

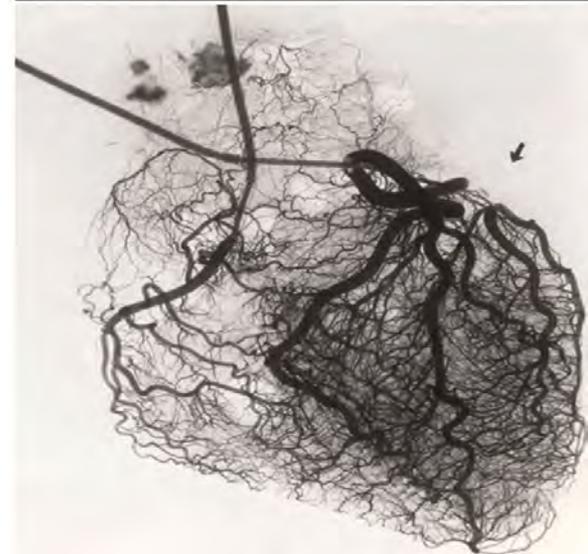


“Donna”

e

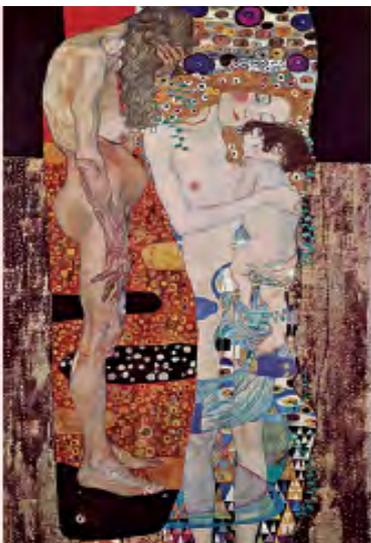
# malattia del microcircolo coronarico

What you don't see . . .



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Massa, Italia

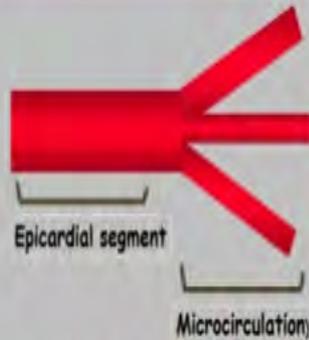


Il “continuum cardiovascolare”  
nel genere femminile:  
tappe di vita, malattia e cura

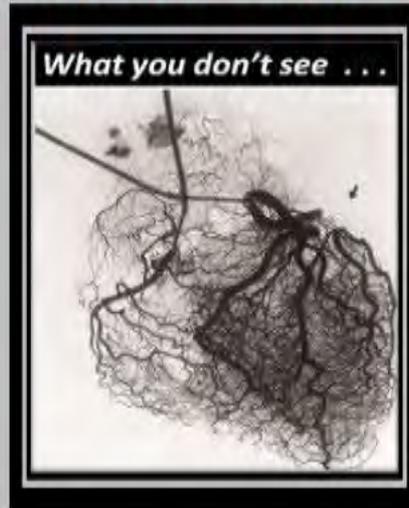
8 marzo 2018, Cinquale (Ms)  
Hotel Eden, Viale A. Gramsci, 26



## Coronary Circulation: segments



*What we can see is only 5% of the total coronary tree.*



Con l'uso dell'angiografia negli anni '70 divenne evidente che una proporzione considerevole pazienti riferiti per **sintomi anginosi** aveva

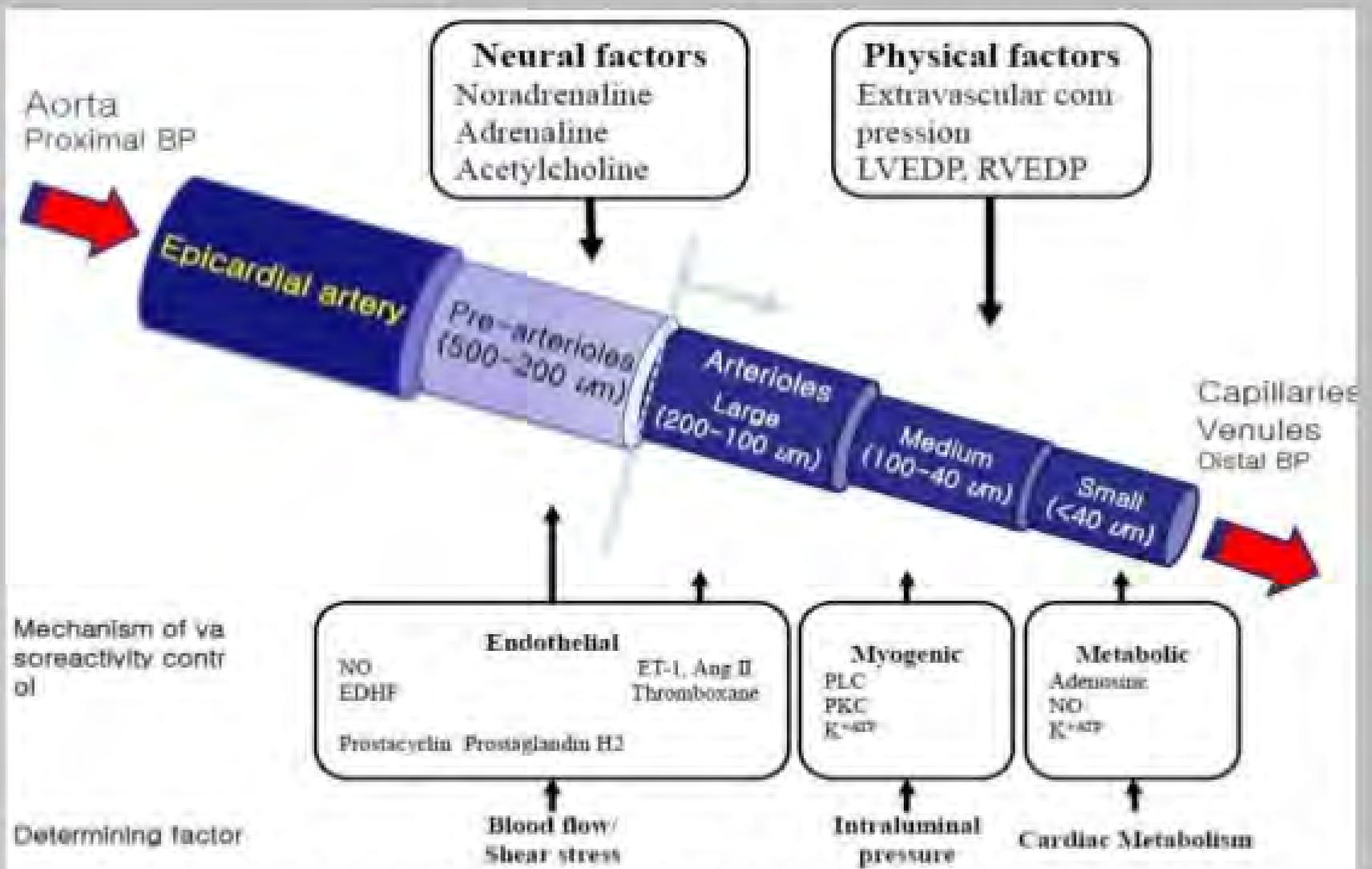
**arterie coronarie angiograficamente normali.**

condizione molto più frequente nelle **donne.**

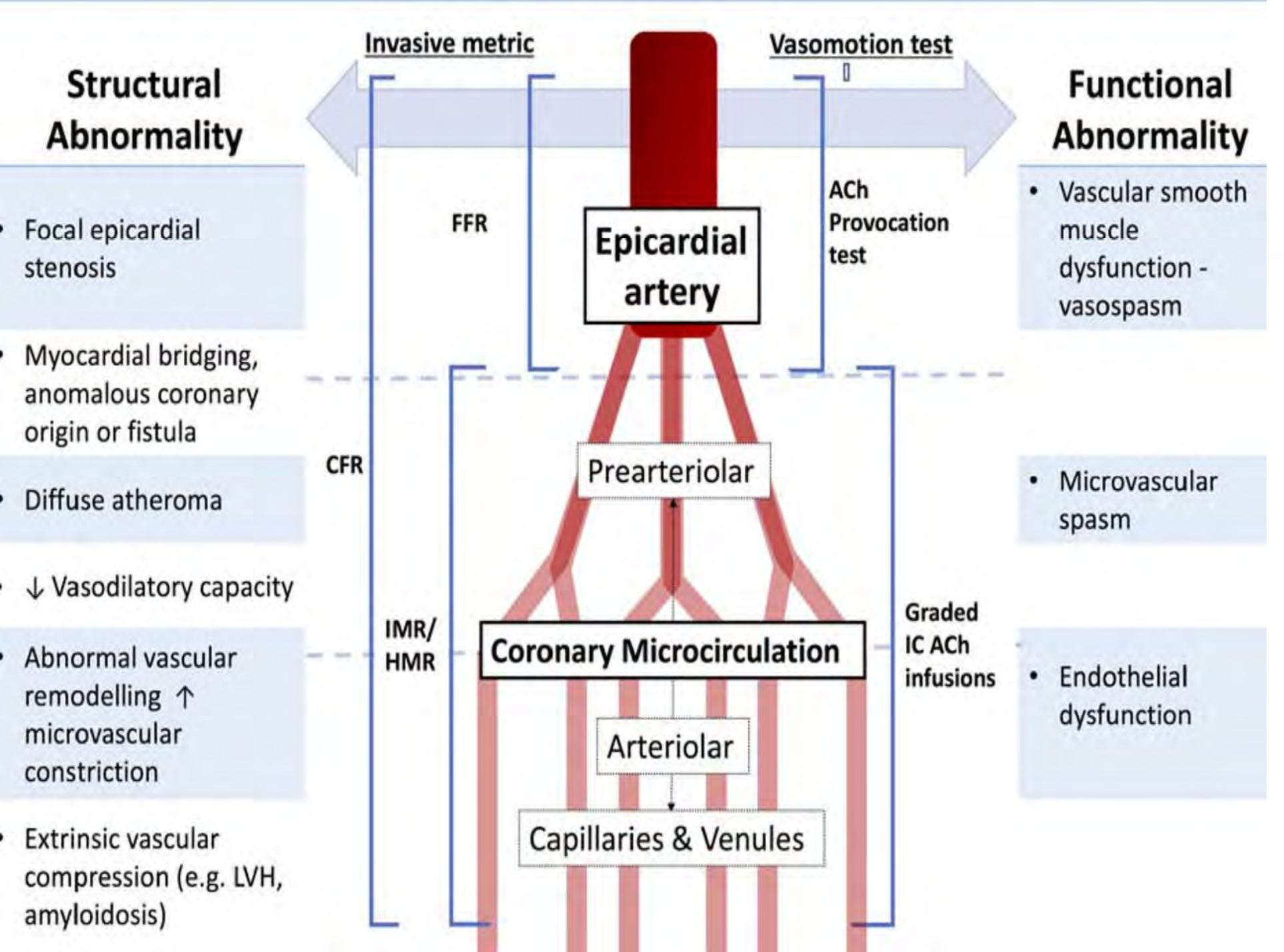
Nel 1985,

Cannon e Epstein introdussero il termine "angina microvascolare" (MVA) per queste pazienti, in cui sembrava essere **aumentata la sensibilità del microcircolo coronarico agli stimoli vasocostrittori associati ad una limitata capacità vasodilatatrice microvascolare.**

**Hanno proposto che la disfunzione di piccole arterie coronarie pre arteriolari intramurali potrebbe essere la causa patogenetica di questa sindrome.**



**Coronary blood flow is driven by the pressure difference between the aorta and the capillary bed and modulated further by various physical and neural factors, which affect the microcirculation. Moreover, the different compartments of the microcirculation are influenced by one main physiological mechanism to control their vascular tone with cardiac metabolism as the final determining factor.**



Negli ultimi 20 anni, tecniche invasive e non come la PET hanno permesso di stabilire il Flusso Miocardico Assoluto (MBF, mL / min / g), la riserva di flusso coronarico (CFR, il rapporto di MBF durante la vasodilatazione coronarica quasi massima rispetto al basale MBF) in volontari sani di diverse età e sesso.

