

COVADIS Summit 2022

Coexisting coronary artery disease and coronary microvascular dysfunction

Peter Ong

Barcelona, August 30th, 2022



Known clinical scenarios



No reflow in STEMI with primary PCI

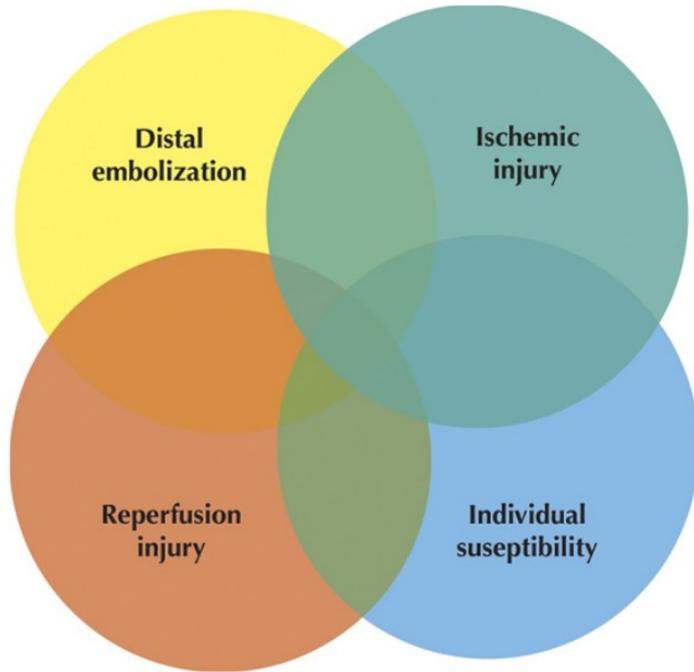
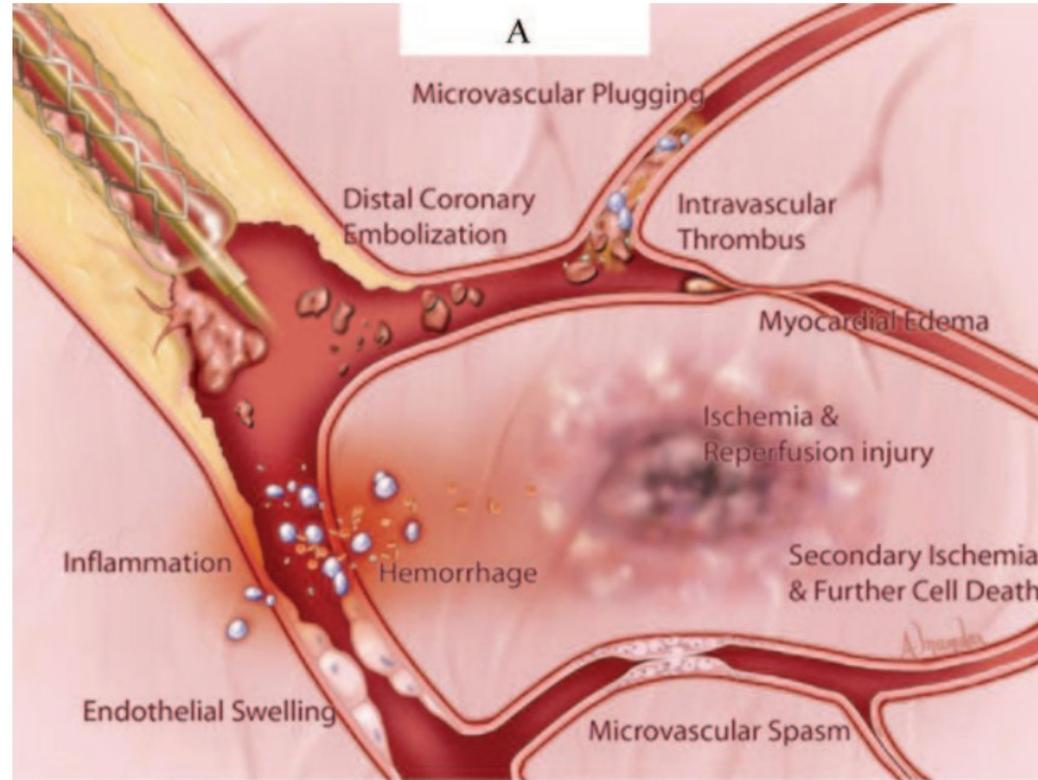
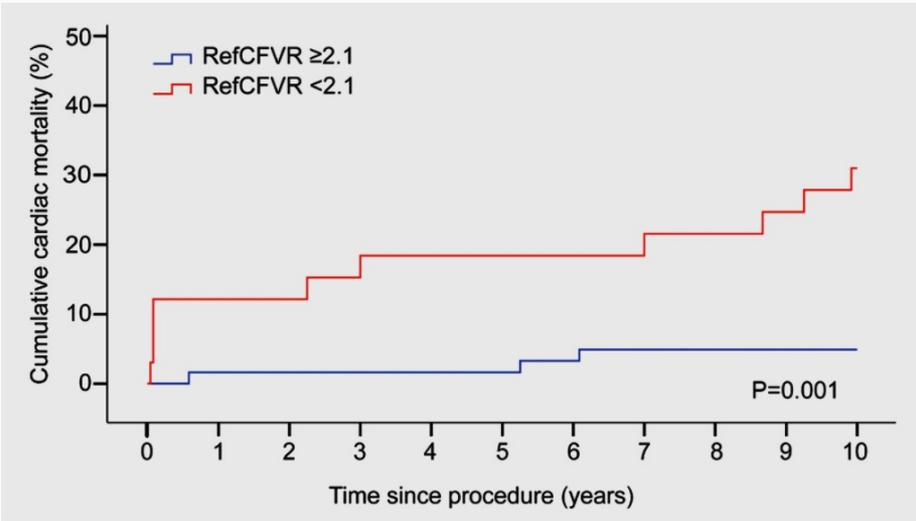


