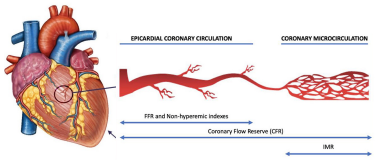
Coronary physiology, Microvascular Assessment and Coronary Vasospasm

Azad Ghuran MB ChB (Edin), MRCP, MD (Edin), FESC
PG Cert Sports Cardiology
Consultant Cardiologist

Coronary physiology

- Coronary circulation can be viewed as a two-compartment model.
  - Large epicardial vessels (> 400 microns), which are also referred to as 'conductance vessels' because they have minimal resistance to blood flow.
  - Arteries smaller than 400 microns, or 'resistive vessels'.
- Myocardial flow is controlled predominantly by resistive vessels.



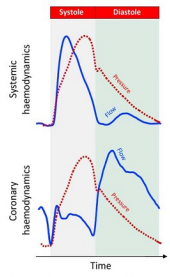
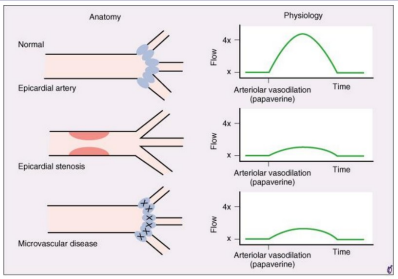
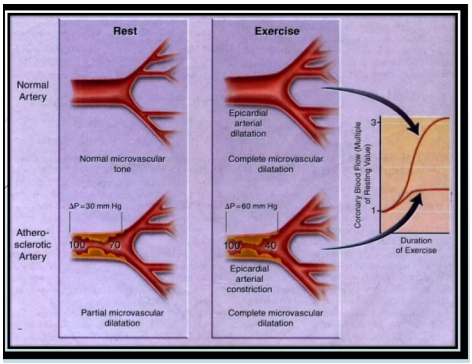


Fig. (1). Difference between the pressure-flow relationship in systemic and coronary arteries. It can be seen that in a systemic artery changes in pressure and flow closely follow each other. In systole they both increase whilst in diastole they both decrease (upper panel). In the coronary circulation (lower panel) this is not the case. After an initial period in systole when pressure and flow increase together, flow velocity plateaus whilst pressure continues to increase. In early diastole it can be seen that pressure falls rapidly whilst flow velocity increases. Such a paradoxical relationship in early diastole cannot be explained by the traditional haemodynamic model of the systemic vessel.

CFR = max flow/ basal flow = sum of flow thorugh epicardial and bed
CFR cannot tell us if the problem is a stenosis or an impaired microcirculation.





REGULATION OF CORONARY CIRCULATION

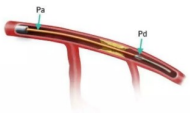
Table 24.2 Regulation of Coronary Circulation

Mechanism	Effector
Autoregulation	Intrinsic vasoconstrictor tone
Perfusion pressure	Aortic or poststenotic pressure
Metabolic activity	Exercise, ischemia
Myocardial compression and myogenic mechanisms	Systolic-diastolic interaction
Neural control	Sympathetic, parasympathetic, pain
Endothelium	EDRF, EDCF
Pharmacologic	Dipyridamole, adenosine, acetylcholine, α-, β-agonists and antagonists, etc.

EDCF, endothelial derived constricting factor; EDRF, endothelial derived relaxing factor.
Modified from Gould L. *Coronary Artery Stenosis and Reversing Atherosclerosis*. 2nd ed. New York, NY: Arnold and Oxford University Press; 1998.

Concept of FFR

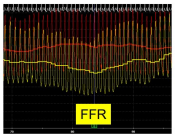
$$FFR = \frac{\text{Distal Coronary Pressure (Pd)}}{\text{Proximal Coronary Pressure (Pa)}} \quad \text{(During Maximum Hyperemia)}$$



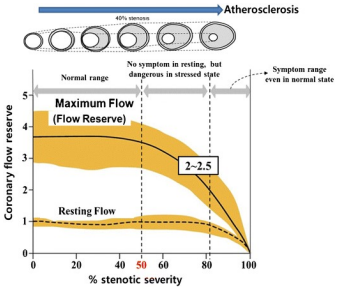
- FFR is defined as a ratio of the maximal myocardial blood flow in the presence of a stenosis to the theoretical normal maximal flow in the same distribution.
- FFR is simply calculated by using the distal coronary pressure of the stenosis divided by the aortic pressure during maximal hyperemia; Pd/Pa

