

Collection Harlequin

**Le coeur  
ne souffre pas**  
E. Marc Jolicoeur



**Telles les licornes, l'angine sur  
coronaires normales n'existe pas!**





**Non pas parce que l'angine ne peut  
survenir sur des coronaires  
exemptes d'athérosclérose**

**Mais bien parce que les coronaires  
normales n'existent pas!**



# Angine

**Les coronaires sont comme les  
belle-mères, elles ne sont jamais  
tout à fait normales**



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## **Conflits intérêts (Marc Jolicoeur)**

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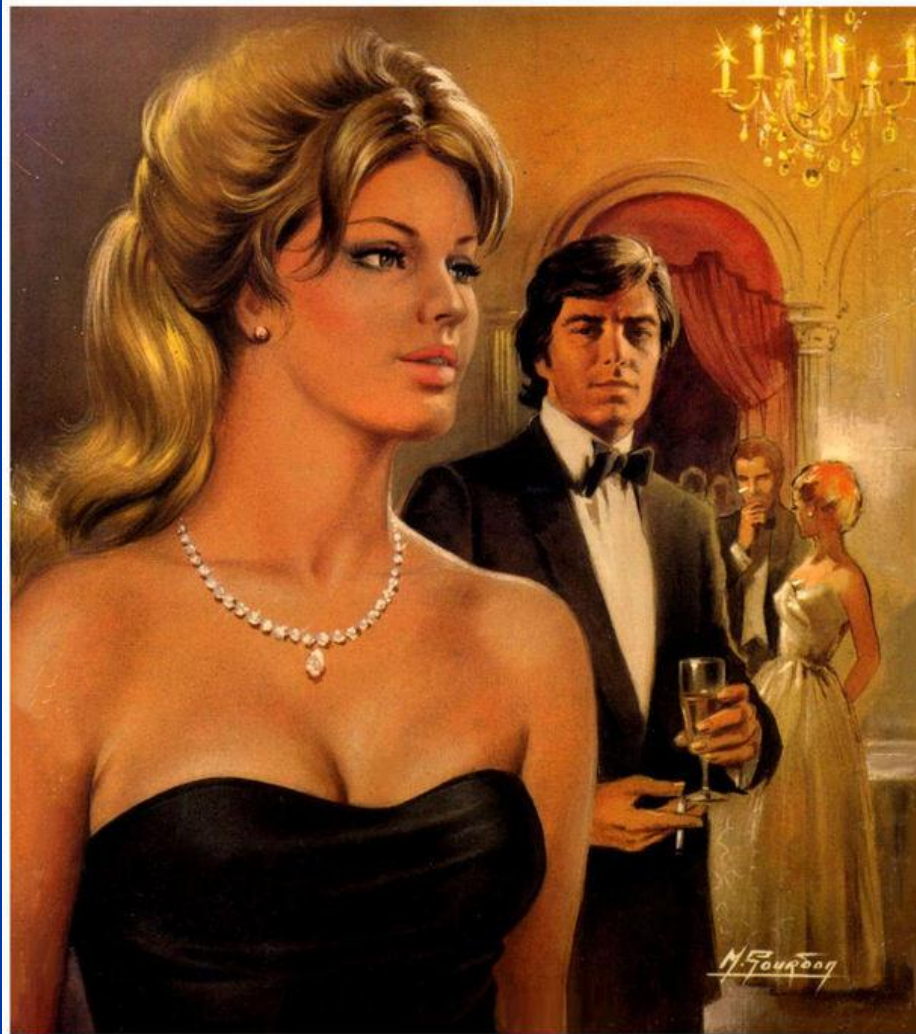
**Fonds de la recherche  
en santé**

**Québec** 



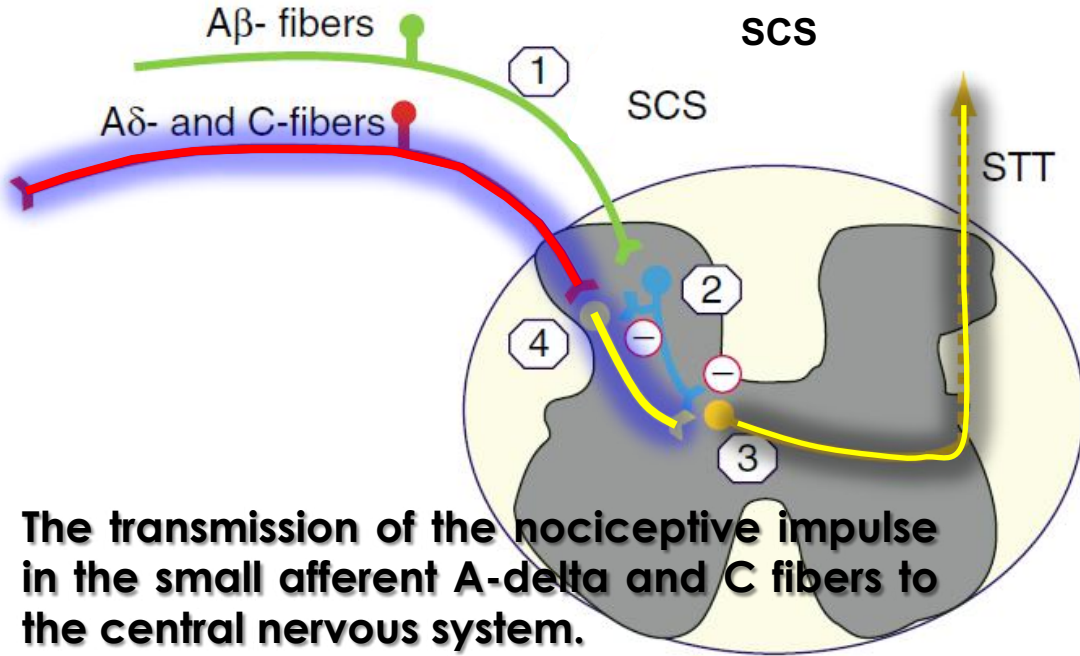
**CIHR IRSC**  
Canadian Institutes of Health Research  
Instituts de recherche en santé du Canada



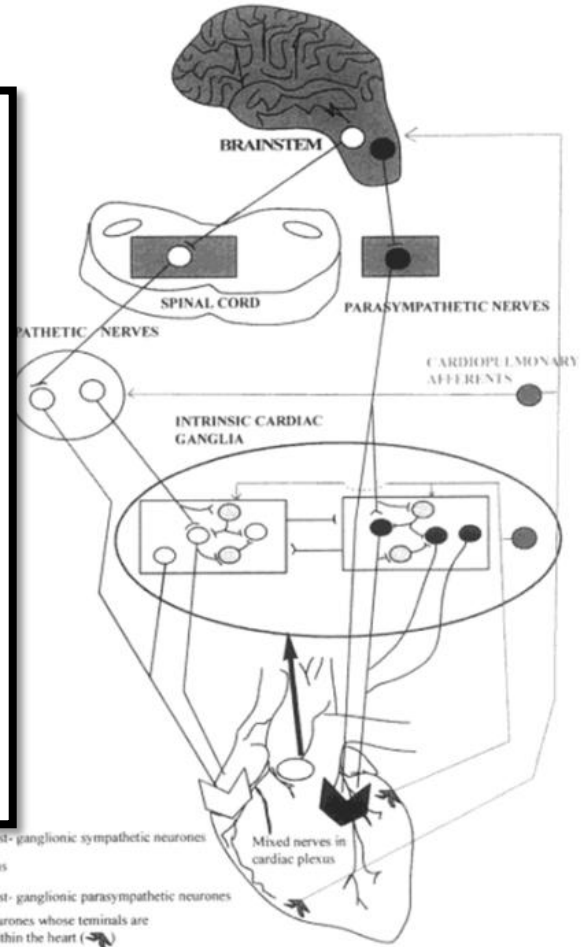


# Objectifs

- **Décrire les pathologies recherchées.**
- **Recommander l'investigation appropriée.**
- **Décrire le traitement recommandé en fonction du diagnostic.**