Figure 3 Mechanisms Responsible for No-Reflow



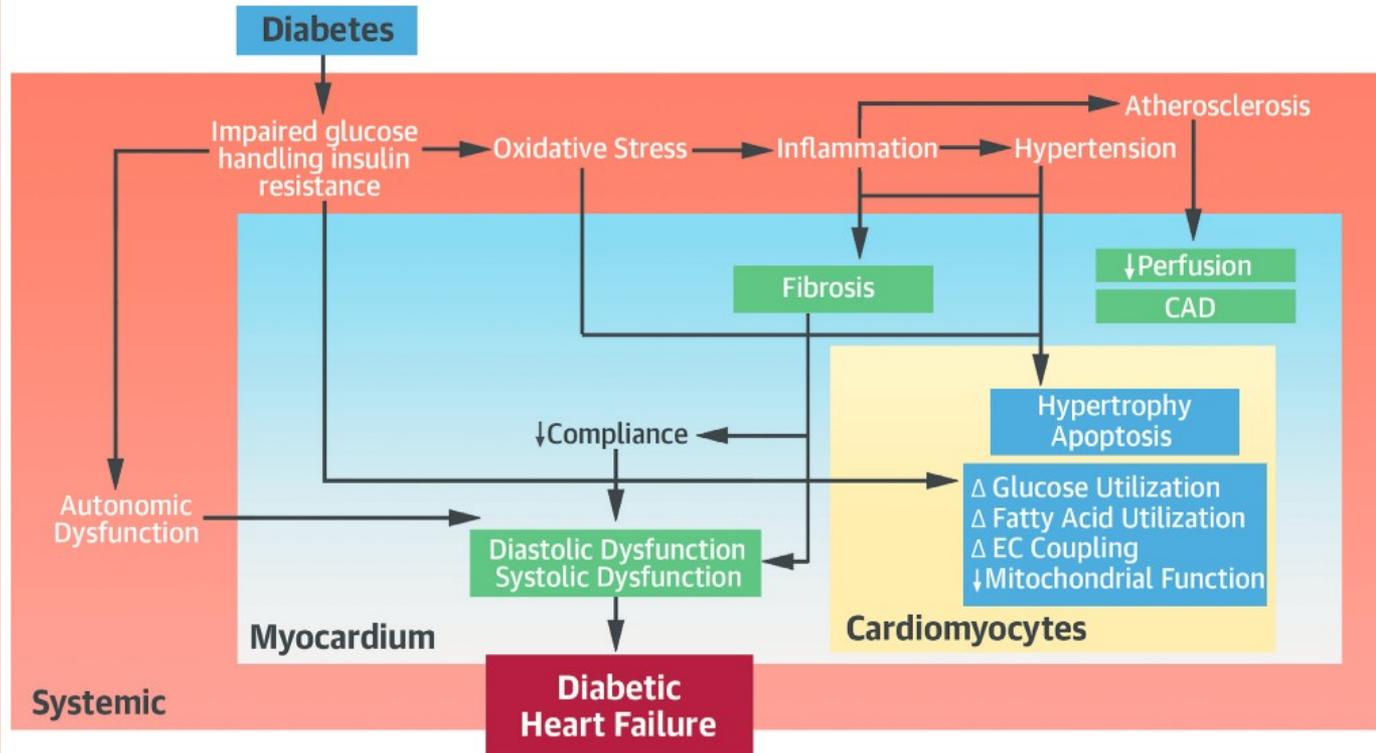
Prognostic relevance of microvascular dysfunction in STEMI



- **Microvascular dysfunction, measured by reference vessel CFVR determined after primary percutaneous**
- **coronary intervention for acute anterior wall ST-segment–elevation myocardial infarction is associated with a significantly**
- **increased long-term cardiac mortality.**