Invasive Translesional Pressure Measurements

$$FFR = \frac{P_{distal}\ (hyper)}{P_{aortic}\ (hyper)}$$



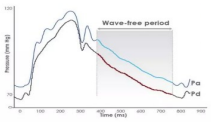
- ***FFR = 0.6 means:*** "Due to this particular stenosis, maximum achievable blood flow to the myocardium supplied by this artery, is only 60 % of what it would be if this coronary artery completely normal"

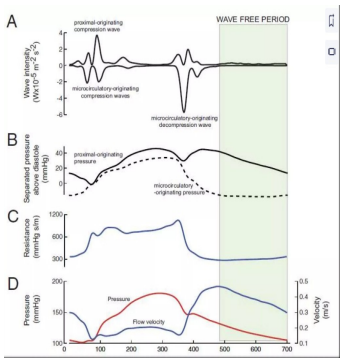


- Stenosis in large epicardial (capacitance) vessel → decreased perfusion pressure → arterioles downstream dilate to maintain normal resting flow.
- As stenosis progresses, arteriolar dilatation becomes chronic, decreasing potential to augment flow an thus decreasing CFR.
- As CFR approaches 1 (vasodilatory capacity "maximum"), any further decrease in PP or increase in MVO2 → ischaemia.

Concept of iFR

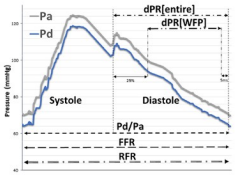
- iFR is a physiological index used to assess the severity of stenosis.
- iFR is calculated by measuring the resting pressure gradient across a coronary lesion during the portion of diastole (wave free period) when microvascular resistance is low and stable.

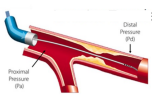




S Sen et al. J Am Coll Cardiol 2012;59:1392–402)

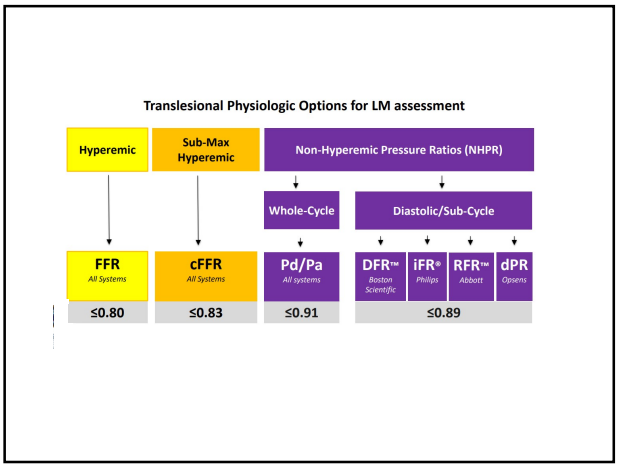
Figure 1



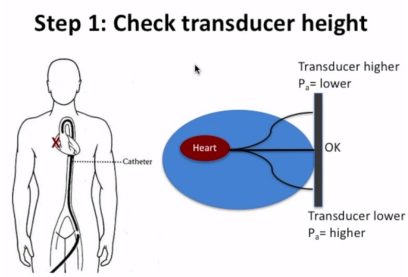


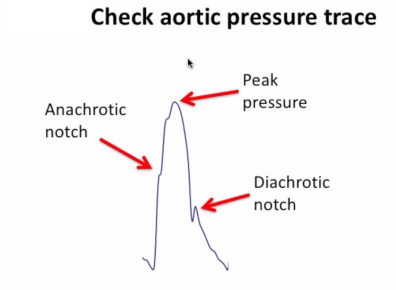
Schematic explanation of the NHPRs and FFR. Diastole starts at the nadir of the dicrotic notch. The dPR[entire] is defined as mean Pd/Pa over the entire diastole. The dPR[WFP] is defined as the mean Pd/Pa value in the wave-free period for 5 heart cycles (from 25% of the entire diastole to 5 ms before the end of diastole; equivalent to the definition of iFR). Whole cycle resting Pd/Pa was calculated continuously throughout the entire cardiac cycle for three heart cycles. FFR is defined as the lowest, artifact-free Pd/Pa during maximal hyperemia over at least three heart cycles (Pd/Pa and FFR are calculated in the same way, just under different conditions, i.e. resting conditions vs hyperemic conditions). RFR is defined as the lowest Pd/Pa value in systole and diastole (mean of 5 consecutive cardiac cycles). dPR[entire], diastolic pressure ratio during entire diastole; dPR[WFP], diastolic pressure ratio during wave-free period; FFR, fractional flow reserve; NHPR, non-hyperemic pressure ratio; Pa, aortic pressure; Pd, distal coronary pressure; RFR, resting full-cycle ratio.