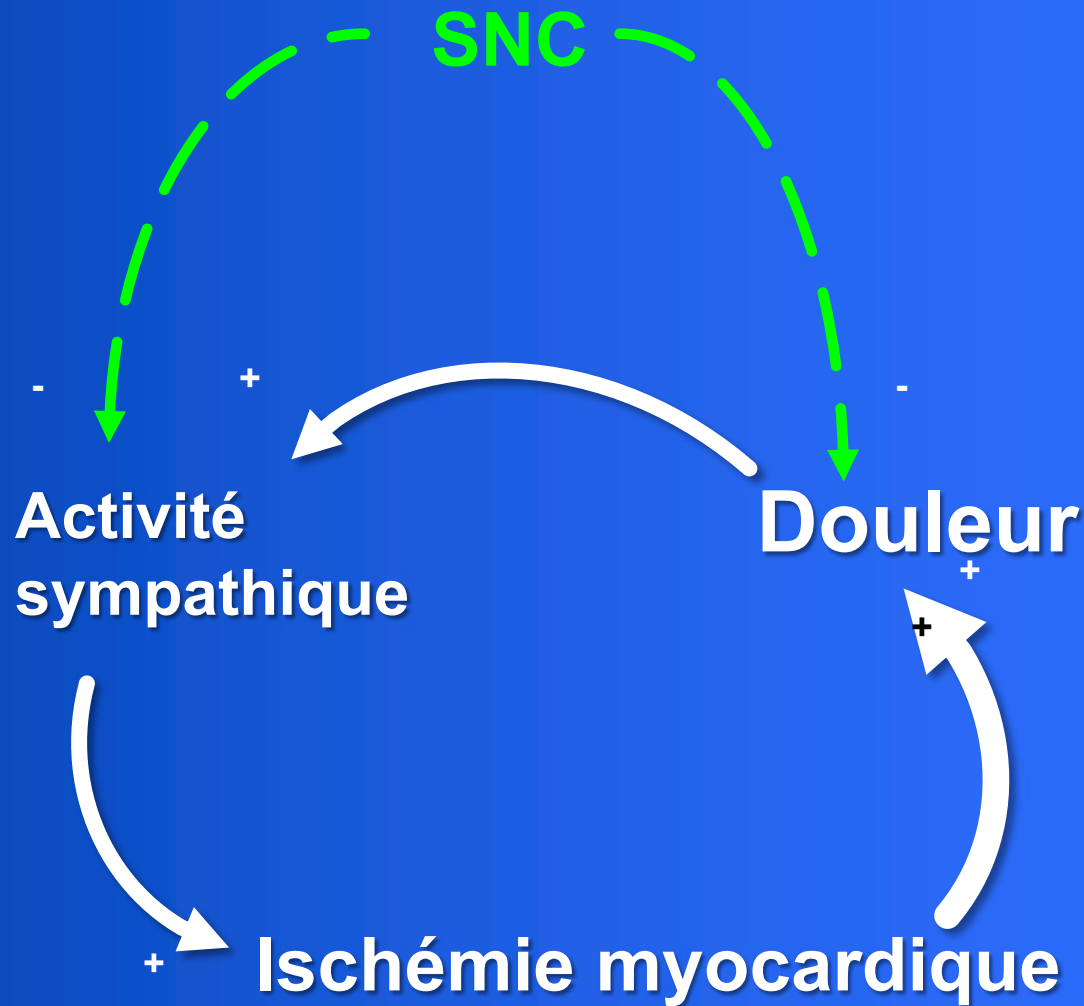
The transmission of the nociceptive impulse in the small afferent A-delta and C fibers to the central nervous system.



Il n'existe pas de nocicepteur connu dans le myocarde. Les nerfs sympathiques permettent la principale efférence nociceptive du myocarde. Le signal nociceptif converge vers les ganglions stellaires et cervicaux, jusqu'à la colonne intermédiolatérale (T2 to T6) Ultimement, le signal converge vers le SNC via les voies spinothalamiques



# Mécanisme d'action:



## Angine ischémique

## Angine neurogénique

Cortex  
cérébral

Absence de  
douleur



Douleur

Absence de  
douleur



Douleur

Thalamus  
(portillon)