Epicardial and microvascular involvement in Diabetes

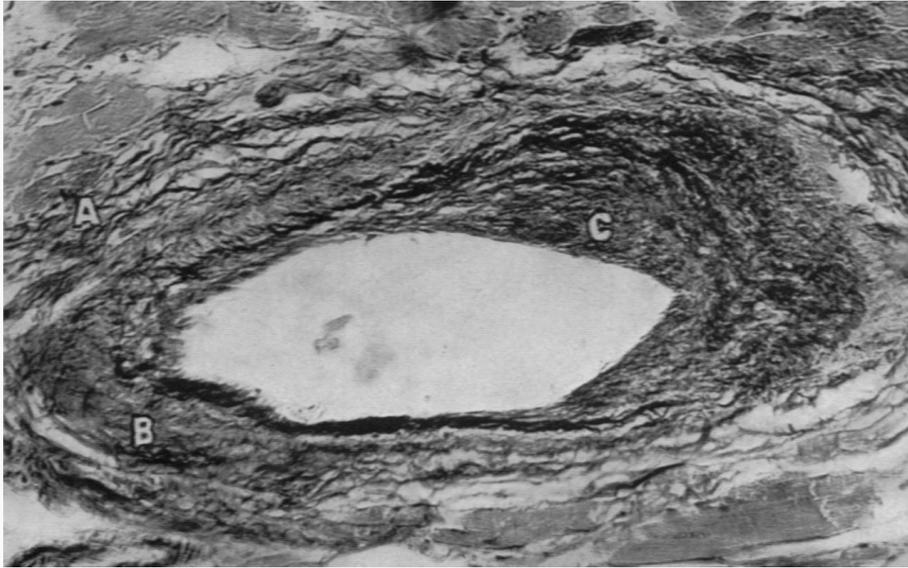
CENTRAL ILLUSTRATION Diabetic Heart Failure: Interactions of Systemic, Myocardial, and Cellular Manifestations



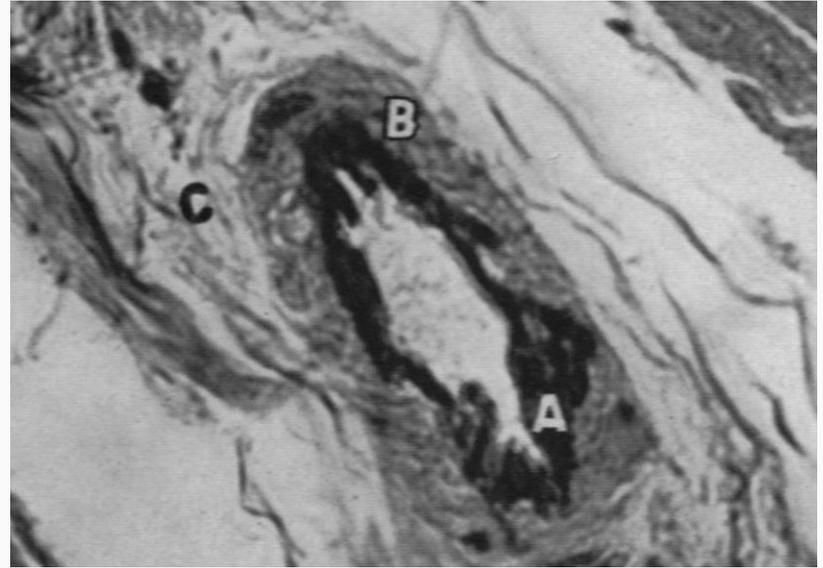
Frequent questions



Do coronary microvessels have a similar structure as epicardial vessels?



Epicardial coronary artery



Coronary arteriole

If yes, can they also develop “atherosclerosis” but we cannot see it with conventional methods?