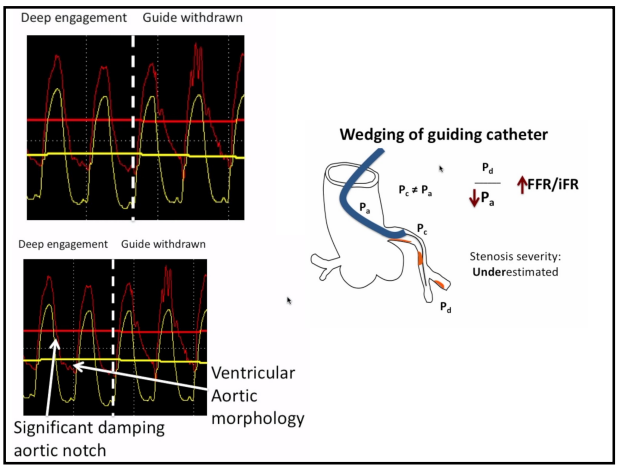
Hendrik Wienemann et. Front Cardiov Med 2021, Vol 8, Article 744181



How to do it – Practical Tips





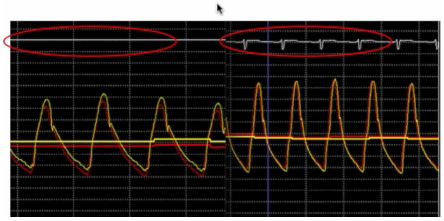


Administer nitrates for all measurements

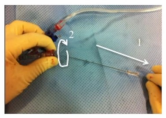
Nitrates 300mcg IC

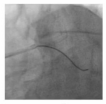
- Give before placing wire into vessel
- Prevent epicardial spasm which will affect physiological measurements
- Ensure epicardial stability and maximal vasodilatation

Good ECG signal is essential

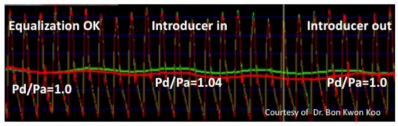


Remove needle introducer before equalisation and iFR/FFR measurement

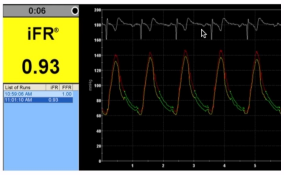




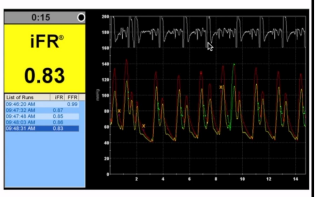
Needle introducer= ↓P_a = ↑iFR



iFR window must be correctly identified

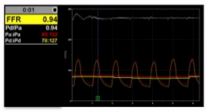


Where is the iFR window?



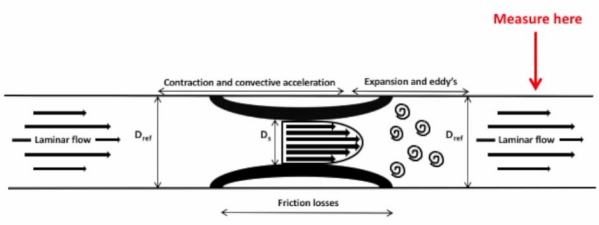
Check for drift

- Bring wire back to normailisation position
- +/- 0.02 drift is considered acceptable
- Check aortic trace
- If there is drift you must re-normalise and re-measure iFR/FFR

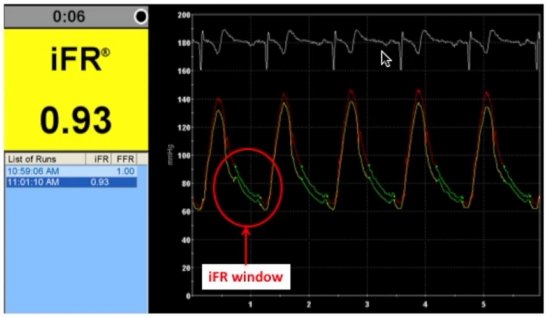


Step 7: Place wire distal to lesion and make measurement

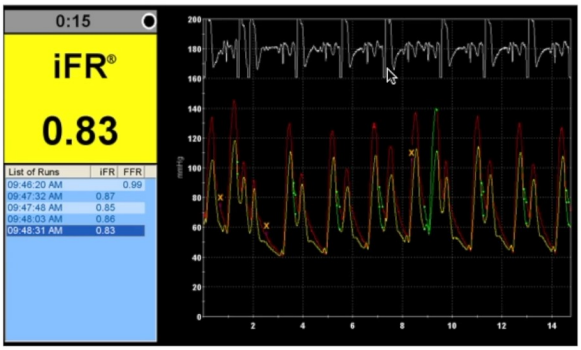
- At least 3 vessel diameters after the stenosis to measure at a location of laminar flow