La disponibilità di valori normali di MBF e CFR ha permesso lo studio della fisiologia coronarica in soggetti ad aumentato rischio di CAD e anche in diverse categorie di pazienti con sintomi e segni, indicativi di IM nonostante i normali angiogrammi coronarici

## Mechanisms of myocardial ischaemia

### Epicardial coronary arteries

### Coronary microcirculation

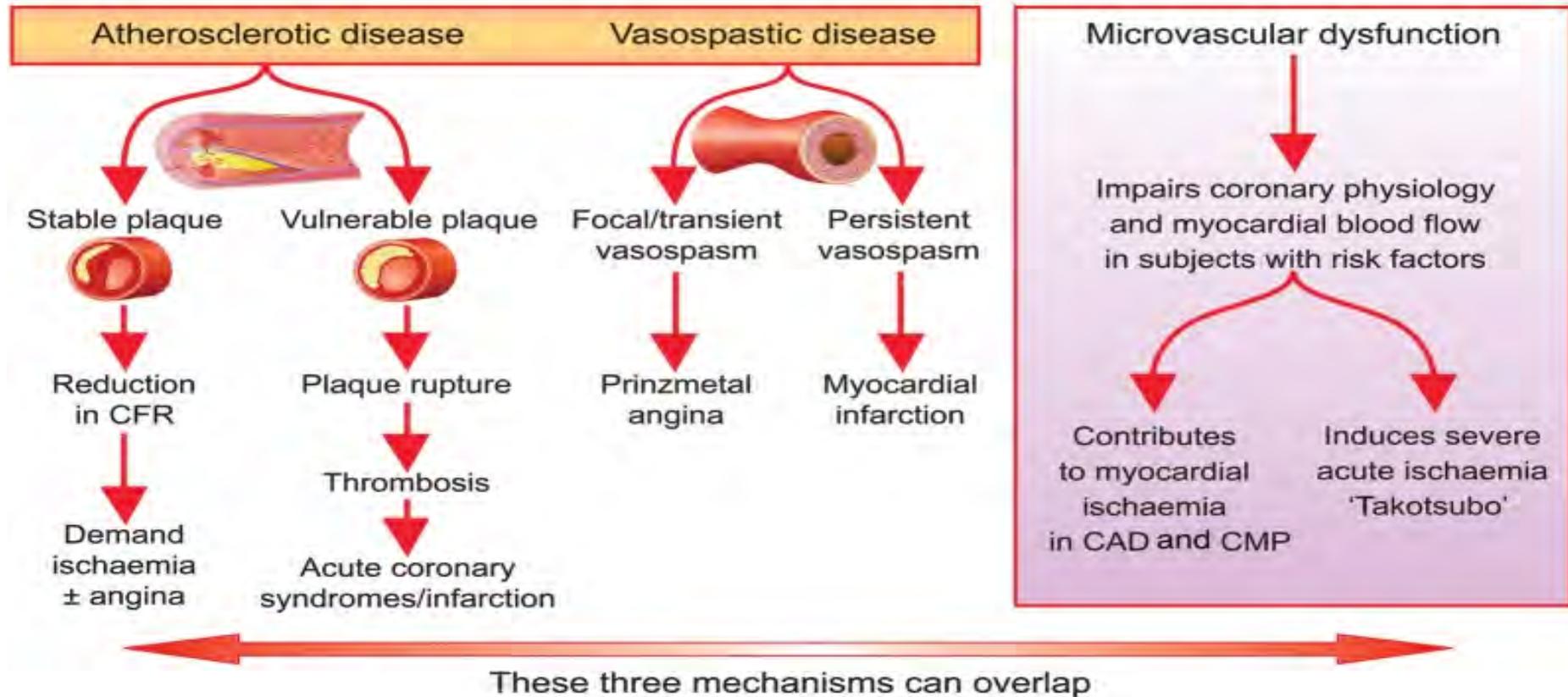
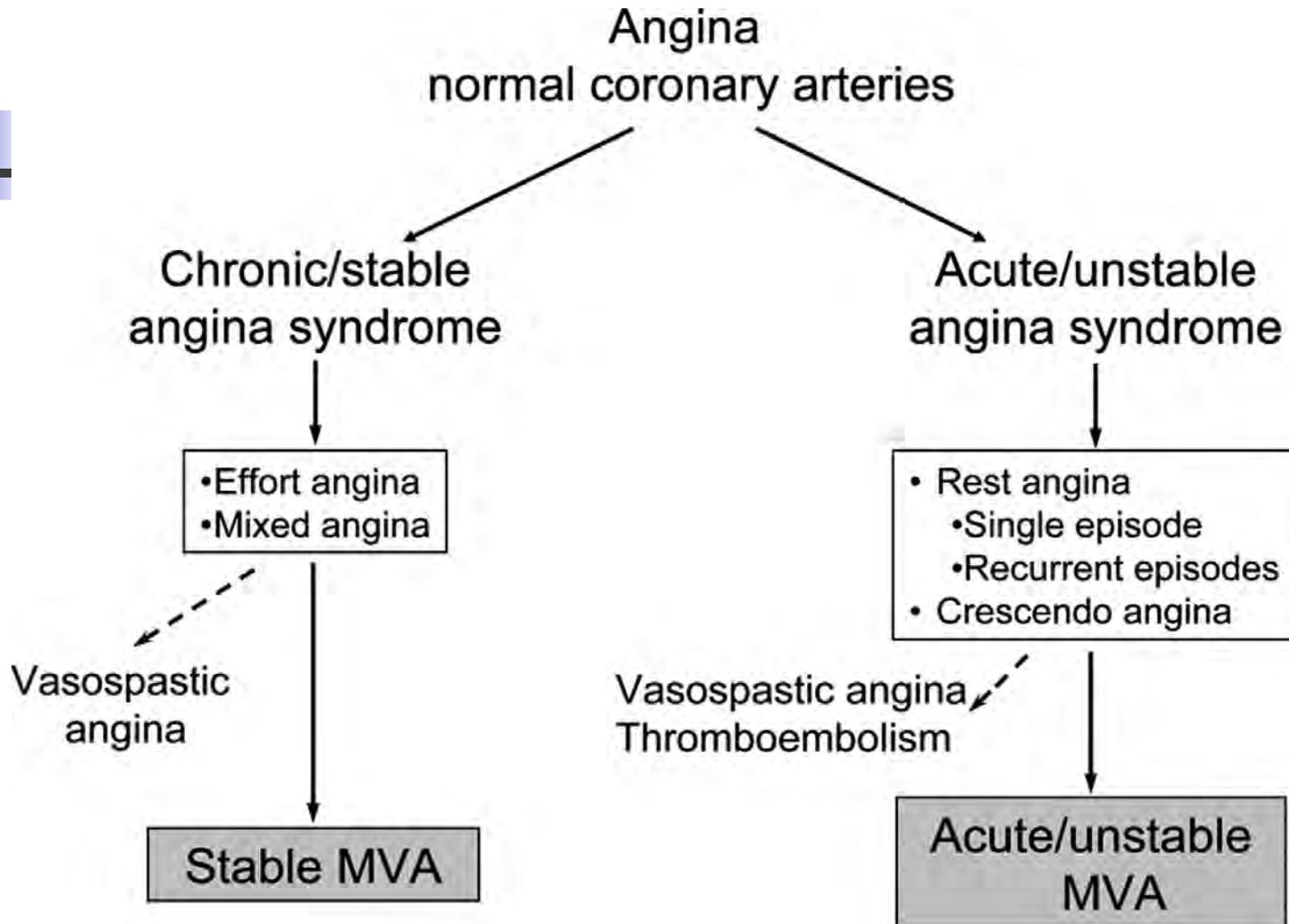


Figure 1. Clinical presentations of MVA and main differential diagnosis.



