Microvascular disease
Prevalence and Management
Obstructive disease of the epicardial coronary arteries was recognized as the cause of *Angina pectoris* >200 years ago.

Sudden thrombotic occlusion of an epicardial coronary artery has been established as the cause of *AMI* for >100 years ago.

*Coronary microvascular dysfunction* (CMD) emerged as a mechanism of myocardial ischaemia in the past 30 years.
an unsolved ‘mystery’ rather than a reality
“definition” of CMD

- Chest pain
- Evidence of myocardial ischemia
- No significant (<50%) coronary artery stenosis
FIGURE 1  Etiologies of Chest Pain Without Obstructive CAD

- Chest Pain Without Obstructive Coronary Artery Disease
<table>
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<tr>
<th>CMVD</th>
<th>Definition</th>
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<td>Type 1</td>
<td>Primary, i.e. in the absence of structural heart disease</td>
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<td>Type 2</td>
<td>In the presence of cardiomyopathies (incl. LVH, HCM, DCM, amyloidosis)</td>
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<td>Type 3</td>
<td>In the presence of obstructive CAD (incl. ACS)</td>
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<td>Type 4</td>
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increased **metabolic activity** leads to **vasodilatation**, which leads to **pressure reduction** in the medium-sized microvessels and myogenic dilation, which, in turn, increases flow upstream resulting in endothelium-dependent vasodilation.
Morning prayer for a prosperous stenting

The coronary angiogram detects only 5% of the total coronary tree
Structural abnormalities of CMD

LVH - HCM
medial wall thickening
(smooth muscle hypertrophy + collagen deposition)
intimal thickening

DCM Amyloid
Functional mechanisms of CMD

- Endothelium-dependent:
  - Diabetes, Obesity, Smoking, other CVRF

- Endothelium-independent:
  - Nitrate resistance owing to reduced production of c-GMP
  - Increased vasoconstriction
CMD: a generalised disorder rather than an isolated entity

impaired vasodilator response
limited hyperaemic response to forearm

sensitivity to vasoconstrictor stimuli
generalised hyper~responsiveness of systemic vascular and nonvascular smooth muscles (Pulmonary airway hyper~responsiveness in CMD~c/w oesophageal motility disorders)

Panic disorder present in at least 30% of CMD patients
Pathophysiology of microvascular angina

Myocardial ischemia — Diabetes — Hypertension

Insulin resistance — Estrogen deficiency — Inflammation

Endothelial dysfunction
Impaired vasodilation
↑ Vasoconstriction

Microvascular dysfunction

Microvascular angina
NIIDM

**DM+normal CFR:** very low annual cardiac mortality
~(CAD without WMA / perfusion defect)

**DM+abnormal CFR:** annual cardiac mortality
~(CAD without DM)

**early detection of cardiovascular abnormalities linked to insulin resistance??**
Dyslipidaemia

reduced CFR in asymptomatic individuals with hypercholesterolaemia and "normal" coronaries

the correlation observed between CFR and LDL
Tobacco smoking

inflammation and oxidative damage to the endothelium

these effects lead to reduced CFR by PET in apparently healthy smokers.

CMD affects both sexes equally

CFR was lower in smoking twins than in nonsmoking co-twins owing to an elevated resting MBF and reduced hyperaemic MBF
Severe impairment of microvascular function and myocardial fibrosis are both considerably more prevalent among patients with HCM who carry **mutations in genes encoding sarcomere proteins** than in mutation-negative patients.

Describing the long-term outcomes of patients with HCM, a **hyperaemic flow value <1.1 ml/min g⁻¹ by PET** was the most powerful independent predictor of **adverse outcome**, with a 9.6-fold increase in age-adjusted **relative risk of death**.
Aortic stenosis

In AS, CMD is caused by an increase in intramyocardial pressure, caused by raised extravascular compressive forces.

Total resting MBF is increased proportionally with LV mass in AS, suggesting that demand of the hypertrophied myocardium was met by an increased baseline MBF.

By contrast, CFR was severely reduced in both the sub-epicardium and the subendocardium, and was inversely correlated with AVA.
CAD

CFR is often abnormal in territories subtended by nonstenotic arteries

known or suspected CAD: (in nearly 4,000 patients)

A global CFR < 2 ($^{13}$NH$_3$-PET) increased MACE/ Mortality/10year F/U

CFR (<1.5) associated with a 5.6-fold increase in the risk of cardiac death vs that in the highest tertile (>2)
Absolute MBF measurements facilitate the recognition of globally impaired responsiveness to vasodilators in heart failure of nonischaemic aetiology and characterized by diffuse CMD, such as Dilated Cardiomyopathy.
microvascular obstruction on cardiac MRI is an independent predictor of adverse clinical outcome, alone or adjusted for other factors such as infarct size and LVEF
CASES
A 57-year-old postmenopausal woman was admitted to the hospital because of worsening *angina pectoris*.