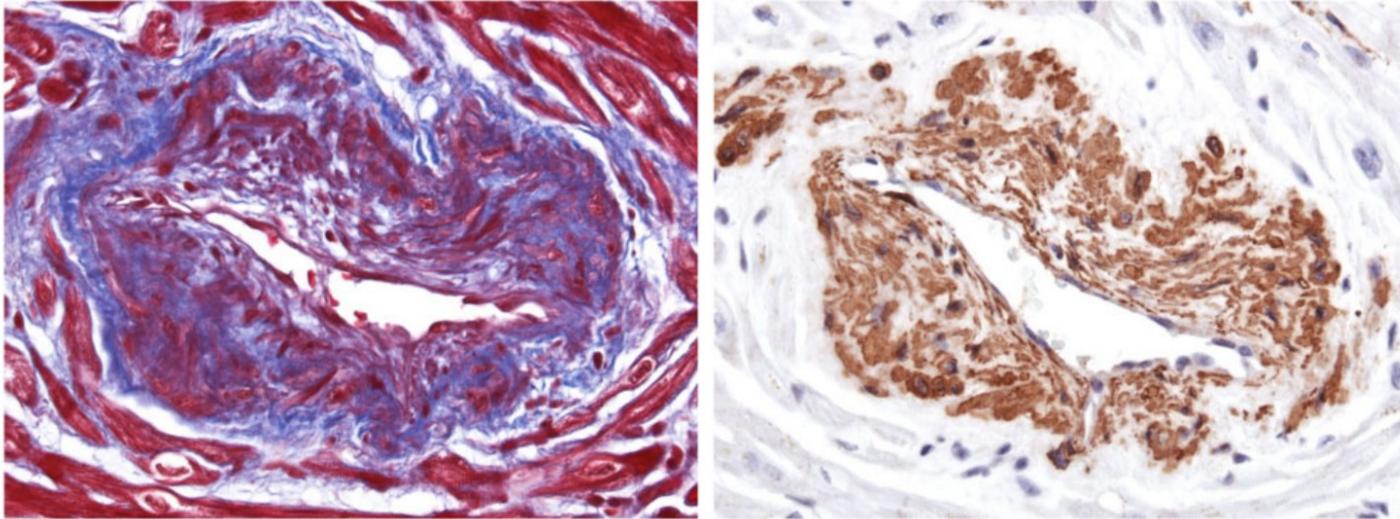
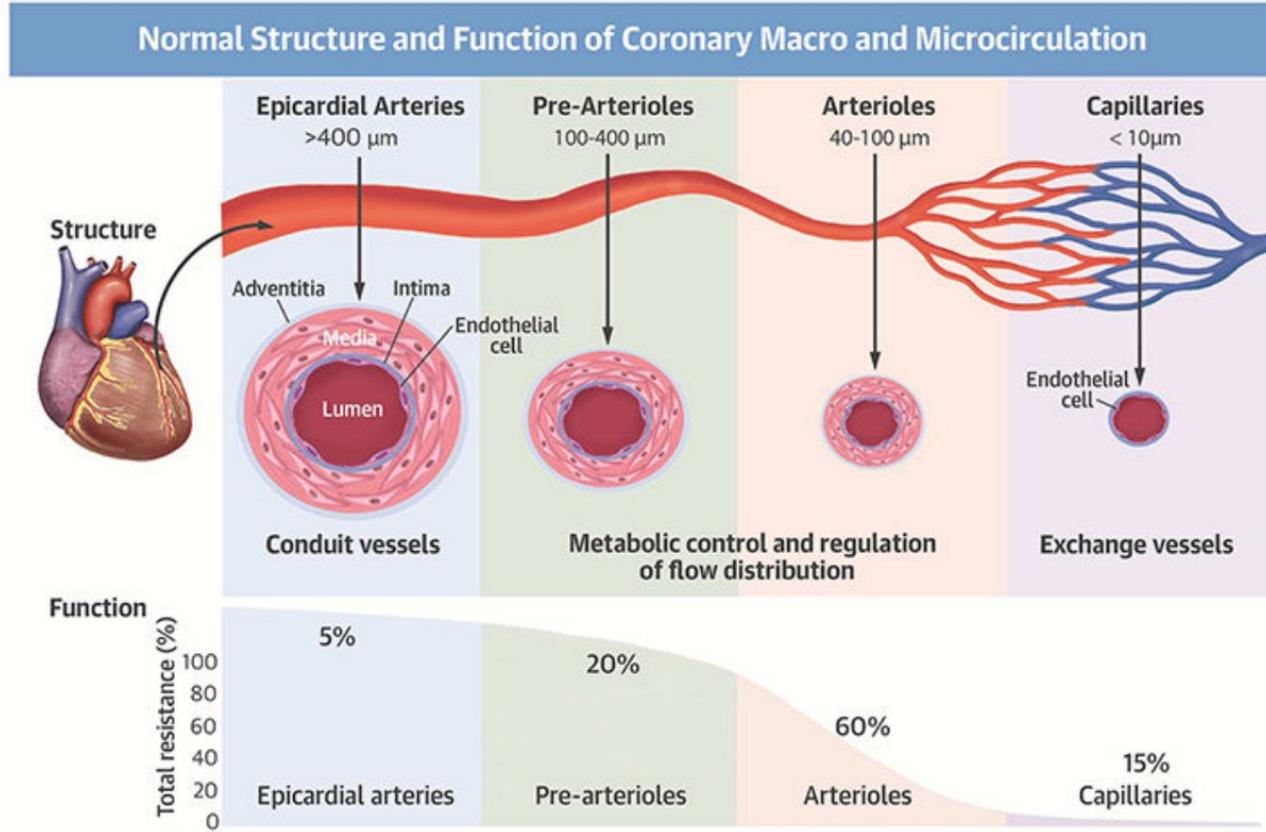


Figure 1 Intramural arteriole of a 59-year-old male patient with ischaemic cardiomyopathy. Left: haematoxylin–eosin staining. Fibrosis is blue and smooth muscle cells are violet. White spaces represent fat accumulation. There is diffuse narrowing of the vessel by a process which resembles vaguely plaque formation in the larger epicardial vessels. Right: same vessel with actin staining. Actin is a marker of smooth muscle cells and shows the irregular proliferation of these cell in the arteriolar wall. Courtesy of Professor Karin Klingel, MD, Director of Cardiac Pathology, Institute of General and Molecular Pathology and Pathologic Anatomy, University of Tübingen, Germany.