Gaetano Antonio Lanza, and Filippo Crea *Circulation*.  
2010;121:2317-2325

*Clinical update*

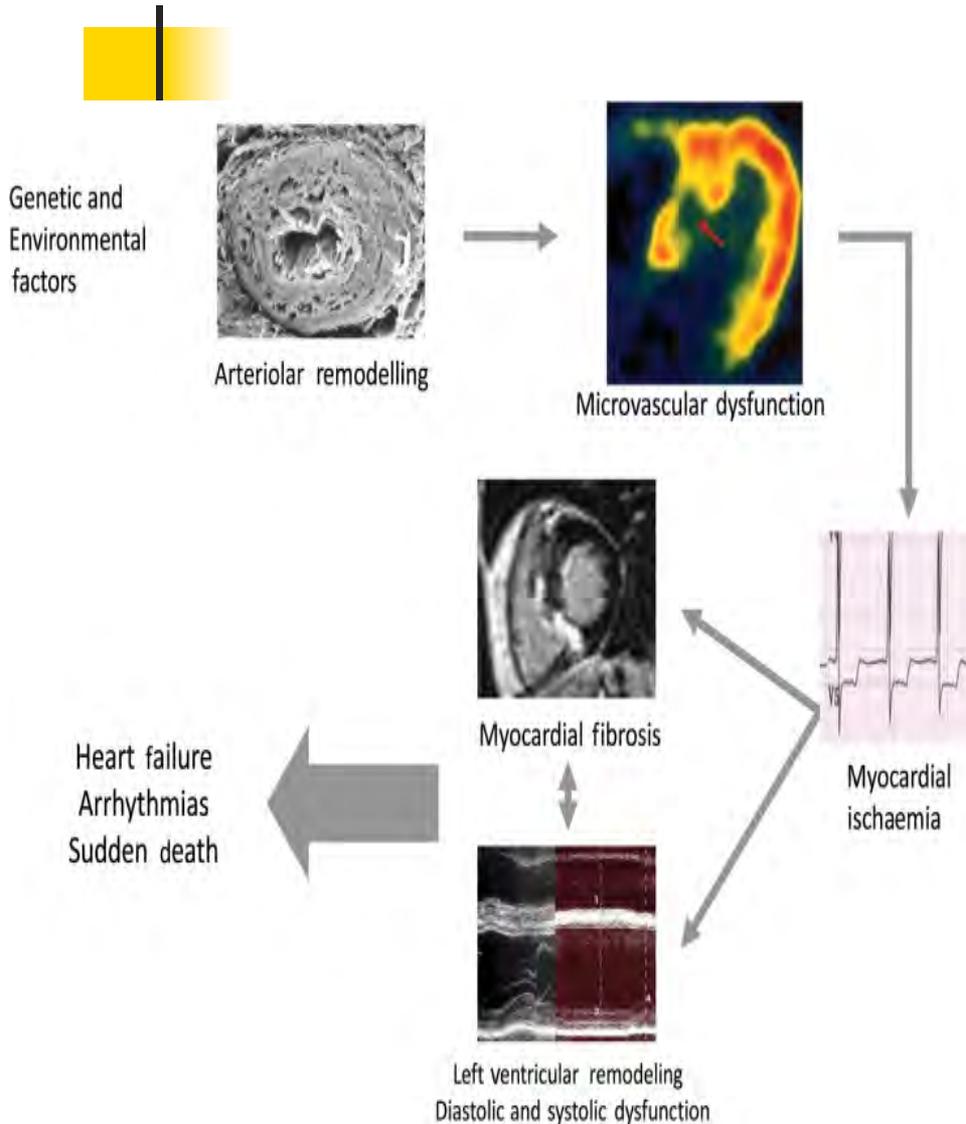
## Coronary microvascular dysfunction: an update

Filippo Crea<sup>1\*</sup>, Paolo G. Camici<sup>2</sup>, and Cathleen Noel Bairey Merz<sup>3</sup>

**Table 1** Classification of coronary microvascular dysfunction

	Clinical setting	Main pathogenetic mechanisms
Type 1: in the absence of myocardial diseases and obstructive CAD	Risk factors Microvascular angina	Endothelial dysfunction SMC dysfunction Vascular remodelling
Type 2: in myocardial diseases	Hypertrophic cardiomyopathy Dilated cardiomyopathy Anderson-Fabry's disease Amyloidosis Myocarditis Aortic stenosis	Vascular remodelling SMC dysfunction Extramural compression Luminal obstruction
Type 3: in obstructive CAD	Stable angina Acute coronary syndrome	Endothelial dysfunction SMC dysfunction Luminal obstruction
Type 4: iatrogenic	PCI Coronary artery grafting	Luminal obstruction Autonomic dysfunction

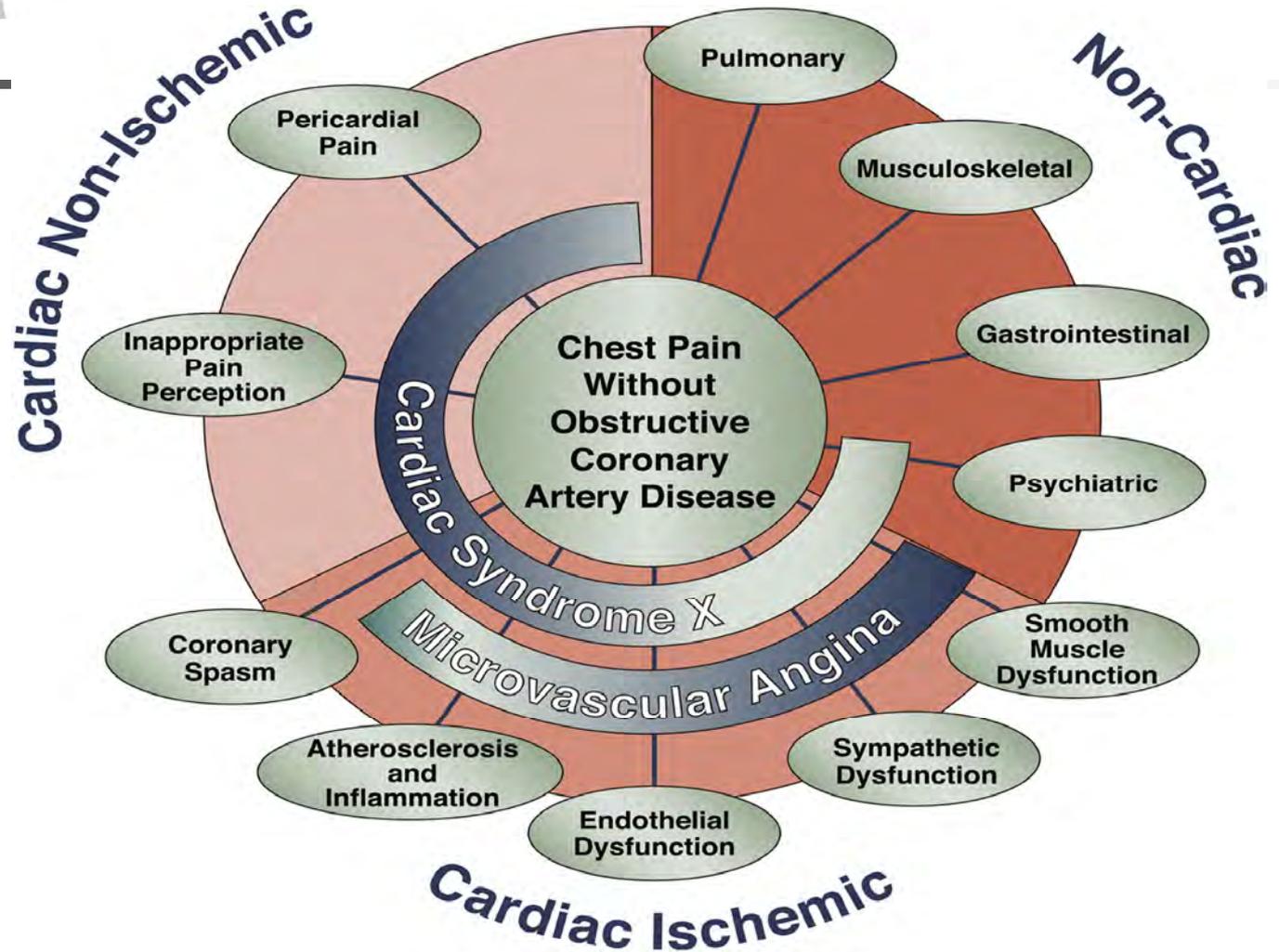
Cascata di eventi nella **cardiomiopatia ipertrofica**, dal rimodellamento arteriolare coronarico anormale che porta **all'ischemia miocardica**, alla fibrosi e al rimodellamento ventricolare sinistro avverso e allo scompenso cardiaco.



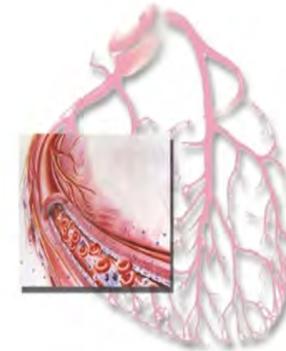
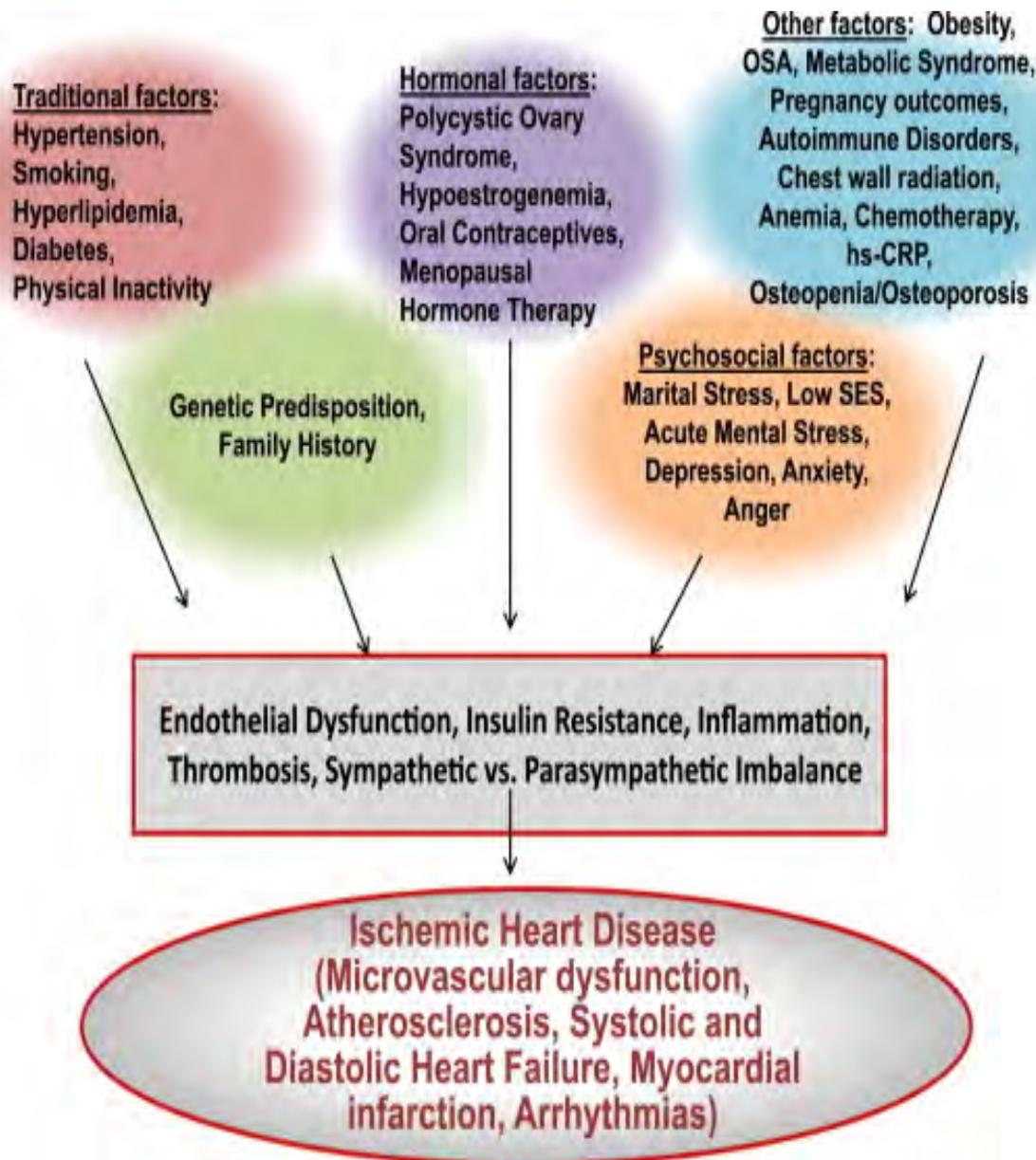
1. alterazioni strutturali piccole arterie coronarie (ipertrofia mediale, iperplasia intimale e la diminuzione del lume, sono considerate il substrato più rilevante che produce CMD e ischemia miocardica)
2. mutazioni del miofilamento del sarcomero dimostrabili sono caratterizzati da una CMD più grave e da una maggiore prevalenza di fibrosi miocardica, rispetto ai soggetti negativi al genotipo.
3. il gadolinium enhancement (LGE) tardivo, come visualizzato dalla CMR, è rappresentativo della fibrosi miocardica in HCM.
4. CMD nel tempo può portare a ricorrenti ischemia e morte dei miociti, agendo quindi come localizzatore della fibrosi sostitutiva
5. l'outcome a lungo termine nei pazienti con HCM; 1/3 dei pazienti, il decorso clinico è invalidante, complicanze come la fibrillazione atriale e l'ictus, morte correlata allo scompenso cardiaco.



