely false positive tests for ischemia

Microvascular spasm

Epicardial coronary artery spasm

Ischemia likely due to severe atherosclerotic coronary artery disease

Coronary Angiography

Coronary stenosis**

- Absent: FFR ≥0.80
- Mild <50%
- Moderate 50-70%
- Severe >70%

** Coronary diameter reduction

*As assessed by ECG, SPECT, ECHO, Cardiac MRI

Moderate 50-70%
Mild <50%
Conclusions

Myocardial ischemia can be due to a number of different mechanisms that act alone or in combination.

- Each mechanism can be investigated using a combination of invasive and non-invasive tests.
- Understanding the underlying mechanism is the pre-requisite for the choice of the most appropriate therapeutic strategy.