iFR window must be correctly identified



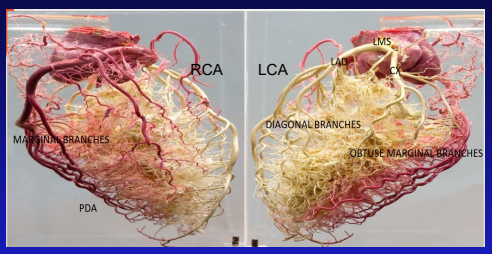
Where is the iFR window?



INOCA

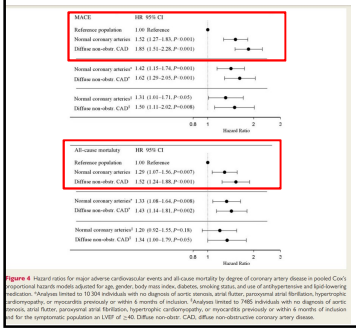
Ischaemia with non-obstructive coronary arteries

MINOCA – myocardial infarction with non-obstructive coronary arteries



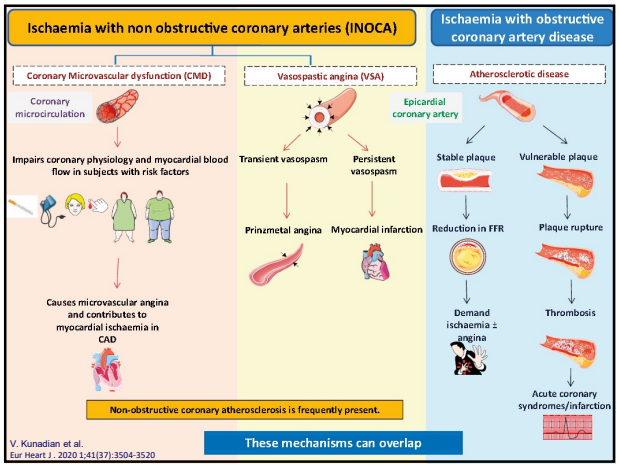
CLINICAL RESEARCH
Coronary heart disease

Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events

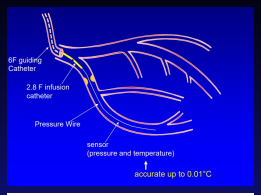


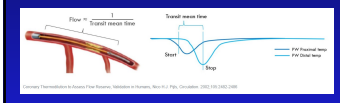
Prognosis of patients with INOCA is far from benign

- Impaired quality of life
- Higher risk of disability
- Increases mortality, morbidity
- Higher recurrence rates of hospital readmissions
- Higher rates of repeated coronary angiograms
- Higher healthcare costs



CMD Assessment





Non-invasive

PET (Positron Emission Tomography)

CMR (Cardiac Magnetic Resonance Imaging)

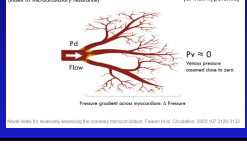
MBG (Myocardial Blush Grade)

TIMI Score (Thrombolysis In Myocardial Infarction)