What are the specifics of the coronary microvessels compared to the epicardial vessels?



Taqueti et al. J Am Coll Cardiol. 2018;72:2625-2641.

Crosstalk between (epicardial) coronary artery disease and microvascular dysfunction



Crosstalk between epicardial and microvascular vessels

- Does microvascular disease may precede epicardial disease?

In patients without obstructive coronary disease, a higher FRS was an independent predictor of reduced CFR.

Variable	Maximal CFR (in response to intracoronary adenosine)			P-value
	≤2.5 (n = 334)	2.6–3.1 (n = 371)	>3.1 (n = 342)	
Age (years)	53.5 ± 12.5	49.9 ± 12.0	46.3 ± 11.6	<.001
Men, no. (%)	69 (21)	137 (37)	174 (51)	<.001
Estimated risk (FRS)				0.012
Mean ± SD	5.8 ± 5.7	5.5 ± 5.4	4.8 ± 4.3	

Rubinshtein et al. Eur Heart J 2010;31:936-942.

Crosstalk between epicardial and microvascular vessels

- How does epicardial disease impact on microvascular function?
- Studies suggested that the pathophysiological consequences of atherosclerosis extend to the microcirculation.



AMERICAN JOURNAL OF PHYSIOLOGY

**HEART AND CIRCULATORY
PHYSIOLOGY.**

Am J Physiol Heart Circ Physiol 320: H2351–H2370, 2021.
First published May 7, 2021; doi:[10.1152/ajpheart.00992.2020](https://doi.org/10.1152/ajpheart.00992.2020)

REVIEW

Vascular Biology and Microcirculation

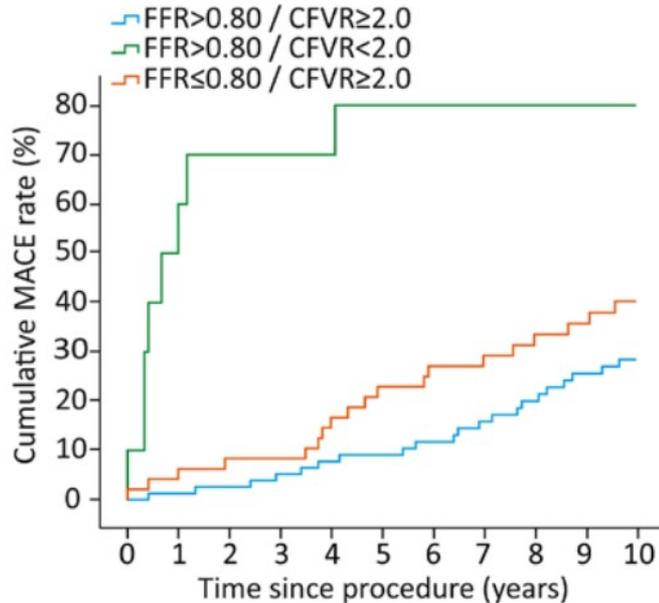
Coronary microvascular adaptations distal to epicardial artery stenosis

 Daphne Merkus,^{1,2,3}  Judy Muller-Delp,⁴ and Cristine L. Heaps^{5,6}

¹Institute for Surgical Research, Walter Brendel Center of Experimental Medicine (WBex), University Clinic, LMU Munich, Munich, Germany; ²German Center for Cardiovascular Research (DZHK), Munich Heart Alliance (MHA), Munich, Germany;

More crosstalk - FFR is influenced by CMD

B



No. at risk:

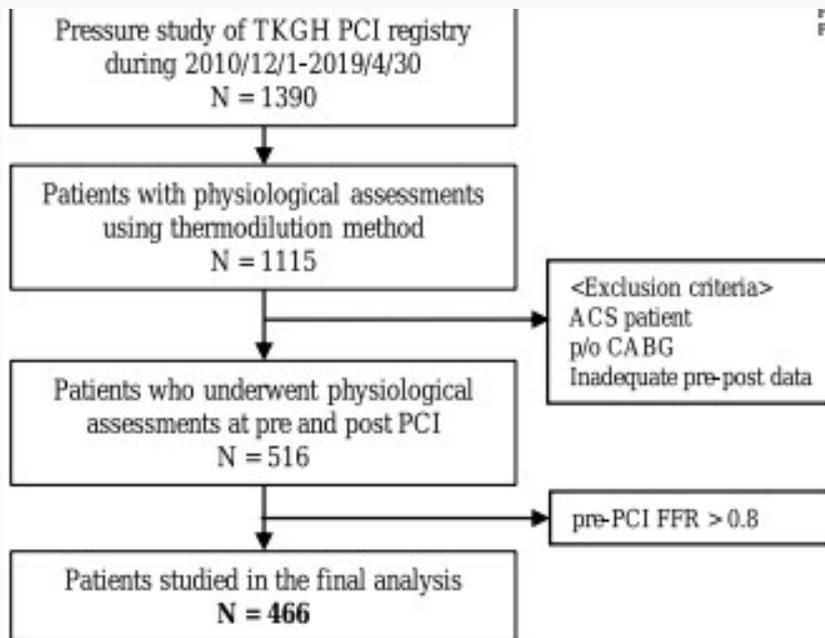
FFR>0.80 / CFVR≥2.0	78	75	71	66	57	48
FFR>0.80 / CFVR<2.0	10	3	3	2	2	2
FFR≤0.80 / CFVR≥2.0	48	44	40	35	31	24