Cosa c'è dietro ad un dolore toracico "angina" tipica / atipica nella donna in assenza di coronaropatia ostruttiva (stenosi > 50%)



# Fattori di rischio



Aorta  
Proximal  
blood pressure

Neural factors  
Noradrenaline  
Adrenaline  
Acetylcholine

Physical factors  
Extravascular compression  
LVEDP  
RVEDP



Capillaries venules  
Distal blood pressure

Mechanisms of  
vasoreactivity  
control

Determining factor	Endothelial	Myogenic	Metabolic
	NO EDHF Prostacyclin	ET-1, Ang II Thromboxane Prostaglandin H2	PLC PKC K <sup>-</sup> ATP
	Blood flow shear stress	Intraluminal pressure	Cardiac metabolism

Determining factor

Blood flow  
shear stress

Intraluminal  
pressure

Cardiac  
metabolism

# 1973 Syndrome X .....nel 1985, angina microvascolare...

## Primary 'microvascular angina'

Stable

Unstable

Predominant effort angina

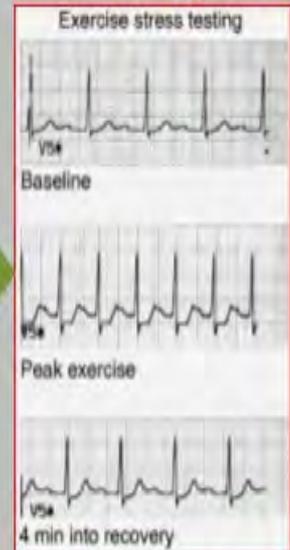
Acute rest angina

Largely investigated form Poorly investigated

## Primary 'Microvascular angina'



Typical Angina



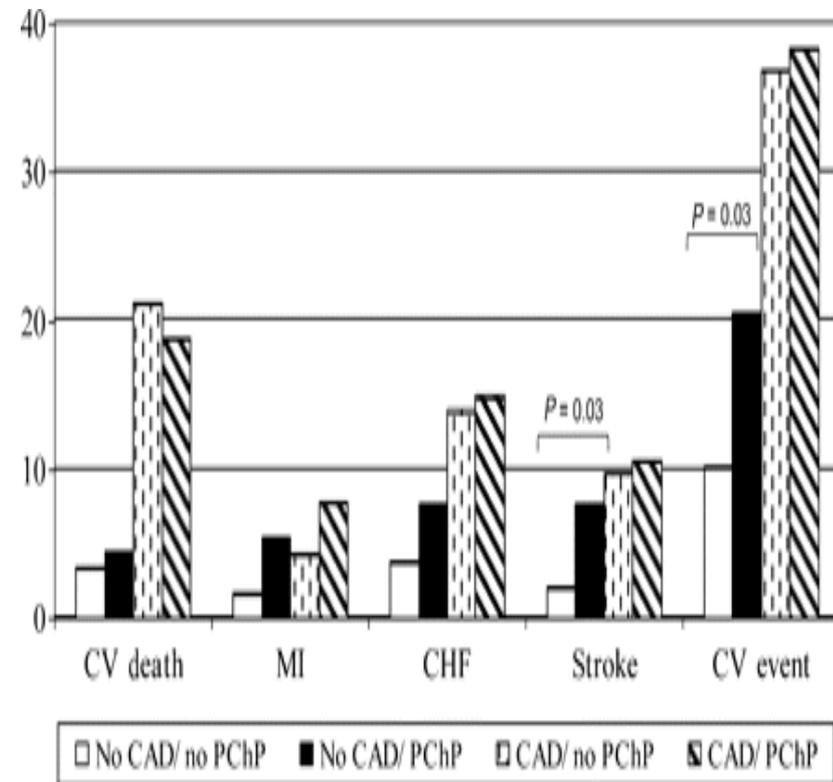
Evidence of stress-induced Myocardial ischemia



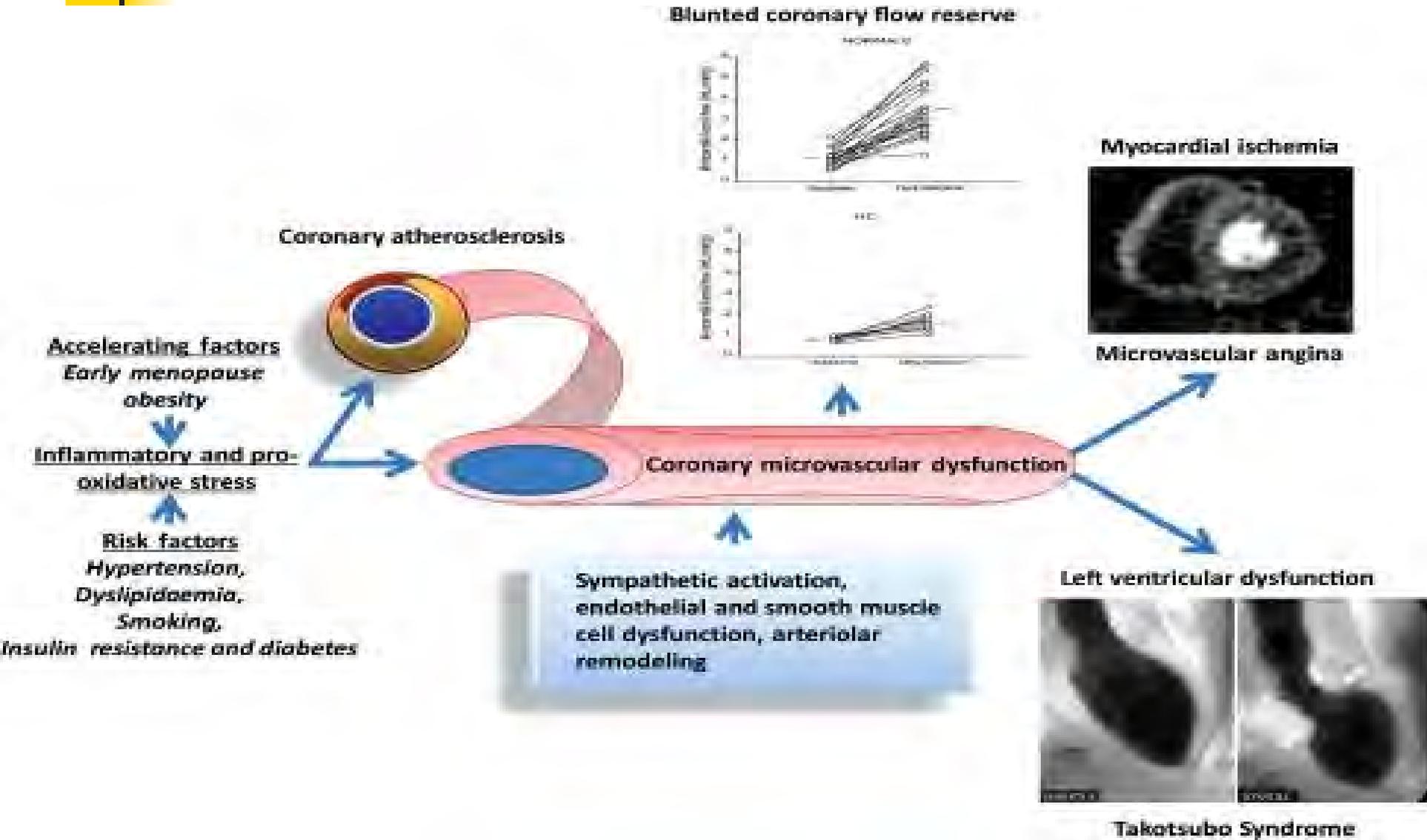
Normal coronary angiogram

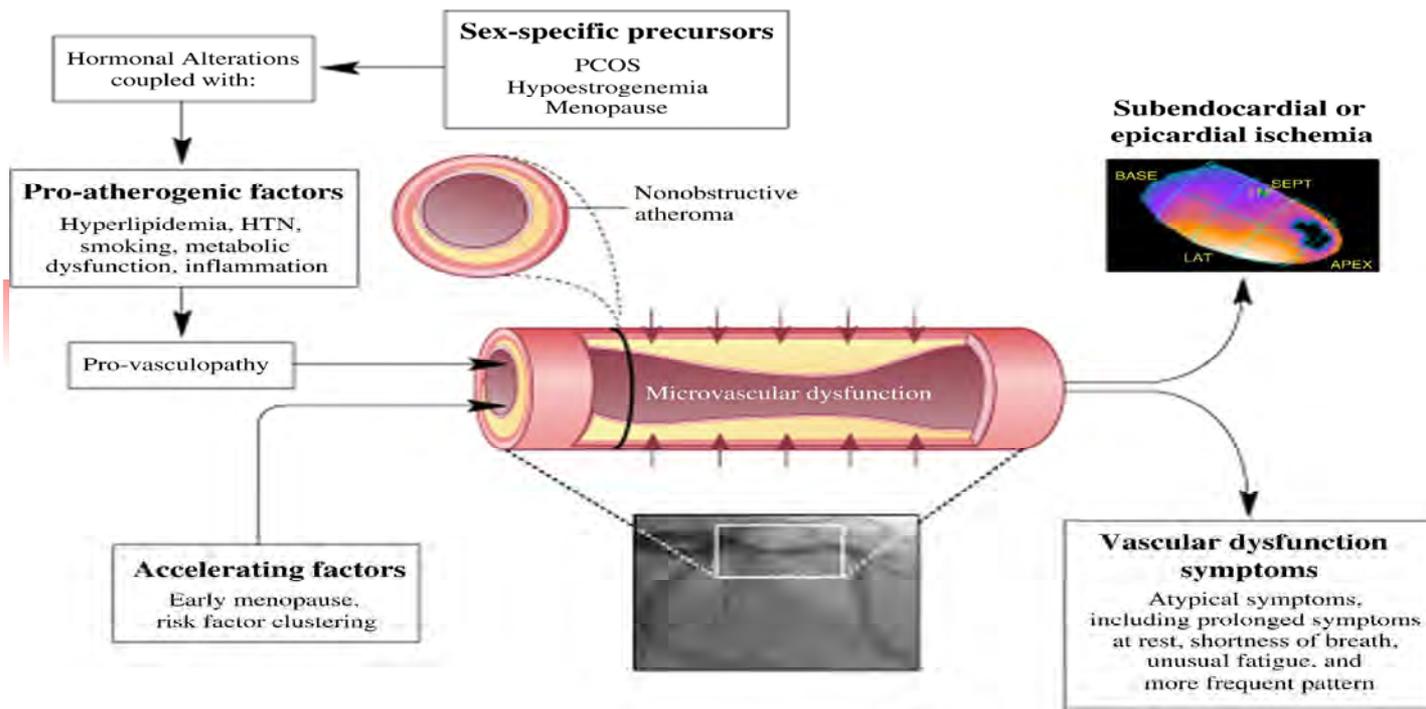
La disfunzione coronarica microvascolare (MCD) : riserva coronarica limitata (CFR) e / o disfunzione endoteliale coronarica è il meccanismo predominante dell'ischemia nelle donne con triade di dolore toracico, assenza di CAD ostruttiva e ischemia evidenziata da stress test.