Coeur



Normal

Angina  
pectoris

Ischémie  
silencieuse

Syndrome X

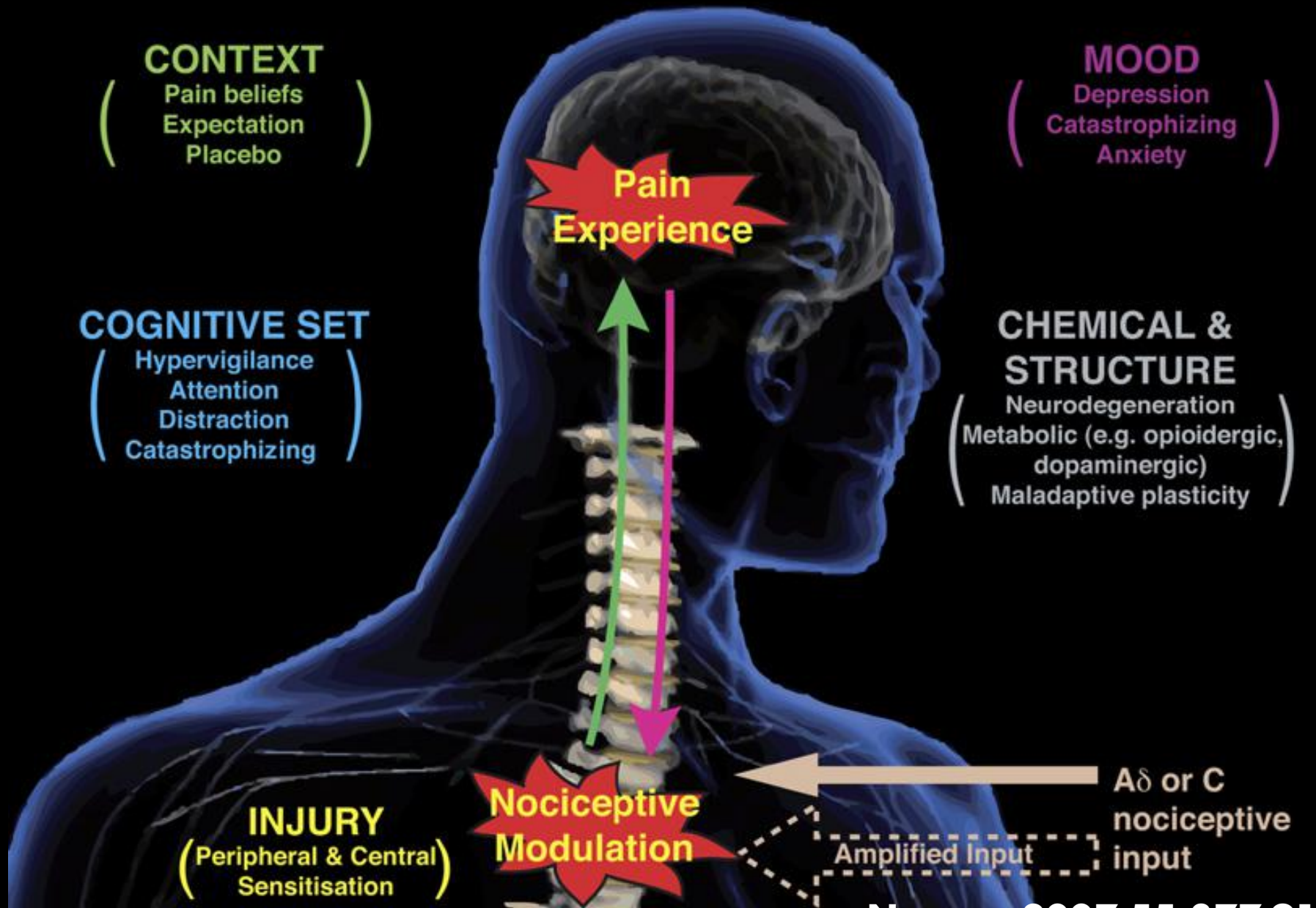
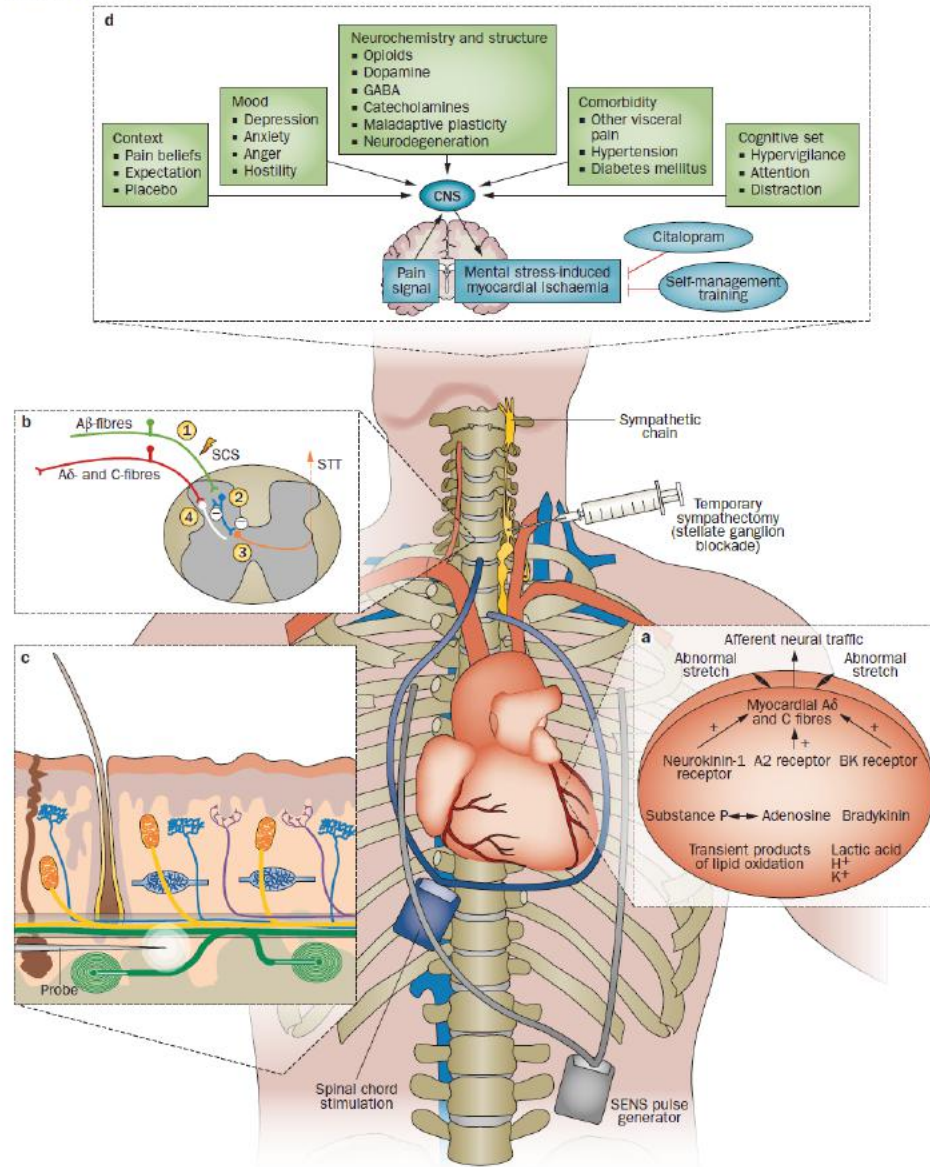


Figure 8



# Message No. 1



**Le coeur ne souffre pas. La douleur cardiaque est un signal nociceptif originant du coeur, transit par les voie efferentes sympathiques et qui est reconstitué au cerveau. N'importe quelles pathologies sur la voie neurogène peut causer de l'angine avec des coronaires normales. On parlera alors d'angine neurogénique**