- **Discordance of CFVR with FFR originates from the involvement of the coronary microvasculature.**
- **Importantly, the risk for major adverse cardiac events associated with FFR/CFVR discordance is mainly attributable to stenoses where CFVR is abnormal.**
- **This emphasizes the requirement of intracoronary flow assessment in addition to coronary pressure for optimal risk stratification in stable coronary artery disease.**

Prognostic Implications of Fractional Flow Reserve and Coronary Flow Reserve after Newer-Generation Drug-Eluting Stent Implantation

Hiroki Ueno, MD^a; Masahiro Hoshino, MD^a; Tomoyo Sugiyama, MD, PhD^a; Tastyua Sakamoto, MD^a; Kodai Sayama, MD^a; Kazuki Matsuda, MD^a; Kai Nogami, MD^a; Tatsuhiro Nagamine, MD^a; Yoshihiro Hanyu, MD^a; Masahiro Hada, MD, PhD^b; Testsuo Sasano, MD, PhD^b; Tsunekazu Kakuta, MD, PhD^a

^aDepartment of Cardiovascular Medicine, Tsuchiura Kyodo General Hospital, Tsuchiura, Japan / ^bDepartment of Cardiovascular Medicine, Tokyo Medical and Dental University, Tokyo, Japan



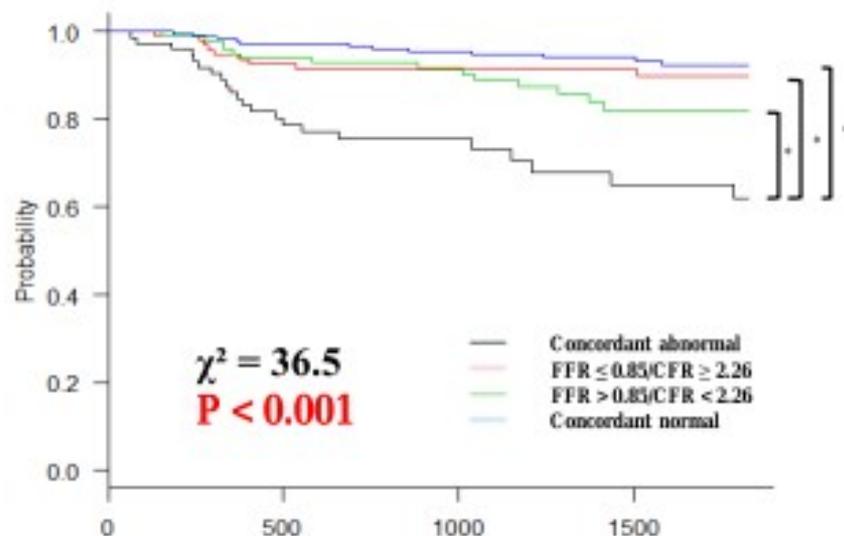
Study design and patient population

We evaluated 466 patients with chronic coronary syndromes (CCS) who underwent pre and post-intervention physiological assessment using thermodilution methods.

Endpoints

5-year major adverse cardiac event (MACE) including all-cause-death, target-vessel myocardial infarction, and target-vessel clinically driven remote revascularizations.

Kaplan-Meier time to event curves for MACE during 5-years follow-up across the groups defined by post-PCI normal/abnormal FFR and CFR



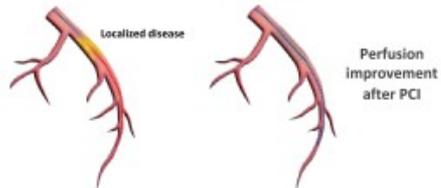
	Period2			
	Number at risk			
Concordant abnormal	76	51	34	23
FFR ≤ 0.85/CFR ≥ 2.26	98	85	74	59
FFR > 0.85/CFR < 2.26	100	89	70	46
Concordant normal	192	169	144	111

Differential Improvement in Angina and Health-related Quality of Life after Percutaneous Coronary Interventions in Focal and Diffuse Coronary Artery Disease

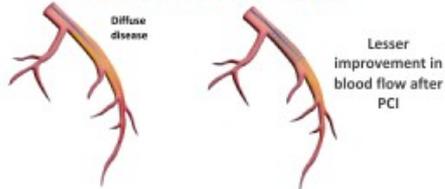
Carlos Collet, Damien Collison, Takuya Mizukami, Peter McCartney, Jeroen Sonck, Thomas Ford, Daniel Munhoz, Colin Berry, Bernard De Bruyne, and Keith Oldroyd