- Lo studio (WISE) (NHLBI), hanno riportato che fino circa il **50%** delle donne con angina aveva angiografia coronarica normale o CAD non ostruttiva. **Sharaf B.L. et al Am J Cardiol 2001)**
- Le donne con CMD sono di solito nelle fasi della vita in perimenopausa o in menopausa, con insorgenza di sintomi tra 40 e 50 anni
- All'IVUS su un campione di 100 donne , 80% documentata ats coronarica con rimodellamento positivo della placca
- **La MCD è da ritenersi una patologia benigna, quale prognosi ?**
- La MCD è associata a un tasso di eventi avversi maggiori del **2,5% annuo** che include morte, infarto miocardico non fatale, ictus non fatale e insufficienza cardiaca congestizia.



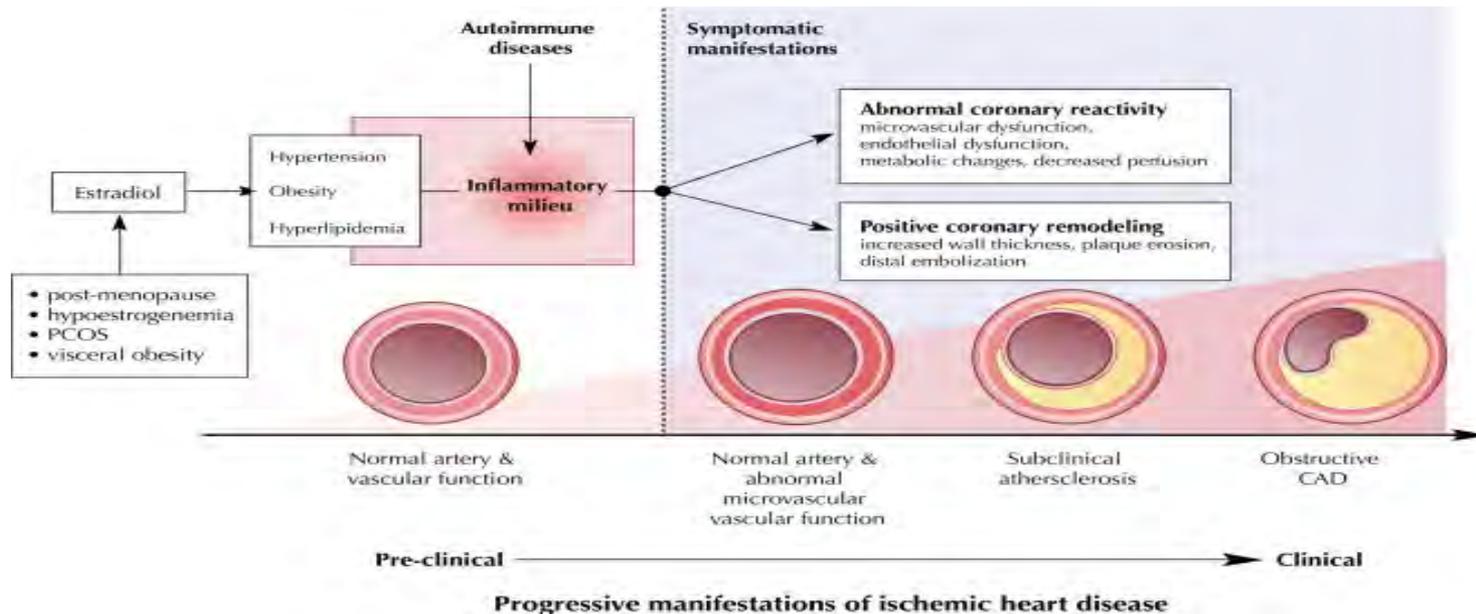
# potenziali cause e conseguenze della disfunzione microvascolare coronarica





Nella donna adulta :  
dalla disfunzione del microcircolo coronarico,

Alla coronaropatia ostruttiva, nella donna anziana

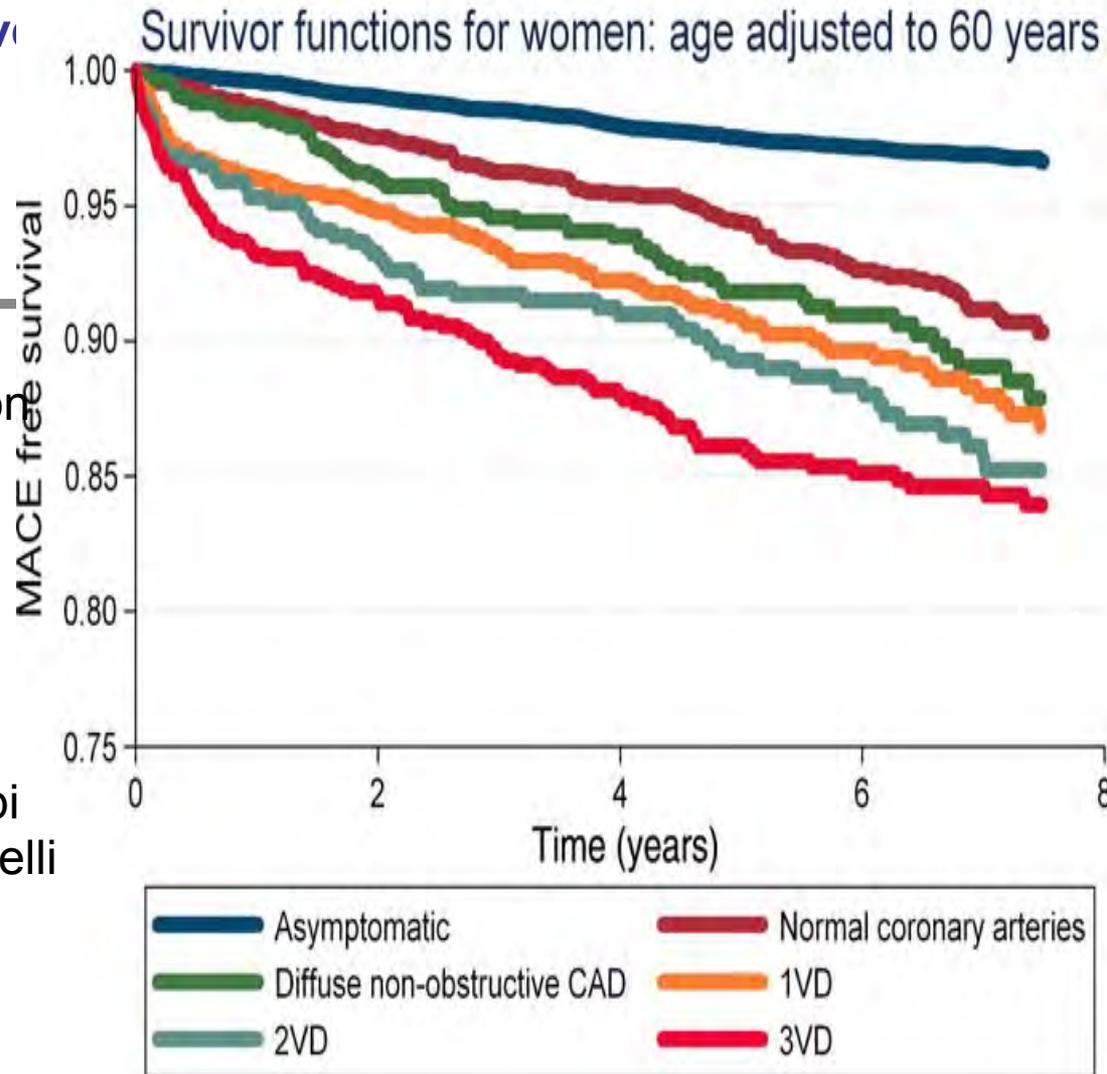


**SA in women with no obstructive CAD is associated with higher risk of MACEs (n=4,711)**

Circa il 20% -30% delle pazienti con MVA stabile sperimenta un progressivo peggioramento dei sintomi con compromissione significativa della qualità della vita.

Tra i soggetti con angina e un normale angiogramma, i sottogruppi ad alto rischio sembrano essere quelli con ischemia documentata, lieve CAD e disfunzione microvascolare.