Echocardiography

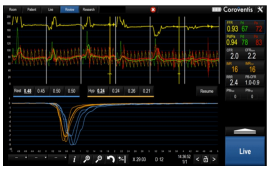
Ohms law, V=IR
R = V/I

IMR-Index of microcirculatory resistance



Patient 1

Patient 2



INOCA

	INOCA endotypes	Pathophysiology	Diagnostic criteria
1	Microvascular angina[a]	CMD	Diagnostic guidewire and Adenosine test
			FFR >0.8
			CFR <2.0
			IMR ≥25[b]
			HMR ≥1.9[b]
			Vasoreactivity (acetylcholine test)
			No or <90% diameter reduction
			+angina
			+ischaemic ECG changes
2	Vasospastic angina	Epicardial spasm	Diagnostic guidewire and Adenosine test
			FFR >0.8
			CFR ≥2.0
			IMR <25
			HMR <1.9
			Vasoreactivity (acetylcholine test)
			≥90% diameter reduction
			+angina
			+ischaemic ECG changes
3	Both microvascular and vasospastic angina	Both CMD and epicardial spasm	Diagnostic guidewire and Adenosine test
			FFR >0.8
			CFR <2.0
			IMR ≥25
			HMR ≥1.9
			Vasoreactivity (acetylcholine test)
			No or <90% or ≥90% diameter reduction
			+angina
			+ischaemic ECG changes
4	Non-cardiac chest pain	None	Diagnostic guidewire and Adenosine test
			FFR >0.8
			CFR ≥2.0
			IMR <25
			HMR <1.9
			Vasoreactivity (acetylcholine test)
			No or <90% diameter reduction
			No angina
			No ischaemic ECG changes
5	Non-flow-limiting CAD[a]	Diffuse coronary artery atherosclerosis	Diagnostic guidewire and adenosine test
			FFR >0.8
			CFR ≥2.0
			IMR <25
			HMR <1.9
			Vasoreactivity (acetylcholine test)
			No or <90% diameter reduction
			No angina
			No ischaemic ECG changes

V. Kunadian et al. Eur Heart J . 2020 Oct 1;41(37):3504-3520

Table 2 Angina pharmacotherapy

Treatment	Angina type	Example	Investigation	Mechanism of action	Common side-effects
β-blockers	MVA, CAD	Bisoprolol 1.25–10 mg	Reduced CFR and/or structural microvascular dysfunction (raised microvascular resistance)	Reduction in myocardial oxygen consumption	Fatigue, blurred vision, cold hands
Calcium channel antagonists	All	Dihydropyridine: amlodipine 2.5–10 mg daily) Non-dihydropyridine (verapamil: 40–240 or diltiazem up to 500 mg, controlled release)	Propensity to coronary vasospasm (epicardial and/or microvascular)	↓ spontaneous and inducible coronary spasm via vascular smooth muscle relaxation and ↓ oxygen demand Vascular smooth muscle relaxation, reduction in myocardial oxygen consumption	Constipation, ankle swelling, flushing
Vasodilators					
Nitrates	CAD, VSA	Isosorbid mononitrate 30–120 mg one time a day (controlled release)	Propensity to epicardial coronary vasospasm	↓ spontaneous and inducible coronary spasm via large epicardial vasodilation, ↓ oxygen demand. Lack of efficacy in microvascular angina with potential deleterious effect	Headaches, dizziness, flushing
Nicorandil	All	Nicorandil 5–30 mg two times a day	All	Potassium channel activator with coronary microvascular dilatory effect	Dizziness, flushing, weakness, nausea
Rho kinase inhibitors	VSA, CMD	Fasudil: 5–20 mg, three times a day	Epicardial and/or microvascular vasospasm	Reduce calcium sensitization of vascular smooth muscle, maintains coronary vasodilation	Rashes, flushing, hypotension
Late Na+-Current inhibitors	MVA, CAD	Ranolazine 375–500 mg two times a day	Reduced CFR	Improves MPRI in patients with MVA and reduced CFR	Nausea, dizziness, headache
L-channel blockers	CAD, MVA	Isradipine: 2.5–7.5 mg two times a day	All	Isradipine has shown anti-ischaemic and antianginal activity	Bradycardia, AV, headache
Partial fatty-acid oxidation inhibitors	CAD, MVA	Perhexiline 50–400 mg daily or Trimetazidine	Plasma concentration required for dose-titration	Perhexiline inhibits carnitine O-palmitoyltransferase 1 and 2, which transfer free fatty acid from the cytosol into mitochondria	Dizziness, unsteady, nausea and vomiting
Improved endothelial function/pleiotropic					
ACE inhibitors	MVA, CAD	Ramipril 2.5–10 mg daily	Hyper-reactivity to stimuli (eg, acetylcholine, exercise, stress)	Improve CFR, reduce workload, may improve small vessel remodelling. Improves endothelial vasomotor dysfunction	Cough, renal impairment, hyperkalaemia
Statins	All	Atorvastatin: 10–80 mg daily Rosuvastatin: 5–40 mg daily	All	Improved coronary endothelial function reduced vascular inflammation	Myalgia, headache, cramps
Hormone-replacement therapy*	MVA	Oestradiol: 1 mg daily	Angina in early menopause	Oestrogen therapy improves endothelial function short-term in CMD	↑ Risk of breast cancer, marginally ↑ risk of CVD
Tricyclic antidepressants (TCA)	MVA with abnormal pain processing	Amitriptyline: 5–10 mg nocte Imipramine: 10–200 mg daily	All	Counteracts enhanced nociception. Thought to exert an analgesic effect on the visceral component associated with cardiac pain.	Blurred vision, dry mouth, drowsiness, impaired coordination
Non-pharmacological	All	Smoking cessation, Exercise, cardiac rehabilitation, Mediterranean diet, cognitive behavioural therapy, weight loss, Yoga	Metabolic syndrome, endothelial dysfunction, cardiovascular risk factors, anxiety/depression		Adjunctive non-pharmacological interventions

*May be helpful in some postmenopausal women. More information on experimentary pharmacotherapy in refractory angina can be found in review by Henry et al.[45]
†In women with obstructive coronary artery disease, MPRI, myocardial perfusion reserve index; MVA, microvascular angina; VSA, vasospastic angina.