Clinical Hypothesis

Focal CAD – High PPG



Diffuse CAD – Low PPG

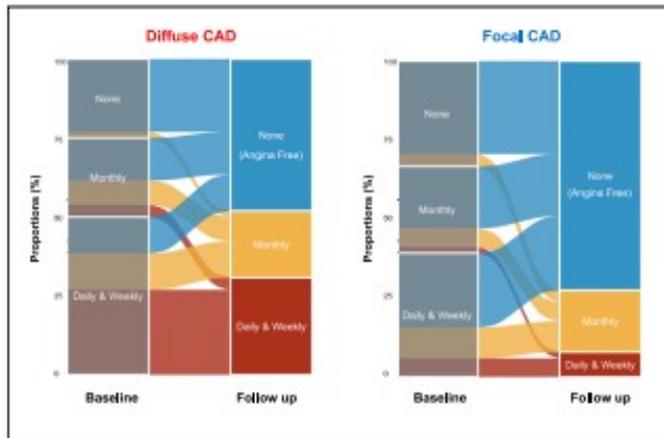
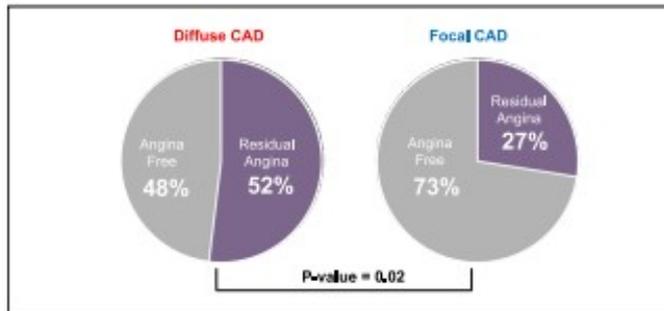


The likelihood of successful angina relief from PCI can therefore be anticipated by the baseline pattern of CAD.

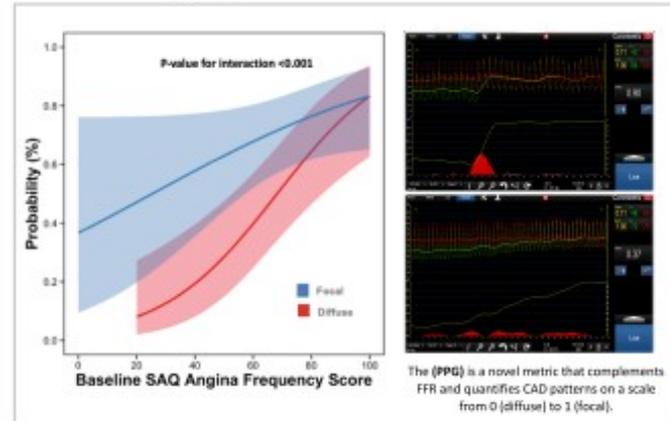
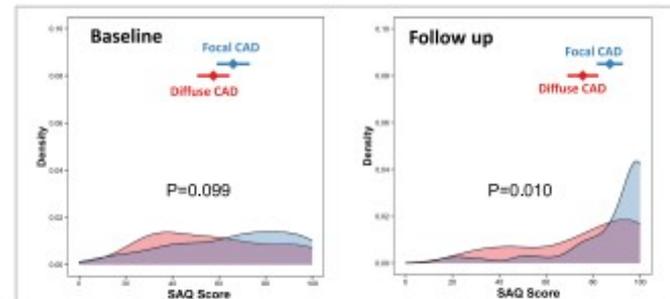
Objective

To investigate the differential improvement in patient-reported outcomes after PCI in focal and diffuse CAD as defined by the pullback pressure gradient (PPG).