Il rischio di eventi epicardici si manifesta durante il follow-up a lungo termine (> 2 anni)



(Jespersen et al, EHJ 2011)

# LOGICA dei TEST PROVOCATIVI

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**SFORZO**



**FARMACO**

**Dobutamina**



**Dipiridamolo**



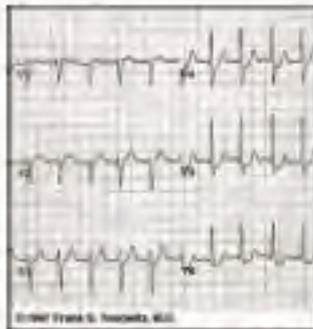
**Adenosina**



**INDUZIONE di ISCHEMIA**

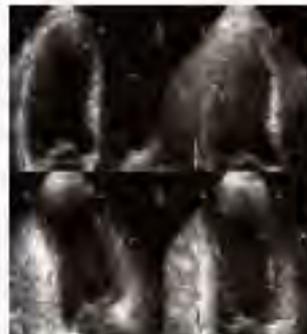
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**ecg**



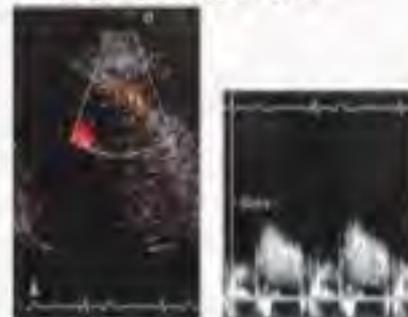
**TEST da SFORZO**

**cinesi**

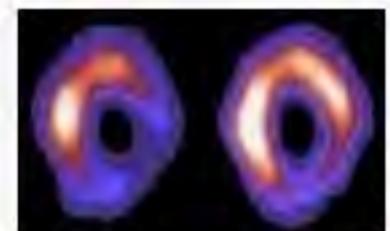


**ECO STRESS**

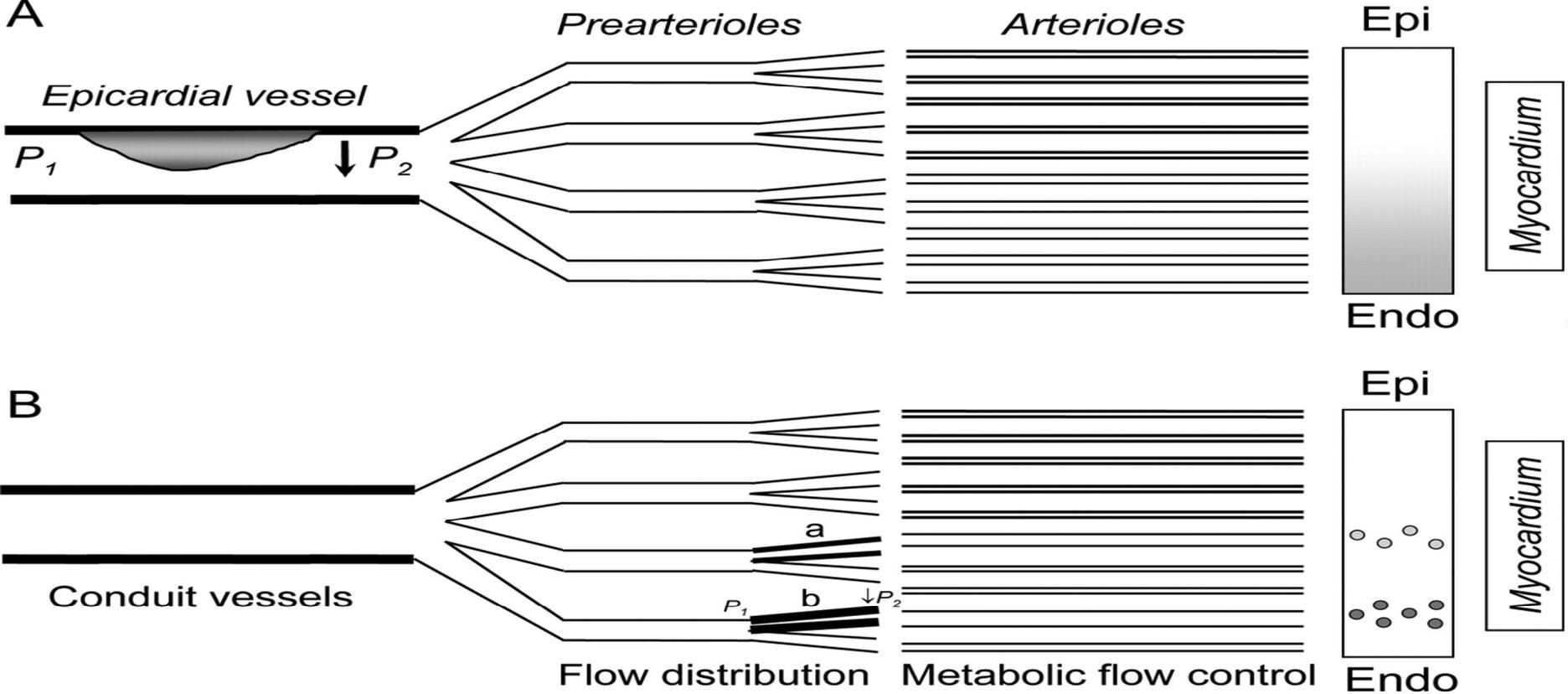
**riserva  
coronarica**



**perfusione**



**SCINTIGRAFIA**



Differenze nell'ischemia miocardica causate da una significativa stenosi coronarica

(A) o da CMVD (B).

A. stenosi epicardica, l'ischemia miocardica coinvolge diffusamente l'intero territorio miocardico ( subendocardico) causando così una disfunzione contrattile regionale.

Nel caso di alterazioni microvascolari, l'ischemia miocardica è localizzata solo in piccole aree subendocardiche e non (piccoli cerchi); non visibili anomalie contrattili a causa della presenza di normali cellule miocardiche contrattili nello stesso territorio.

Technique	Mechanism	Stressor Agent	Measurement	Diagnostic techniques
<b>Invasive</b>				
Coronary angiography	Endothelium-dependant vasodilation	Acetylcholine	CFR $\leq 50\%$ or increases in coronary diameter $\leq 20\%$ after maximum dose of acetylcholine	Intracoronary Doppler flow wire and quantitative coronary angiography
	Endothelium-independent vasodilation	Adenosine	CFR $< 2.5$ or CFVR $< 2.24$	Intracoronary Doppler flow wire and quantitative coronary angiography
Inflammatory markers and vascular tone modifiers		N/A	CRP, homocysteine, endothelin-1 and nitric oxide levels	Standard testing through blood draws
<b>Non-invasive</b>				
Stress echocardiography	Endothelium-independent vasodilation	Adenosine	CFR $< 2.0$	Doppler echocardiography
Contrast echocardiography	Myocardial perfusion	Dipyridamole	Myocardial blood flow reserve $< 2.0$	Ultrasound contrast agent (Definity) and intermittent/ultraharmonic imaging modality
PET imaging ( $H_2^{15}O$ and $C^{15}O$ , $^{13}N$ - $NH_3$ , $^{82}Rb$ , $^{18}FDG$ )	Myocardial perfusion and cellular metabolism	Dipyridamole or adenosine	CFR $< 2.5$	Quantitative and qualitative myocardial perfusion
MR spectroscopy	Cellular metabolism (measurement of myocardial high energy phosphates)	Isometric handgrip exercise	Drop in phosphocreatine: ATP ratio during handgrip $> 2$ SD below mean in controls.	Magnetic resonance spectroscopy
Stress CMR	Myocardial perfusion	Adenosine	CFR cut off variable in different studies.	Quantitative and qualitative myocardial perfusion
Peripheral endothelial testing	Reactive hyperemia Digital reactive hyperemia	Cuff inflation for 5 min Cuff inflation for 5 min	Brachial artery flow mediated dilation Reactive hyperemia index	Brachial artery ultrasonography Peripheral arterial tonometry using Endo-PAT device
Autonomic function testing	Sympathetic/parasympathetic activity	N/A	Heart rate variability	24-h ambulatory ECG monitors

**49-year-old woman** with chest pain

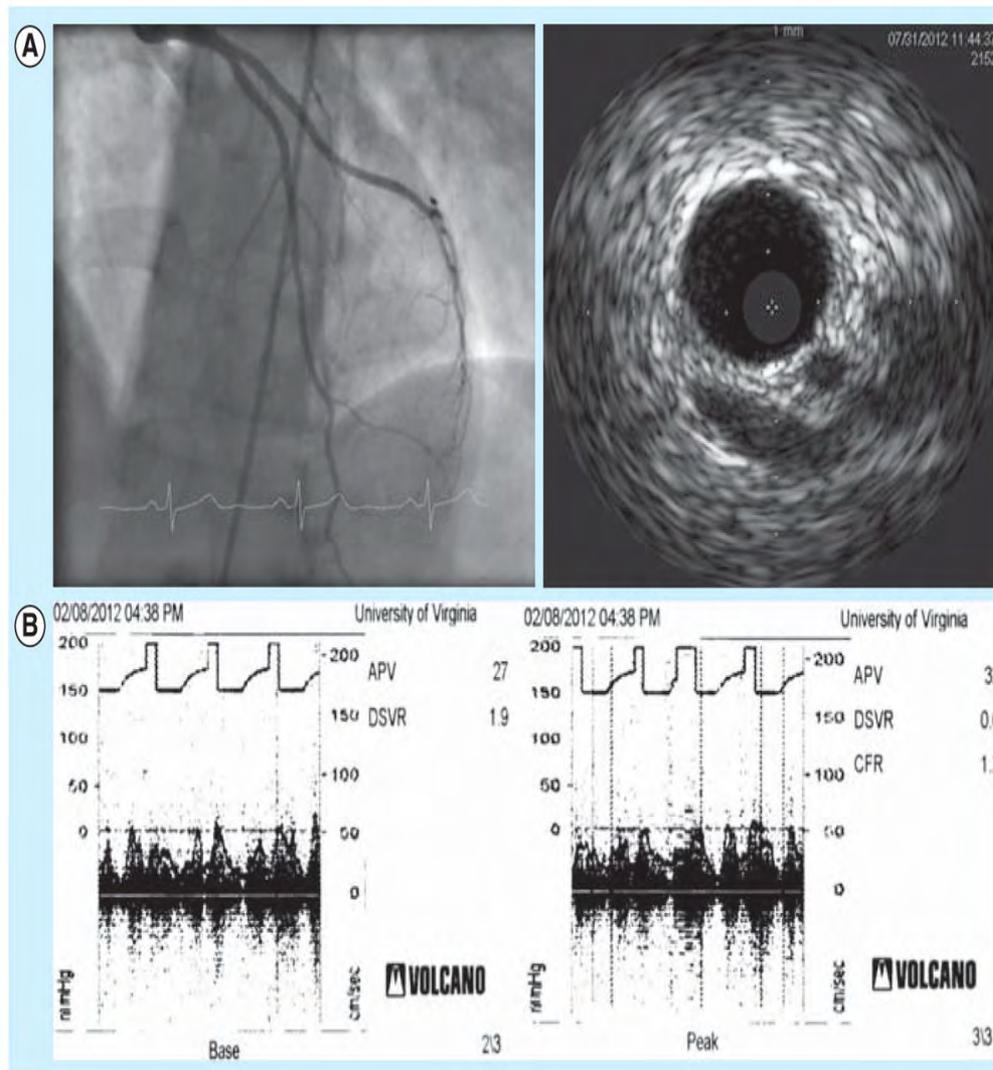
A. Cardiac catheterization showed minimal disease in left anterior descending artery.