Pharmacologic Treatment

- Aspirin
- PDE-5 inhibitors
- L-arginine
- Aminophylline
- Endothelin receptor blockers

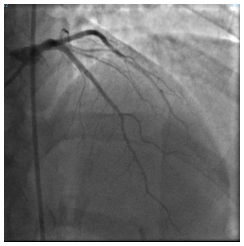
Non-Pharmacologic Treatment

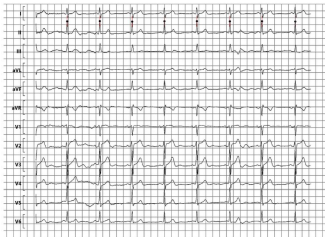
- Exercise
- Cognitive behavioural therapy
- TENS

T Ford, Colin Berry. Heart 2020;106:387-398
C. Noel Bairey Mertz et al. Circulation 2017;135:1075

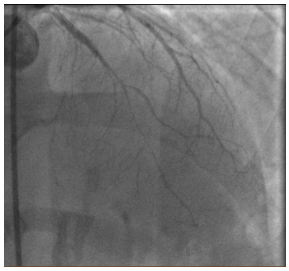
Mr. DK – 37 yr.
Recurrent chest tightness – exertion and rest.
Awoke at 3 am, chest tightness "someone was sitting on chest". Radiated to his neck and associated with sweating. Eased after 30 minutes.
A&E. Normal ECG, chest x-ray, and blood tests (FBC, CRP, D-dimer, clotting, liver function test, U&Es and troponin). Advised Gaviscon. Already on Omeprazole 20 mg daily.

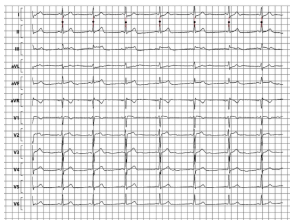
PMHx: Raynaud's disease. Previous CTCA: no obstructive disease.

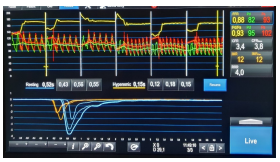


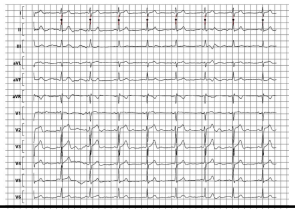


Mr. DK









Clinical History :

HT

73 yr. old Asian male
Crescendo angina
Angio 2019 moderate RCA disease
Possible significant LAD disease.
Awaiting knee surgery turned down due to anginal symptoms. If possible within 1 month

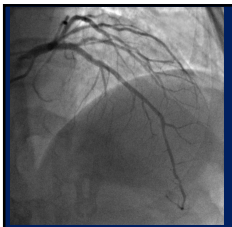
Coronary angiogram. RRA. 6F

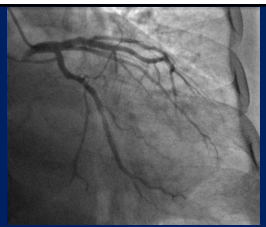
LMS: unobstructed
LAD: mild disease in proximal and mid course. Mild-moderate disease in distal LAD at apex
Cx: 40% hazy lesion in mid course
RCA: mild disease in proximal and mid course. Diffuse moderate disease in distal PDA with slow flow.

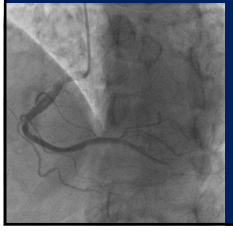
XB3 Guide.
Pressure wire X in Cx. RFR/FFR = 1.
Coronary flow reserve: 1.8
Index of myocardial resistance: 40

Diagnosis: coronary microvascular disease. Stop ISMN (which can sometimes paradoxically worsen anginal symptoms, and start Ranolazine 375mg BD. Can be listed for orthopaedic surgery from a cardiac perspective.