**ASSUMONS UN INSTANT QUE  
DANS LE CAS QUI NOUS  
INTÉRESSE, IL Y AIT VÉRITABLEMENT  
ISCHÉMIE MYOCARDIQUE**



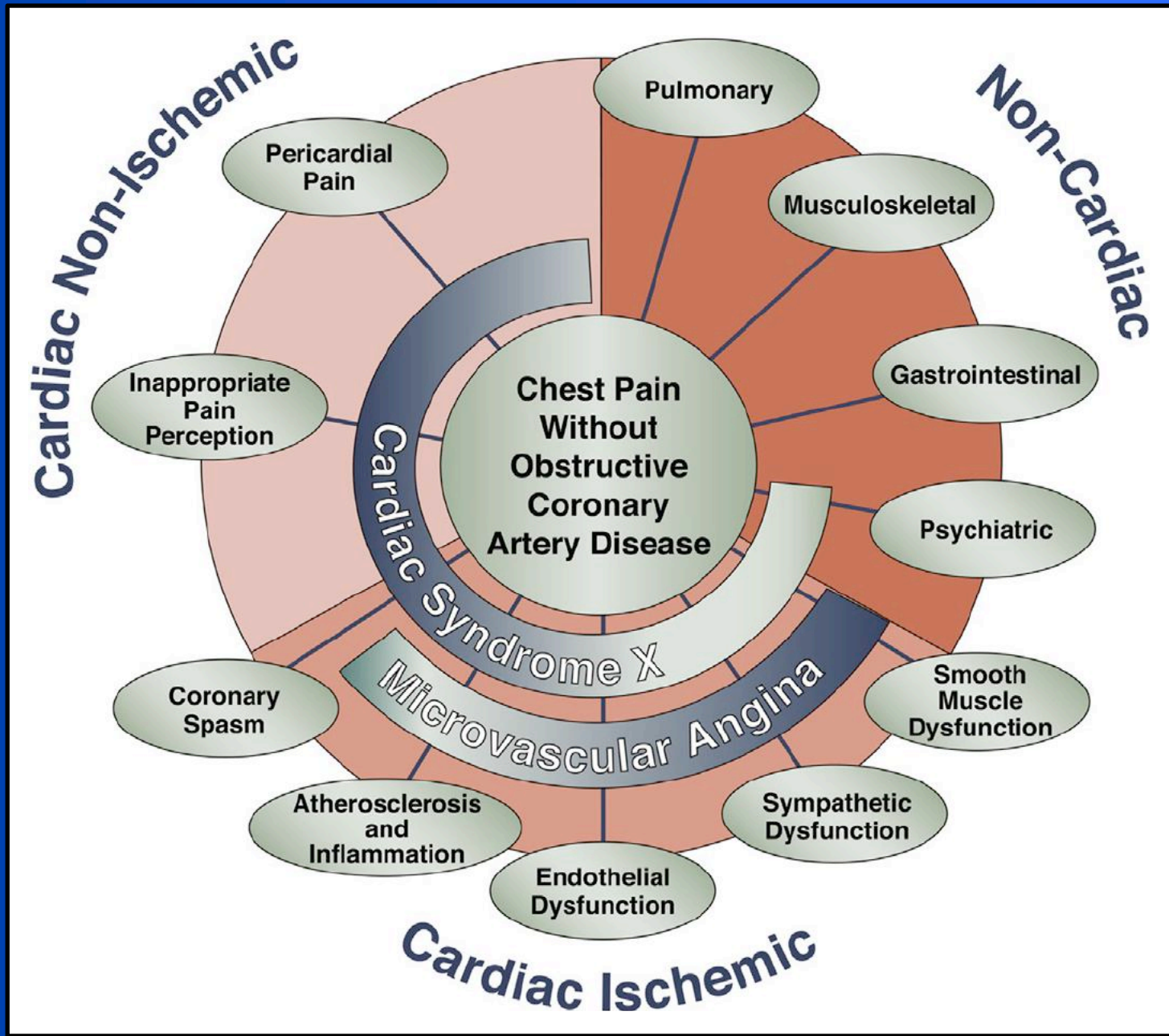
**Art: Antoine Tava; « Screaming heart »**

# **Au-delà de la coronnaire**

**Épicarde  
Microcirculation  
Myocarde  
mitochondrie**

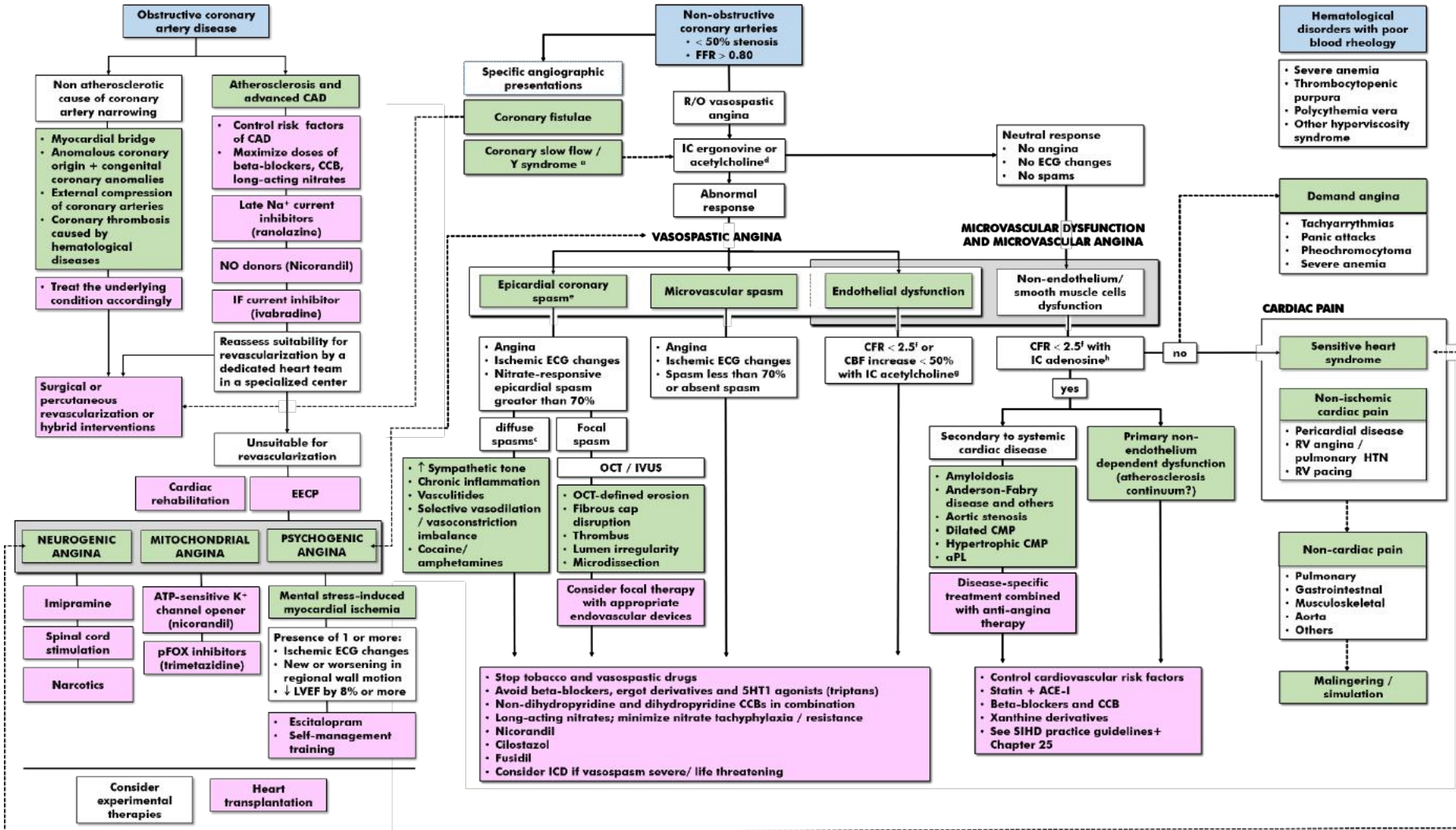
# Quelques définitions

- **Syndrome X (syndrome de Campeau):** triade couplant angine + depression ST au stress (effort) + coronaires exemptes d'athérosclérose
- **Angor microvasculaire:** ischémie myocardique en absence de lésion épicardique significative (athérosclérose des petits vaisseaux)
- **Douleur cardiaque:** signal nociceptif originant du coeur sans évidence d'ischémie myocardique
- **Angine vasospastique:** sténose paroxystique coronaire, réversible par nitrates avec ou sans MCAS
- **Ischémie myocardique induite par le stress mental:** depression ST objectivée lors d'un stress mental