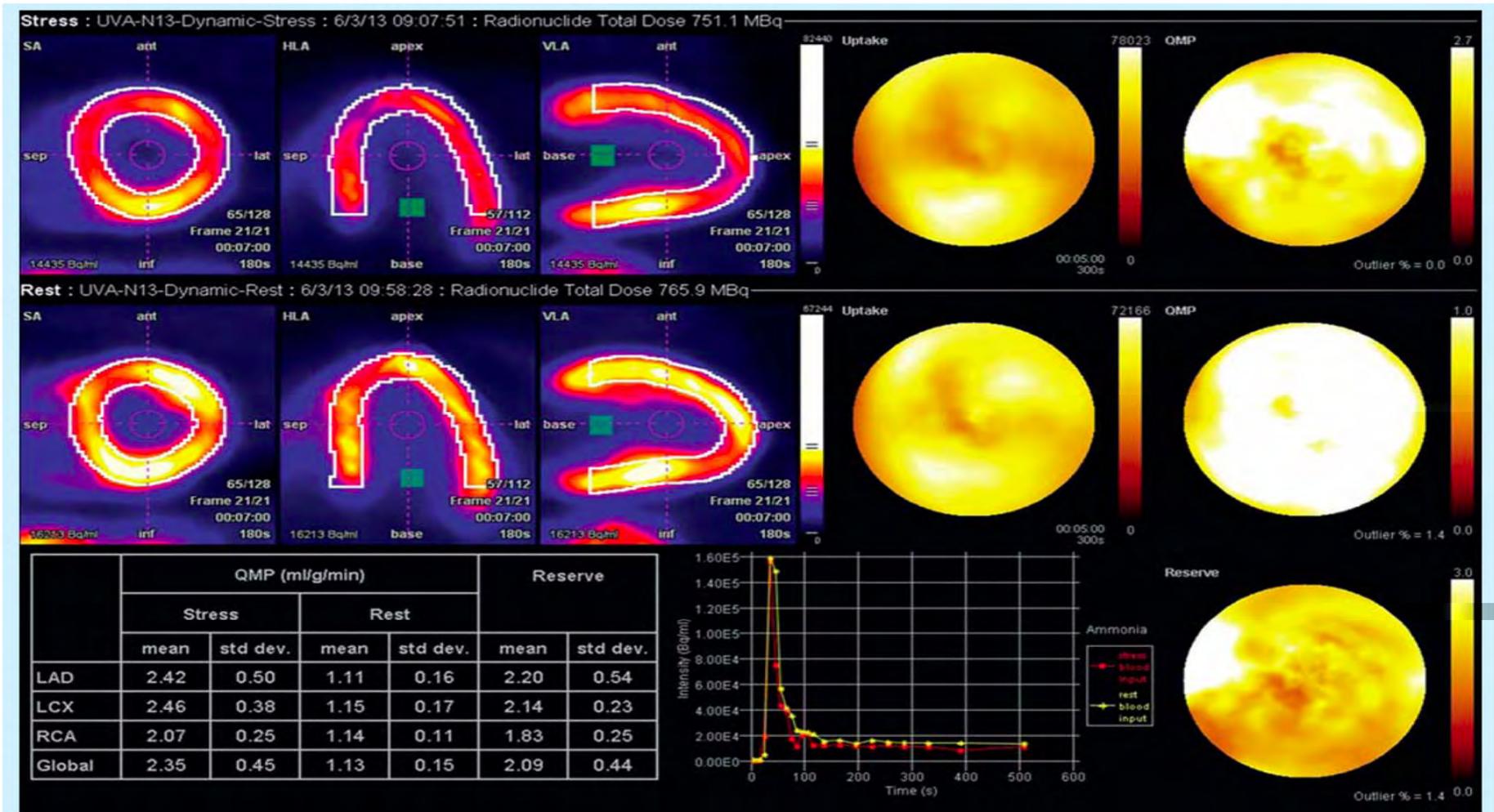
Intravascular ultrasound (right) showed 15% plaque burden in the LAD .

B. Coronary flow reserve (CFR) testing for patient in (A) as performed with intracoronary Doppler blood flow velocity wave forms before adenosine (left), and after adenosine infusion (right).

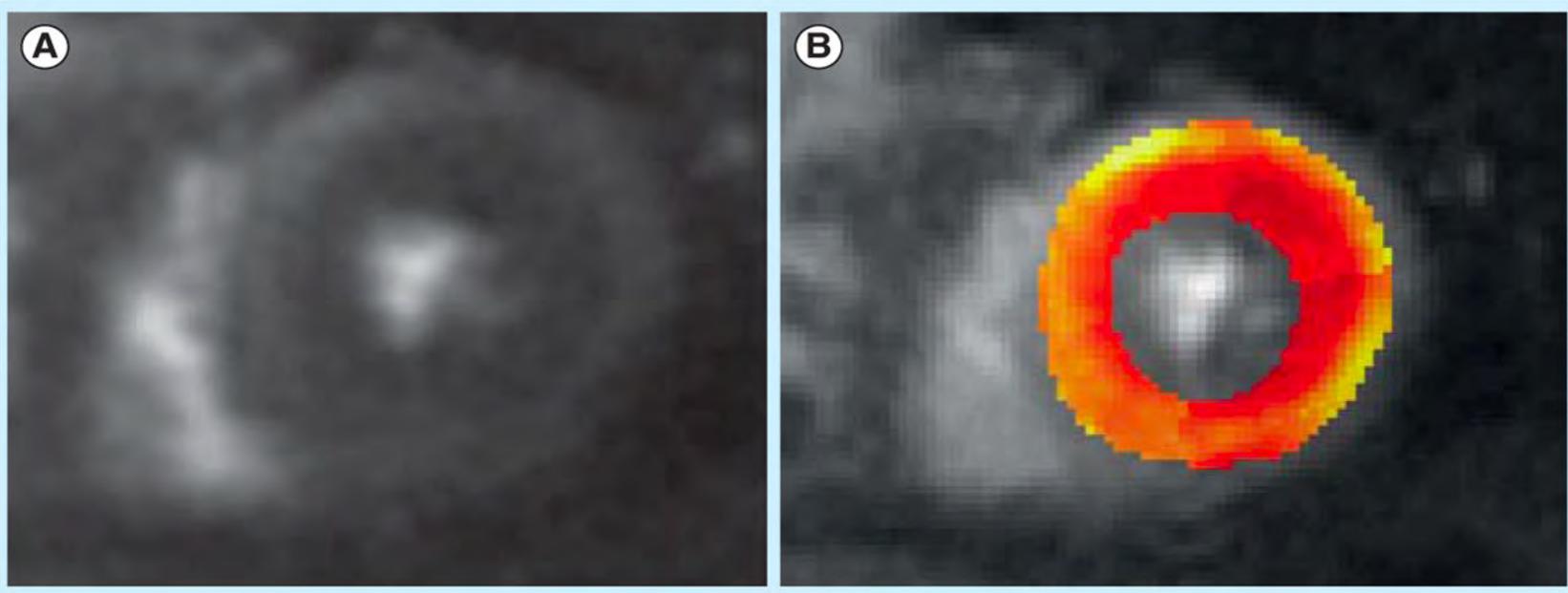
CFR is the ratio of average peak velocities before and after adenosine

The measured CFR was 1.2 and suggestive of coronary microvascular dysfunction





**56-year-old woman** with recurrent angina, positive stress test and multiple cardiac catheterizations showing minimal coronary artery disease  $^{13}\text{N-NH}_3$  PET perfusion imaging shows impaired increase in global perfusion post adenosine administration. Measured CRF = 2.09.



**57-year-old woman** with persistent chest pain and non-obstructive coronary artery disease on cardiac catheterization.

### Stress cardiac magnetic resonance

A. Mid-ventricular short axis view containing both papillary muscles. (

B. Perfusion image of the same short axis with a superimposed perfusion map with color coded areas. Red : decreasing blood flow all the way to yellow, which shows maximum perfusion.

This patient has reduced subendocardial and a normal increase in epicardial perfusion following adenosine infusion.

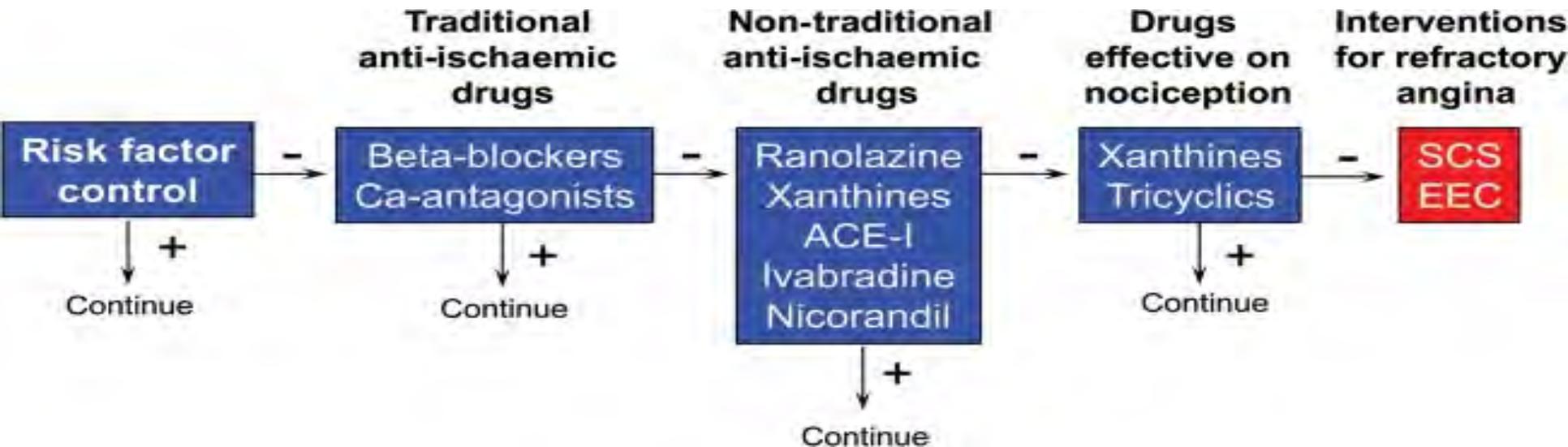
Calculated coronary flow reserve in this case was 1.42 and suggestive of coronary microvascular dysfunction

# Diagnosis and Treatment Based on Fractional Flow Reserve and Coronary Flow Reserve Values

	FFR $\leq$ 0.80	FFR $>$ 0.80
CFR $>$ 2.0	<p><b>Diagnosis</b> Flow-limiting stenosis Preserved microvascular function</p> <p><b>Treatment</b> PCI</p>	<p><b>Diagnosis</b> Non-flow-limiting stenosis Preserved microvascular function</p> <p><b>Treatment</b> Medical therapy, no PCI</p>
CFR $<$ 2.0	<p><b>Diagnosis</b> Flow-limiting stenosis CMVD</p> <p><b>Treatment</b> PCI</p>	<p><b>Diagnosis</b> Non-flow-limiting stenosis CMVD</p> <p><b>Treatment</b> Medical therapy, no PCI</p>

# Algoritmo di trattamento per pazienti con angina microvascolare.

Per le donne con evidenza di ischemia ma nessuna CAD ostruttiva, le terapie antianginose e anti-ischemiche possono migliorare i sintomi, la funzione endoteliale e la qualità della vita.