HT







GR

Mrs. GR – 74 yr.
Hypertensive, Dyslipidaemia, Paroxysmal AF.
Possible diagnosis of coronary spasm /syndrome X, 2004 after normal coronary angiogram
SOBE – RACPC. Referred for CTCA. Long waiting list (COVID)
Admitted to Lister Hospital with Chest tightness
Echo: normal

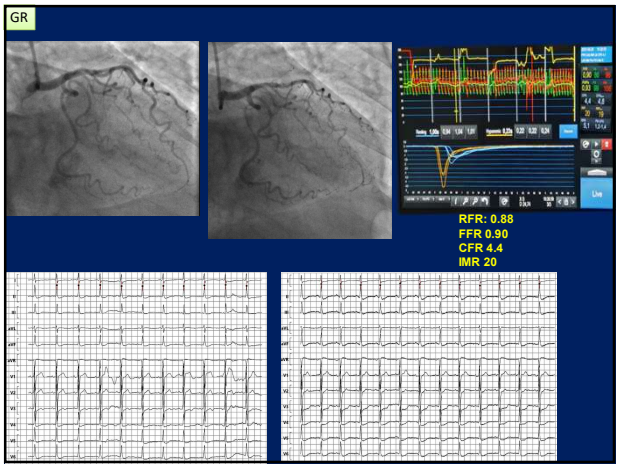
Referred for invasive coronary angiography, MVD and vasospastic assessment.

ECG showed diffuse non-specifically repolarization changes whilst in sinus rhythm. In view of her history and because of the difficulties in getting a CT coronary angiogram I admitted her today for a formal assessment.

The procedure was performed using a right transradial approach. The left main stem was unobstructed. There was a 30% stenosis in the mid LAD after a diagonal artery. The circumflex artery was unobstructed and tortuous. The right coronary artery is dominant with mild plaque disease in the mid-course.

An XB3 guide catheter was used to intubate the left main stem and the RFR in the LAD was 0.88. The FFR was 0.91 confirming that the disease in the midcourse was not functionally significant. The coronary flow reserve was 4.4 and index of myocardial resistance was 20, which exclude significant microvascular disease. Intracoronary acetylcholine was administered in slow boluses of 2µgm, 20µgm, 100µgm and 200 µgm. After the 100µgm bolus developed significant chest, jaw and arm pain associated with ST depression leads V2 to V6. There was moderate spasm in the distal LAD. The diagnostic criteria for significant epicardial coronary spasm is over 90%. She therefore has certainly microvascular spasm and possibly epicardial coronary artery spasm. During the procedure she had short runs of atrial tachycardia.

GR



AD

Clinical History :

Seen in RACPC. CTCA. 50-69% non calcifed stenosis in prox.
Cx and partially calcifed 50-69% stenosis in mid LAD.
Dr. Ghuran's list please

Exertional pressure like pain associated with SOB. Good history for anginal symptoms

Right radial artery. 6F
Almost separate ostium of LAD And CX.
LAD: Mild to moderate disease in mid LAD
Cx: Mild disease in proximal Cx
RCA: Dominant with mild disease in mid RCA.

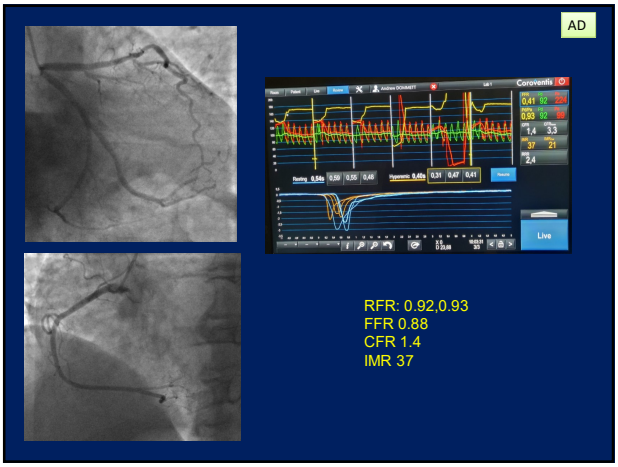
XB 3 Guide.