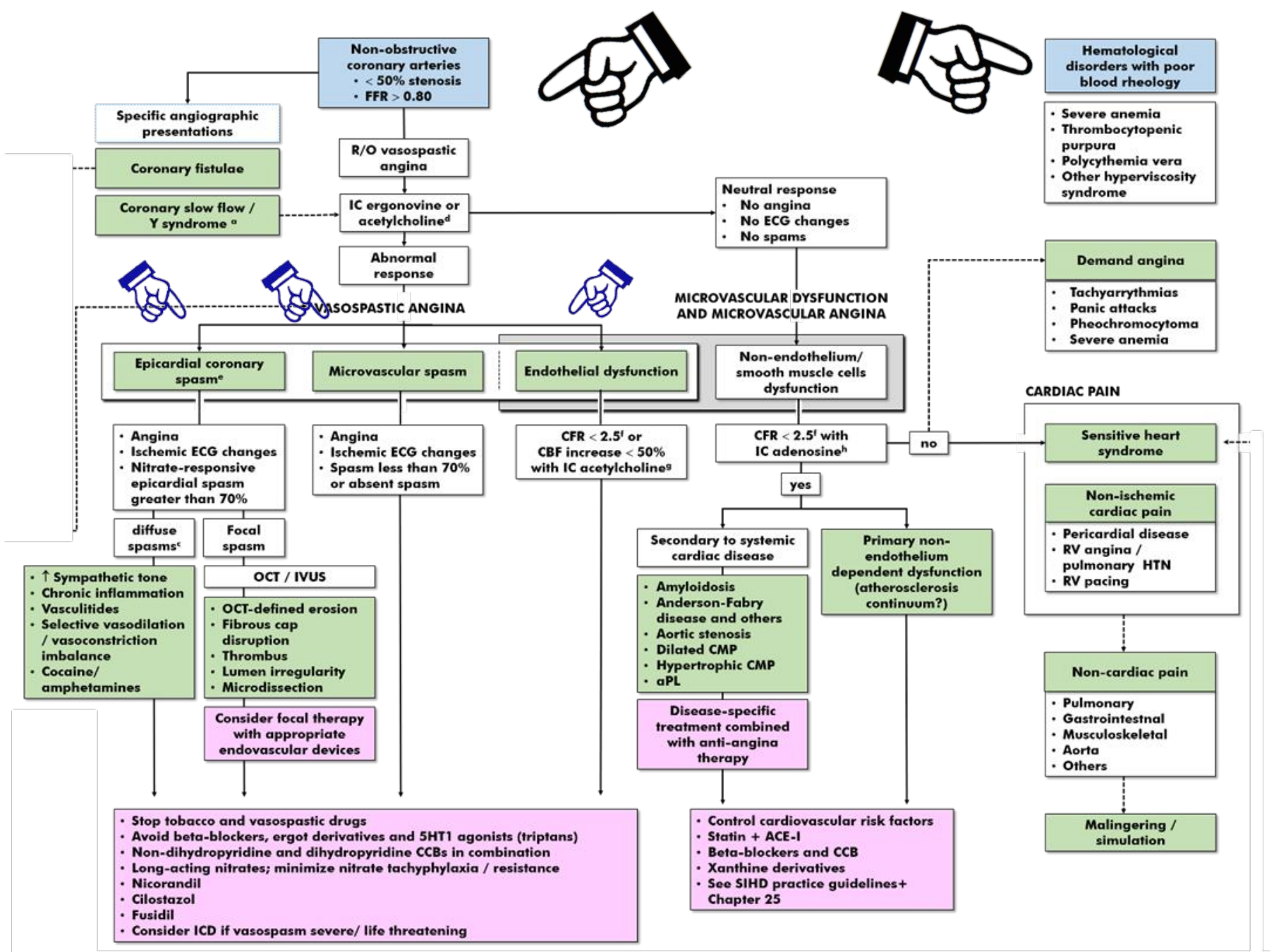




# Angines réfractaires







# Mental stress-induced myocardial ischemia

Syndrome cœur sensible

Viscosité

Dysfonction microvasculaire

Douleur cardiaque

Simulation

Hémoglobinopathie

Cardiomyopathie infiltrative

Embolie coronaire

Fistules coronaires

**CORONAIRES NORMALES**

Syndrome Y  
Syndrome X

# Message No. 2



**Les coronaires normales n'existent pas. Une patiente (ou un patient) qui accuse éésente des douleurs cardiaques présente le plus souvent un spasme coronaire, une maladie microvasculaire, un pont myocardique malin, ou une ischémie induite par le stress mental**

# Cas clinique

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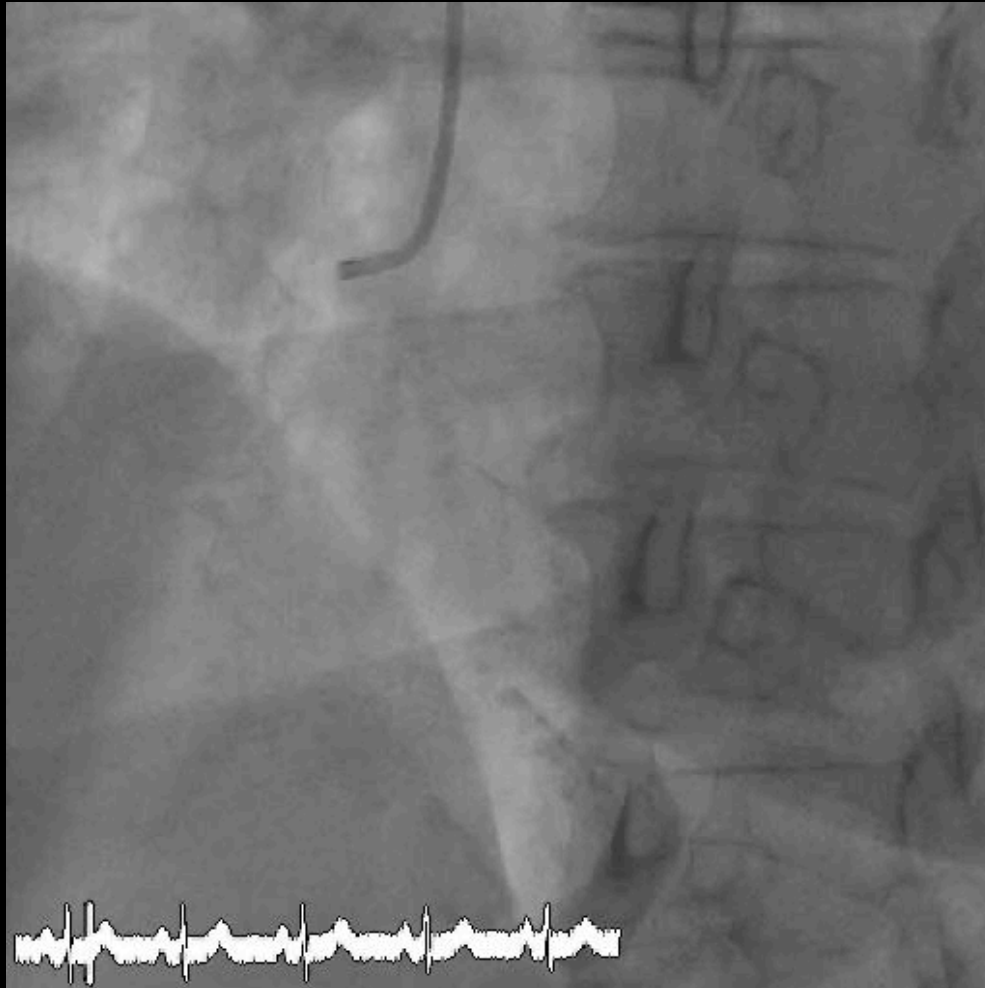
- **Femme de 58 ans**
- **Fumeuse, HT, DLP**
- **ATCD: migraine sévère.**
  