# Old anti-anginals

<b>DRUG CLASS</b>	<b>VASODILATION</b>	<b>HEART RATE</b>	<b>MYOCARDIAL CONTRACTILITY</b>
Short acting nitrate - <b>sublingual</b>	↑		
Beta-blockers		↓	↓
Long-acting nitrates	Limited effect in coronary microcirculation		
Calcium channel blockers	<u>DHP</u> <i>Amlodipine</i> ↑	<u>Non-DHP</u> <i>Diltiazem and Verapamil</i> ↓	↓

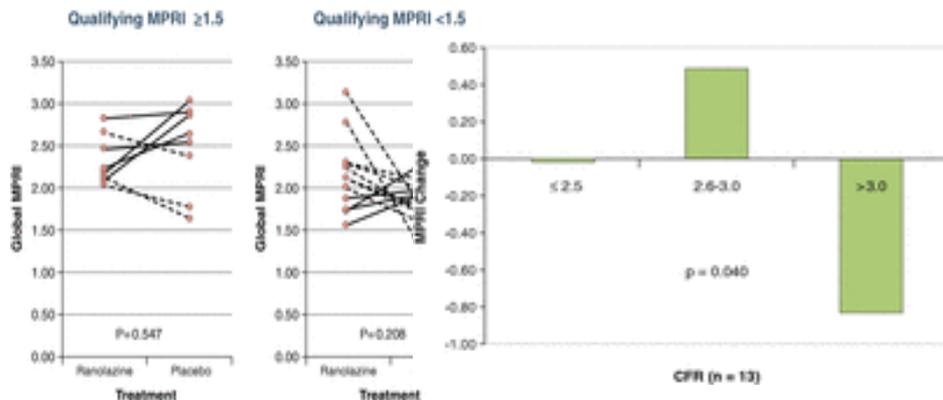
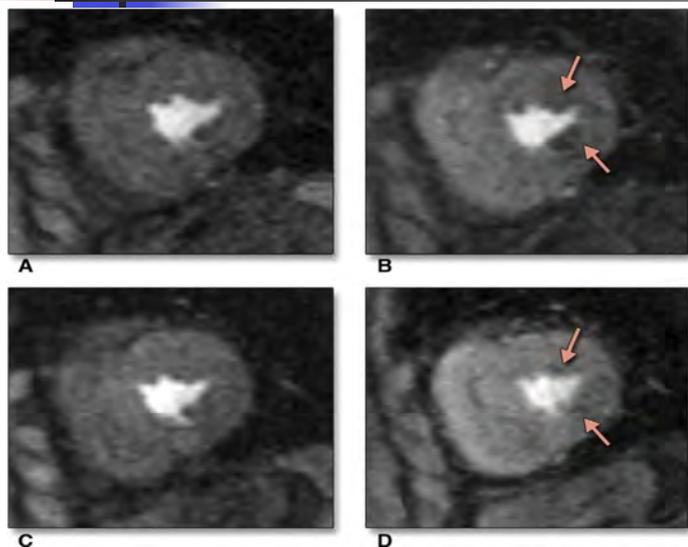
# Newer anti-anginals

<b>Drugs</b>	<b>Main anti-ischemic effects</b>
Ranolazine	Improvement of left ventricular relaxation and diastolic function during ischemia
Ivabradine	Reduction of heart rate
Nicorandil	Vasodilation through ATP/K-channel opening and nitrate-like effects
Trimetazidine	Improved cardiac metabolism during ischemia

# Ranolazine Improves Angina in Women With Evidence of Myocardial Ischemia But No Obstructive Coronary Artery Disease

Puja K. Mehta, et al . JACC: Cardiovascular Imaging, May 2011

Nelle donne con angina, evidenza di ischemia e assenza di CAD ostruttiva, questo studio pilota randomizzato ha rivelato che la ranolazina migliorava l'angina, la qualità della vita, l'ischemia miocardica può migliorare, che le anomalie di perfusione in particolare tra le donne con CFR basso.



-derivato piperazinico, agisce sul miocardio ischemico tramite l'inibizione della corrente  $\text{Na}^+$  tardiva verso l'interno, che interrompe il sovraccarico di calcio ( $\text{Ca}^{2+}$ ) nei miociti ischemici. Un aumento del sovraccarico di  $\text{Ca}^{2+}$  nel miocardio ischemico è stato associato a disfunzione diastolica ventricolare sinistra.

Studi hanno dimostrato che la ranolazina migliora la funzione diastolica ventricolare sinistra nei pazienti con cardiopatia ischemica

## Additional drugs

<b>Drugs</b>	<b>Main anti-ischemic effects</b>
<b>ACE inhibitors</b>	<b>Improved endothelial function; antagonism of angiotensin II</b>
<b>Statins</b>	<b>Improvement of endothelial function</b>
<b>Xanthines</b>	<b>Redistribution of coronary blood flow towards ischemia areas</b>
<b><math>\alpha</math>-antagonists</b>	<b>Anti-<math>\alpha</math> vasoconstrictor effects</b>
<b>Estrogens</b> (Post-menopausal women)	<b>Improvement of endothelial function</b>

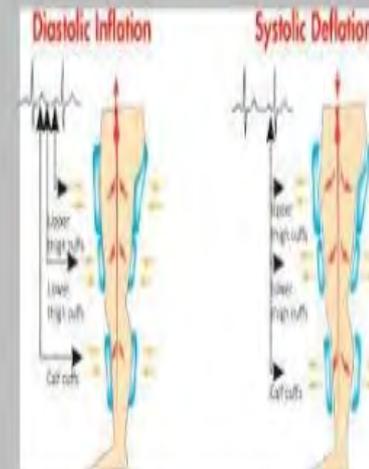
## Additional alternative therapies proposed for patients with refractory microvascular angina

## Spinal cord stimulation

Therapy	Anti-angina effects
Imipramine	Inhibition of visceral pain transmission
<i>Non-pharmacological Treatments :</i>	
Spinal cord stimulation	Modulation of pain transmission and processing; modulation of ischemic sympathetic effects
Enhanced external counterpulsation	Improvement of endothelial function; development of coronary microvessels
Rehabilitation programs	Training effect; reduction of sympathetic tone
Psychologic interventions	Improvement of pain tolerance; reduction of anxiety



## Enhanced external counterpulsation



# Treatment in patients with MVA

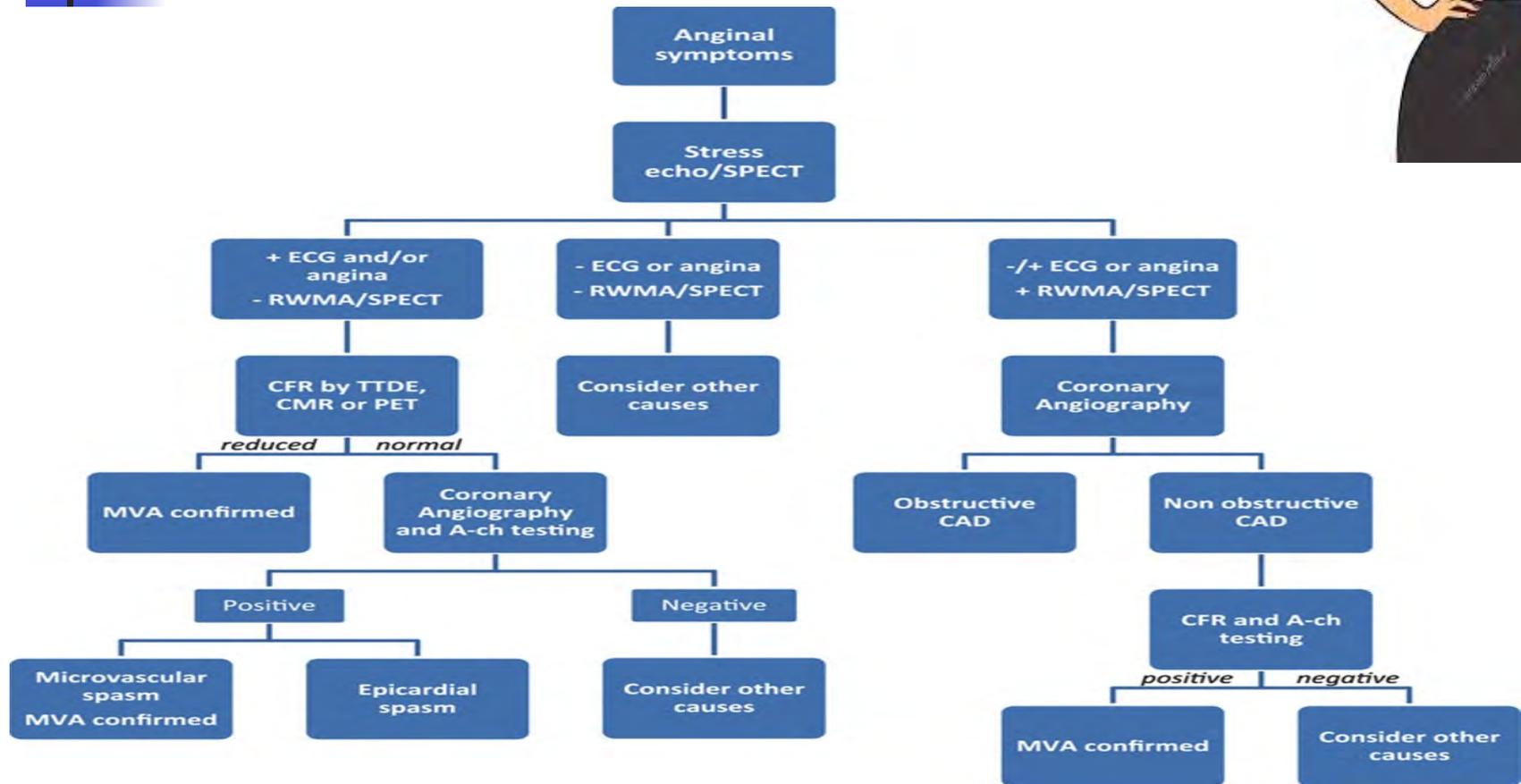


Recommendations	Class	Level
It is recommended that all patients receive secondary prevention medications including <b>aspirin and statins</b> .	I	B
<b>β-blockers</b> are recommended as a first line treatment	I	B
<b>Calcium antagonists</b> are recommended if β-blockers do not achieve sufficient symptomatic benefit or are not tolerated.	I	B
<b>ACE inhibitors</b> or <b>nicorandil</b> may be considered in patients with refractory symptoms	IIb	B
<b>Xanthine</b> derivatives or nonpharmacological treatments such as <b>neurostimulatory techniques</b> may be considered in patients with symptoms refractory to the above listed drugs.	IIb	B



## Microvascular Angina A Women's Affair?

Proposed algorithm for the diagnosis of microvascular angina (MVA).





***Grazie !!***