LAD

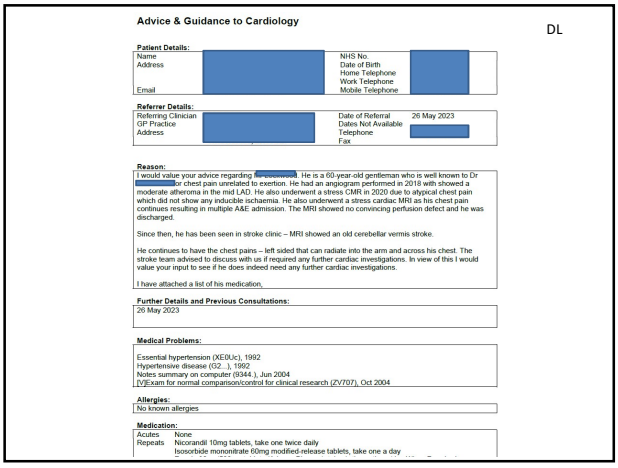
RFR: 0.92,0.93
FFR 0.88
CFR 1.4
IMR 37

Low coronary flow reserve and high myocardial resistance consistent with coronary microvascular disease and microvascular angina.

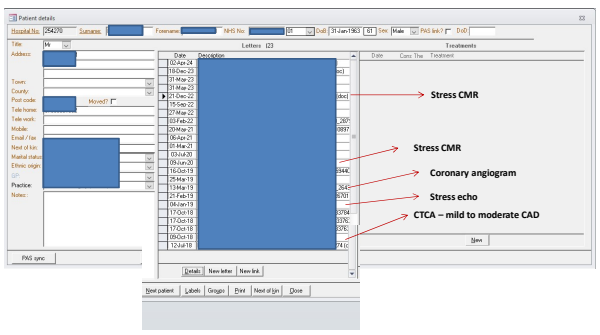
AD



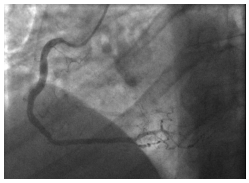
DL

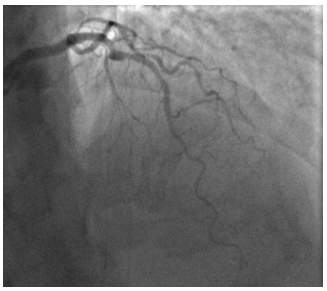


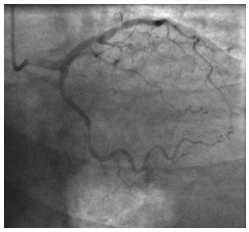
DL



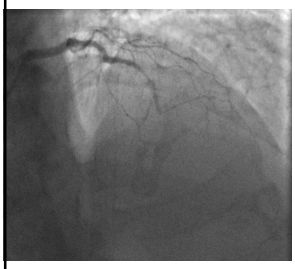
DL

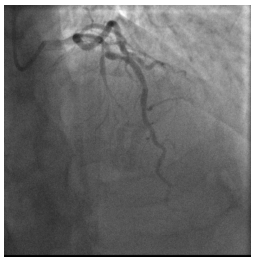






DL





Thank You

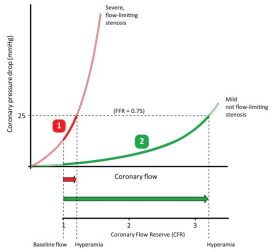
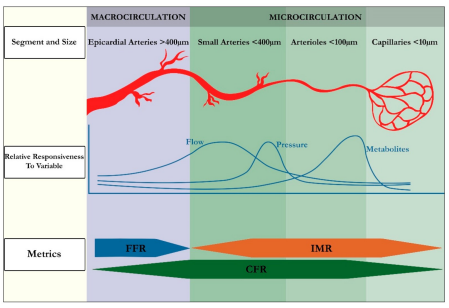
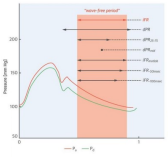


Figure 1. How can a low fractional flow reserve (FFR) value be generated? Schematic representation of the relationship between pressure gradient and flow across a coronary stenosis. The same FFR value (in this example, 0.75, equivalent to a pressure drop of 25 mmHg) can be generated via 2 different mechanisms. In (1), even a small magnitude of hyperemic flow is sufficient to generate a 25-mmHg drop in a severe, flow-limiting lesion. In (2), much higher hyperemic flow rates are needed for the same 25 mmHg to be created in a mild stenosis. Stenosis (1) is very likely causative of myocardial ischemia, whereas stenosis (2) is by definition not significantly flow limiting, despite displaying the same FFR classification.



Invasive Translesional Pressure Measurements

$$\textbf{FFR} = \frac{P_{distal}\ (hyper)}{P_{aortic}\ (hyper)}$$



Non-hyperemic Pressure ratios, NHPR

$$\textbf{iFR} = \frac{P_{distal}\ (rest,\ wfp)}{P_{aortic}\ (rest,\ wfp)}$$

$$\textbf{Pd/Pa} = \frac{P_{distal}\ (rest)}{P_{aortic}\ (rest)}$$