- **Médication: Almotriptan, Amitriptyline, Pregabalin, Estradiol.**
  
- **Médication: Aspirine, Atorvastatin, Irbesartan, Diltiazem 30mg 3x/d.**
  
- **Symptômes: Douleur d'angine au repos, la nuit, avec deux visites à l'urgence en 2 semaines**

# Cas clinique

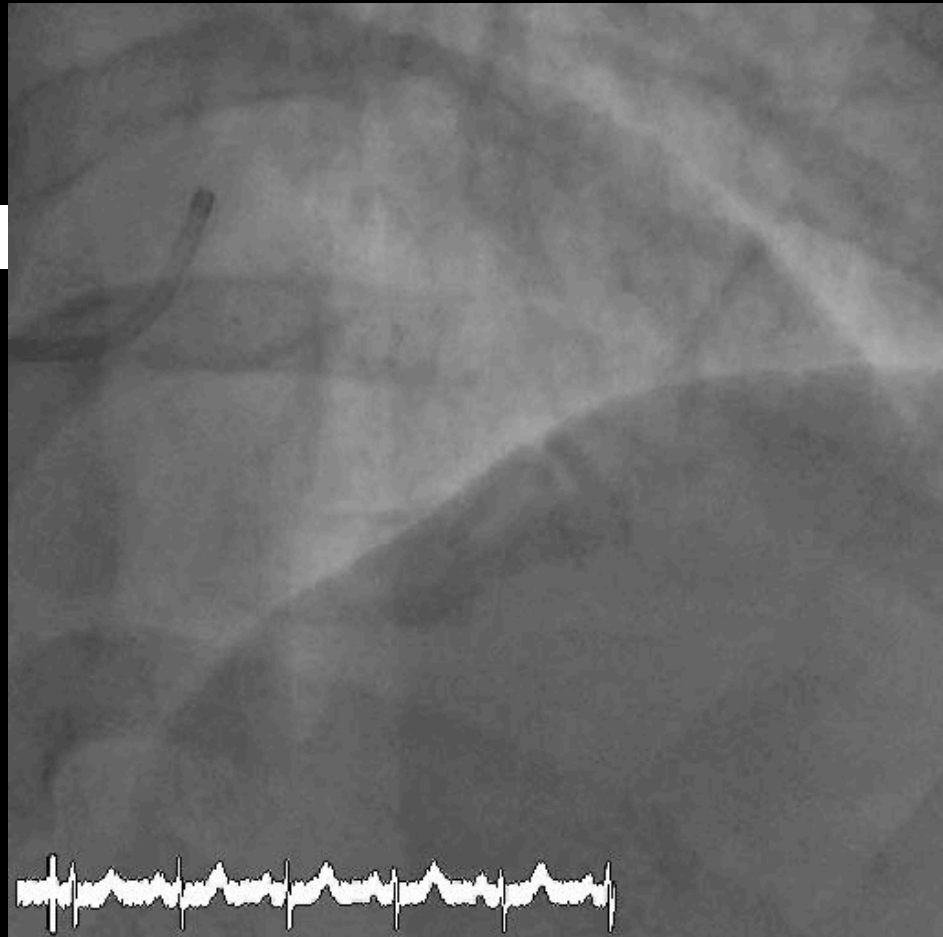
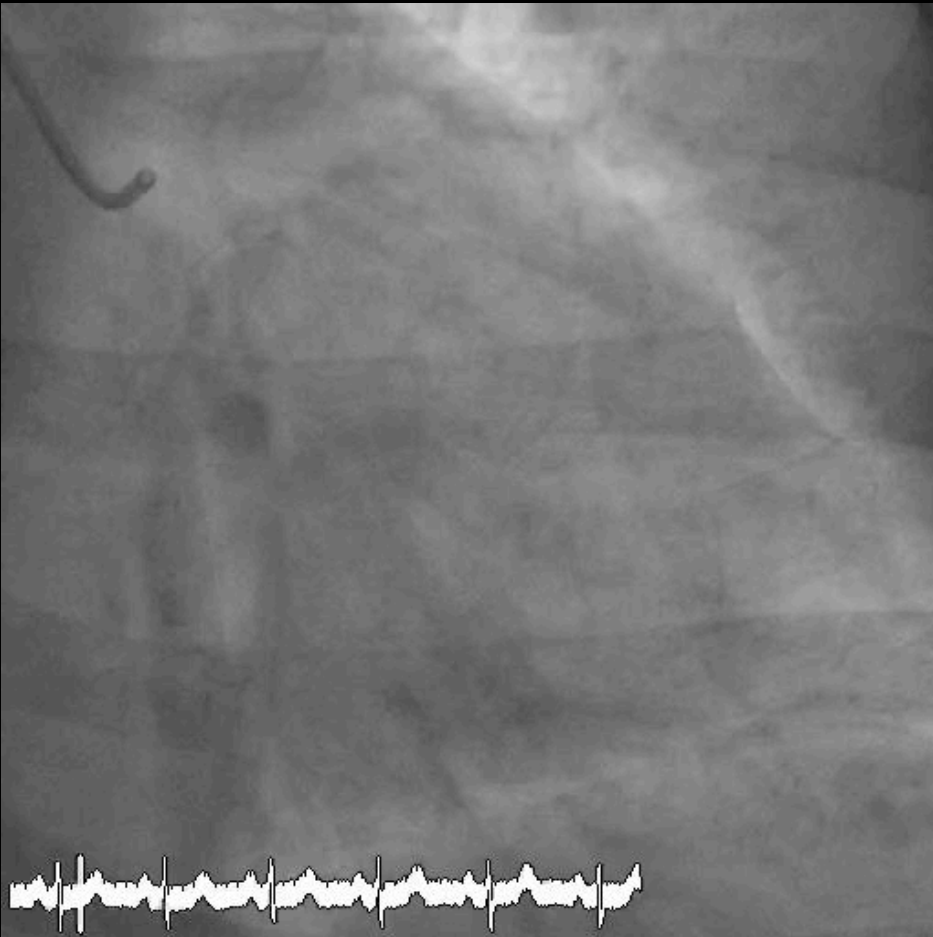
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- **TA = 95 / 65 mmHg; HR = 70/min; saturation = 93%.**
- **Auscultation normale, aucun signe de défaillance cardiaque**
  - **ECG: Sinusal, RAS.**
  - **Écho: FEVG = 60%.**
  - **MIBI: Suspicion d'ischémie antérieure.**