A diagnosis of **syndrome X 3 years earlier** on the grounds of *chest pain*, positive ETT, and *angiographically* normal coronary arteries.

RF: hypertension, overweight, hypercholesterolemia.

Angina persisted despite use of *diltiazem*, *nitrates*, *simvastatin*, and *imipramine*.

**ETT**: *chest pain*, *2-mm ST-segment depression*, 5 min

**Sestamibi**: *reversible defect* in the anterior region
- Exertional Angina
- Abnormal SPECT

**Coronary microvascular dysfunction**  
**BEFORE you see the plaque?** (unless you do IVUS)

- Diffuse atherosclerosis by IVUS~ occult plaque of the proximal LAD occupying 45% of the vessel area, with vessel remodelling

- False positive SPECT or False negative angiogram?
seeing is believing
ischaemia related to **microvascular constriction** in humans

intra-coronary injection of **acetylcholine**.

In normal coronary arteries, these agents can cause chest pain and objective evidence of **myocardial ischaemia** in the absence of relevant changes to epicardial arteries.
74 yrs female with exertional Chest pain and SOB

CV risk factors

ETT: Chest pain/SOB but no ECG changes

Coronary angio: 50% distal LCx ~ LVEDP 25mmHg
Figure 2. Left circumflex artery and the 12-lead ECG after 200 μg acetylcholine (left) showing ST-segment depression in leads V₄ through V₈ but no significant epicardial vasoconstriction. The patient had full reproduction of her usual symptoms. After intracoronary nitroglycerine (right), symptoms and ECG shifts normalized.
Transient Myocardial Ischemia During Acetylcholine-Induced Coronary Microvascular Dysfunction Documented by Myocardial Contrast Echocardiography

Peter Ong, MD; Anastasios Athanasiadis, MD; Heiko Mahrholdt, MD; Benoy N. Shah, MBBS; Udo Sechtem, MD; Roxy Senior, MD
Abnormal *regional* glucose uptake has been demonstrated using PET scanning, reflecting the presence of anaerobic glycolysis resulting from myocardial ischaemia. *Circulation* 1990; 82: III249.
Uncertainty results in Therapeutic
control of chest pain and improvement in the quality of life

**Beta-blockers** ~ increased sympathetic activity.

**Calcium channel blockers** ~ Nifedipine, Diltiazem

**Nitrates** are effective only in 40-50% of patients.

**ACE inhibitors** ~ RAS affects coronary vasomotion

**Statins**

**Imipramine** ~ aminophylline ~ estrogen
a female pattern phenotype of ischaemic heart disease
Thank you
Εὐχαριστώ σας!
- Exertional Angina
- Abnormal SPECT
- NO obstructive CAD, good LVEF, LVEDP 18mmHg
Physiopathology-based approach to the treatment of patients with microvascular angina.
Assessment of coronary microcirculation

no technique allows direct visualization

Coronary flow reserve (adenosine, dipyridamole)

Transthoracic Doppler echocardiography

Myocardial contrast echocardiography

Positron emission tomography

Cardiac MRI
Algorithm for the diagnosis of patients with suspected microvascular angina.
No reflow
**FIGURE 5** Assessment of Microvascular Inducible Ischemia Using CMR

**Invasive Coronary Angiography**

- **LAD**
  - IMR 62
  - FFR 0.94

- **LCx**
  - IMR 37
  - FFR 0.94

**CMR Perfusion**

- **REST**
- **STRESS**

**MPRI**

**LGE**

**PET/CT risk stratification in low-moderate risk ED patients**

- Normal: 22%
- CAD/Calc: 36%
- CMD: 42%

**CFR**

- Normal: 2.61
- CAD/Calc: 1.87
- CMD: 1.59
The functional responsiveness of the microcirculation can be influenced by increased heart rate, reduced diastolic time, decreased driving blood pressure, and LV inotropism, which need to be considered when assessing microvascular function.
Homeostasis of Subendocardial blood flow
Microvascular angina

angina at rest,
prolonged duration of pain,
poor response to sublingual nitrates
It is clear that a positive stress ECG can no longer be interpreted as merely false-positive in a symptomatic patient just because the coronary angiogram is normal and does not disclose any epicardial coronary artery disease. Similarly, when
Pathophysiology

Myocardial ischaemia - caused by functional or anatomical abnormality in coronary microcirculation

Metabolic disorder affecting the handling of energy substrates by the heart muscle

Sensitivity to algogenic stimuli arising from a variety of organs including
electrocardiographic exercise testing is normal in such situations, we must remember the low sensitivity of this test in such cases and should not hesitate to resort to stress-thallium as it would identify a reasonable number of cases though, unfortunately, about one-third will still go undetected.
CFR values range: 6,5~9,0!