PPG (pre-PCI) and Angina post-PCI



Patient-reported outcomes before and after PCI stratified by PPG

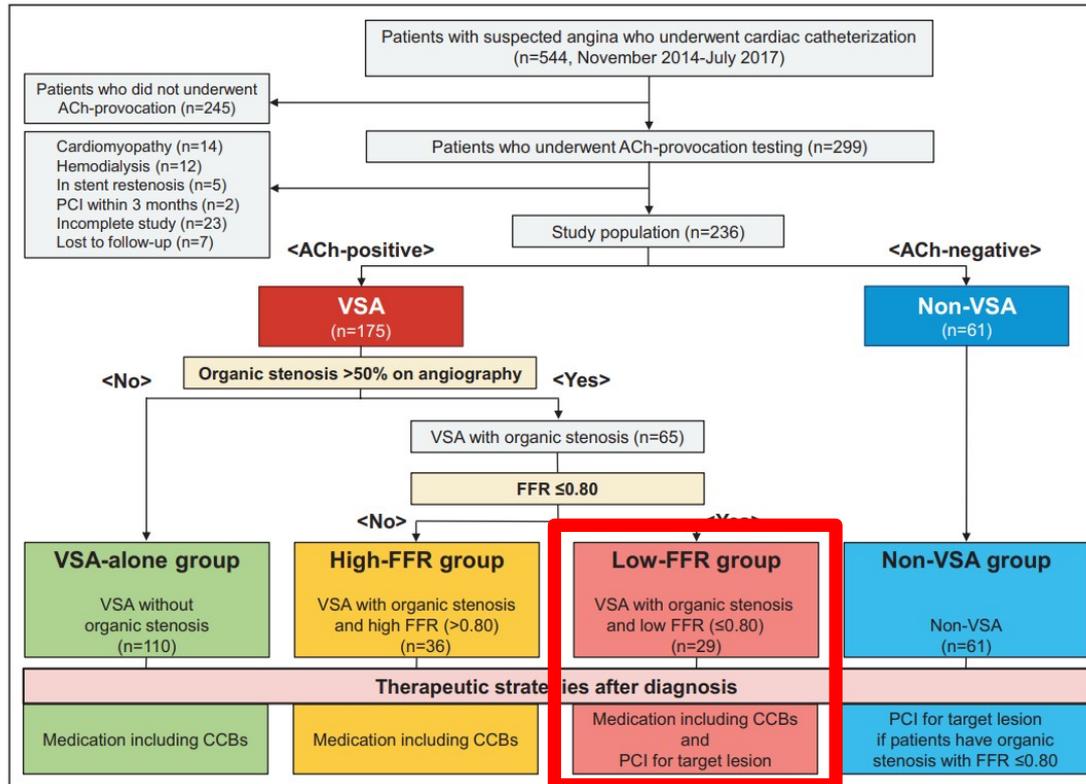


What we don't really know

- What are the frequency and the patterns of coronary vasomotor dysfunction BEFORE patients undergo myocardial revascularization (PCI/CABG)?



We know a little bit about coronary spasm testing in patients with epicardial stenosis



- Invasive spasm testing was safe - also in patients with FFR ≤ 0.80

Hao et al. J Am Heart Assoc.
2021 Jan 16;10(2):e017831.
doi:
10.1161/JAHA.120.017831.

We know a little bit about coronary spasm in patients after successful bypass surgery

Common problem:
Recurrent angina after
successful CABG



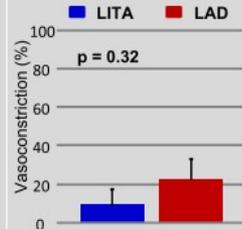
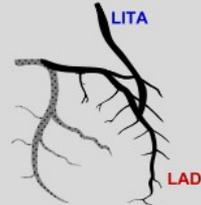
Repeated angiography:
No progression of CAD,
no relevant stenosis



**Invasive acetylcholine
spasm provocation
testing via LITA bypass
(n=54)**

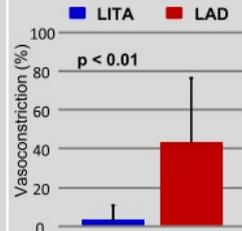
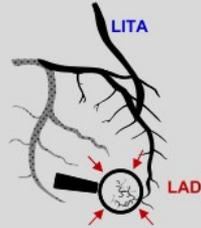
Normal acetylcholine test

19%



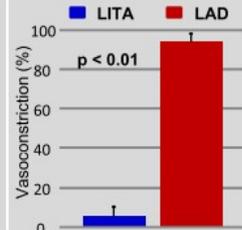
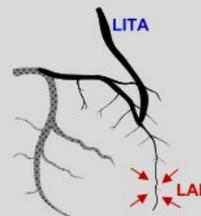
Microvascular spasm

55%



Epicardial spasm

26%



- Coronary spasm (especially microvascular spasm) is common in patients with recurrent angina after CABG
- Spasm occurs only in native coronaries but not in bypass vessels
- Another finding pointing towards coexistence of CAD and CMD

Pirozzolo et al. Clin Res Cardiol.
2021;110:172-182.



Conclusions

- **Coronary artery disease and microvascular dysfunction can coexist beyond the already known clinical scenarios**
 - **There are complex interactions in both directions with consequences for patient management**
 - **The highlighted gaps in evidence should stimulate us to concentrate our research efforts on these topics**
 - **We could contribute to a new understanding of “coronary disease”**
-

**Thank you very much
for your attention!**



In patients with ANOCA and microvascular dysfunction, what causes the events?

> [Atherosclerosis](#). 2012 Aug;223(2):384-8. doi: 10.1016/j.atherosclerosis.2012.05.034.

Epub 2012 Jun 19.

Coronary microvascular dysfunction is associated with higher frequency of thin-cap fibroatheroma

Saurabh S Dhawan ¹, Michel T Corban, Ravi A Nanjundappa, Parham Eshtehardi, Michael C McDaniel, Collins A Kwarteng, Habib Samady

Affiliations + expand

PMID: 22766333 DOI: [10.1016/j.atherosclerosis.2012.05.034](#)