**Coronarographie de la  
coronaire droite**



**Coronarographie de la  
coronaire gauche**

# 2013 ESC guidelines on the management of stable coronary artery disease

## The Task Force on the management of stable coronary artery disease of the European Society of Cardiology

**Table 24** Diagnostic tests in suspected vasospastic angina

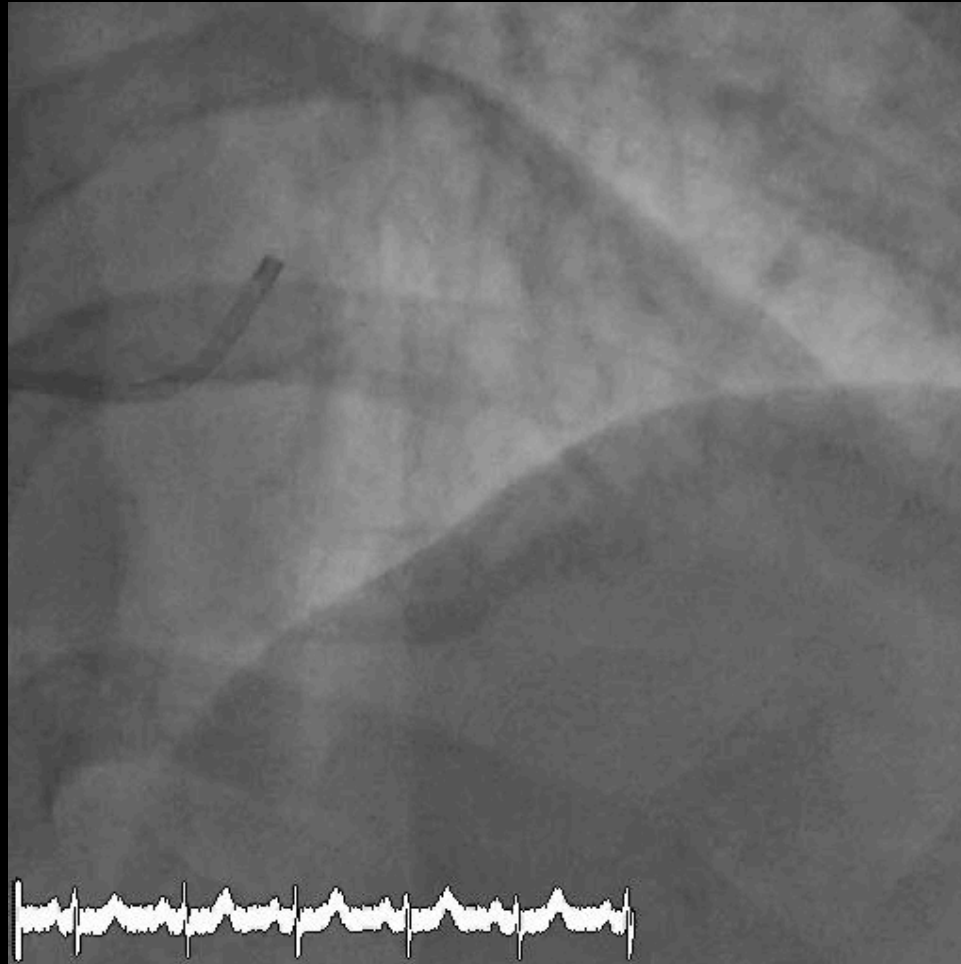
Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
An ECG is recommended during angina if possible.	I	C
Coronary arteriography is recommended in patients with characteristic episodic resting chest pain and ST-segment changes that resolve with nitrates and/or calcium antagonists to determine the extent of underlying coronary disease.	I	C
Ambulatory ST-segment monitoring should be considered to identify ST-deviation in the absence of an increased heart rate.	IIa	C
Intracoronary provocative testing should be considered to identify coronary spasm in patients with normal findings or non obstructive lesions on coronary arteriography and the clinical picture of coronary spasm to diagnose the site and mode of spasm.	IIa	C



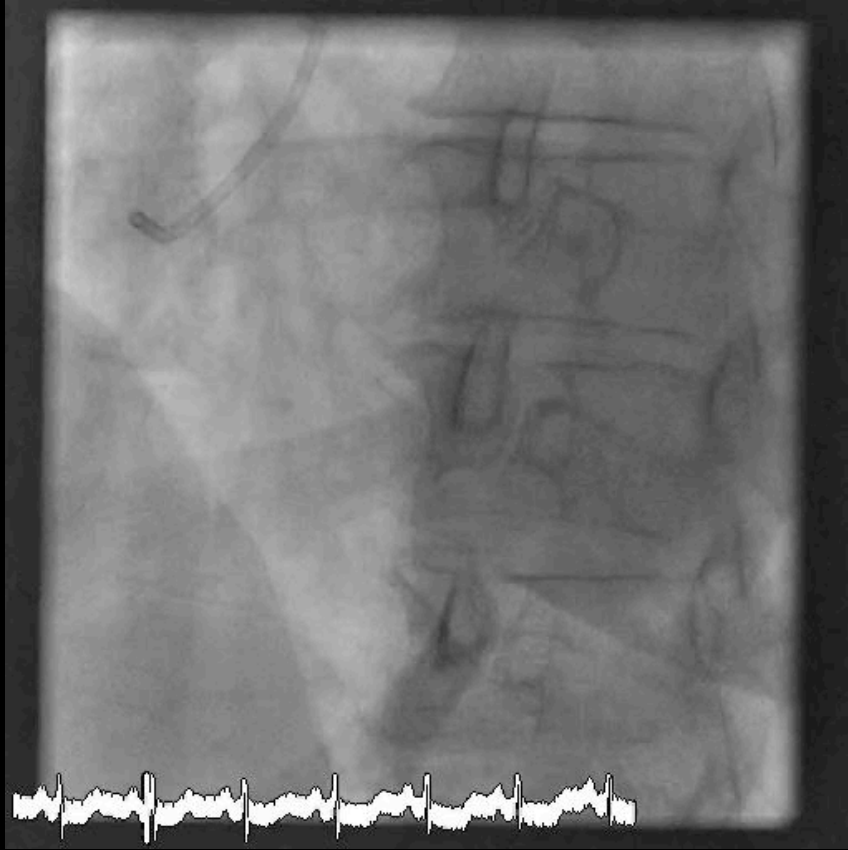
**Table 23** Investigation in patients with suspected coronary microvascular disease

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Exercise or dobutamine echocardiography should be considered in order to establish whether regional wall motion abnormalities occur in conjunction with angina and ST-changes.	IIa	C
Transthoracic doppler echocardiography of the LAD with measurement of diastolic coronary blood flow following intravenous adenosine and at rest may be considered for non invasive measurement of coronary flow reserve.	IIb	C
Intracoronary acetylcholine and adenosine with Doppler measurements may be considered during coronary arteriography, if the arteriogram is visually normal, to assess endothelium dependent and non-endothelium dependent coronary flow reserve, and detect microvascular/epicardial vasospasm.	IIb	C



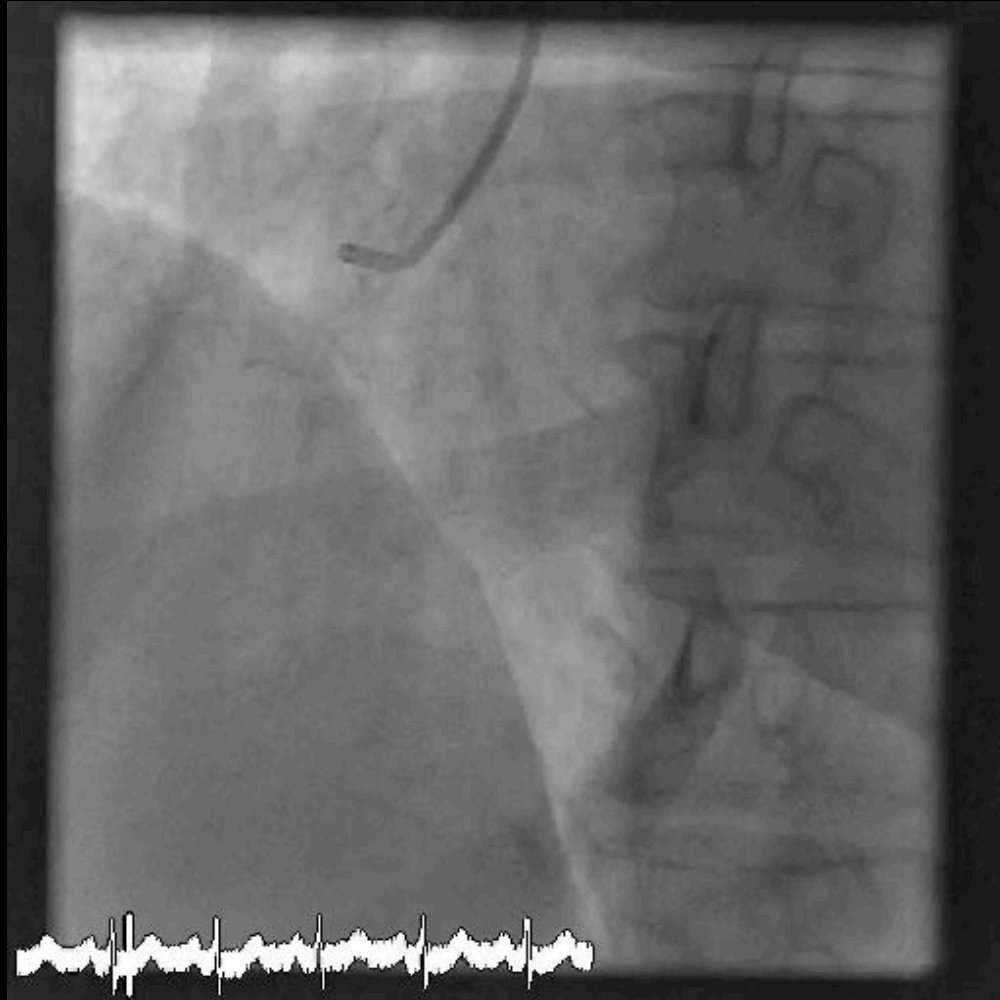


**Ergonovine 60mcg IC  
gauche**



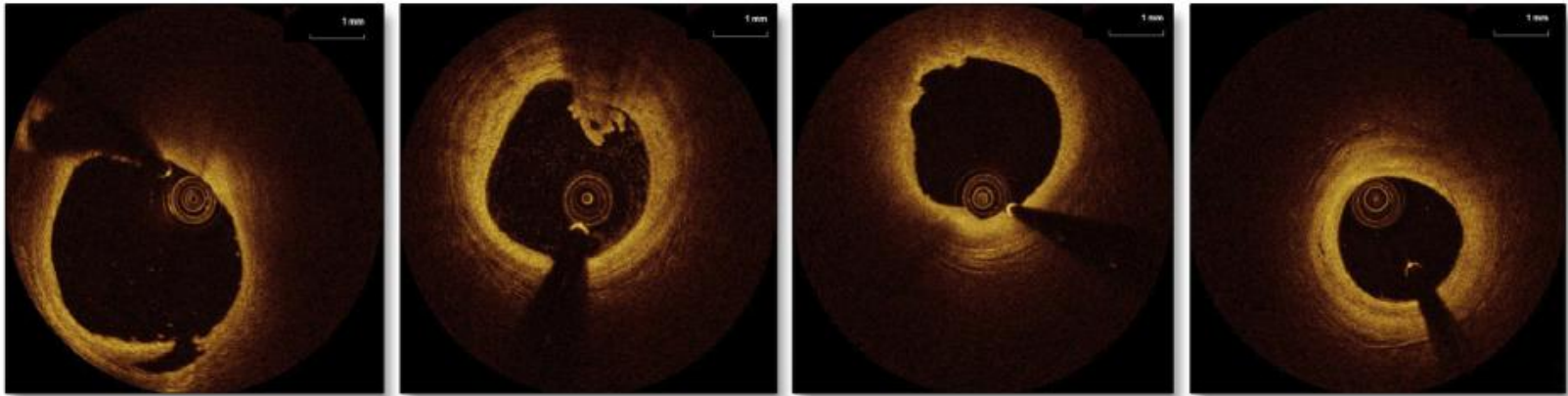
**Ergonovine 40mcg IC  
droite**





**Nitro 1mg IC**

**FIGURE 2** Characteristics of Spasm Sites as Assessed by OCT in Patients With Vasospastic Angina



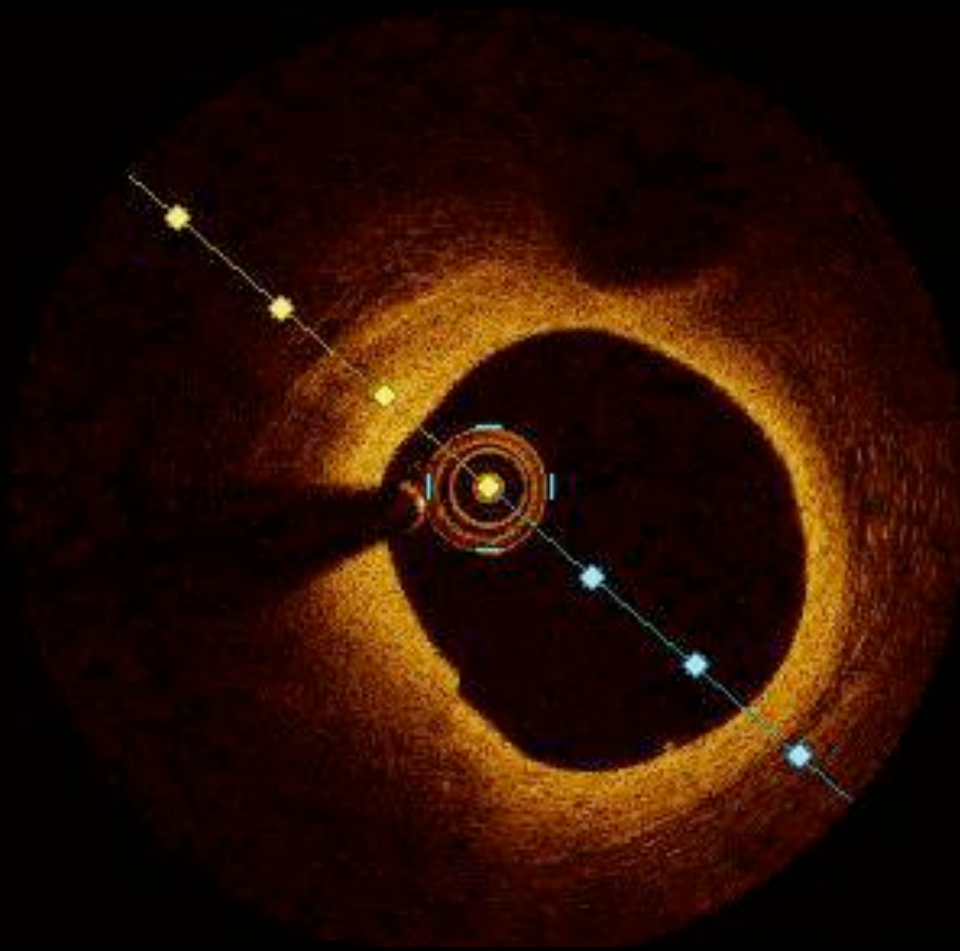
**Fibrous Cap Disruption:**  
Fibrous cap discontinuity  
with or without a cavity  
formed inside the plaque

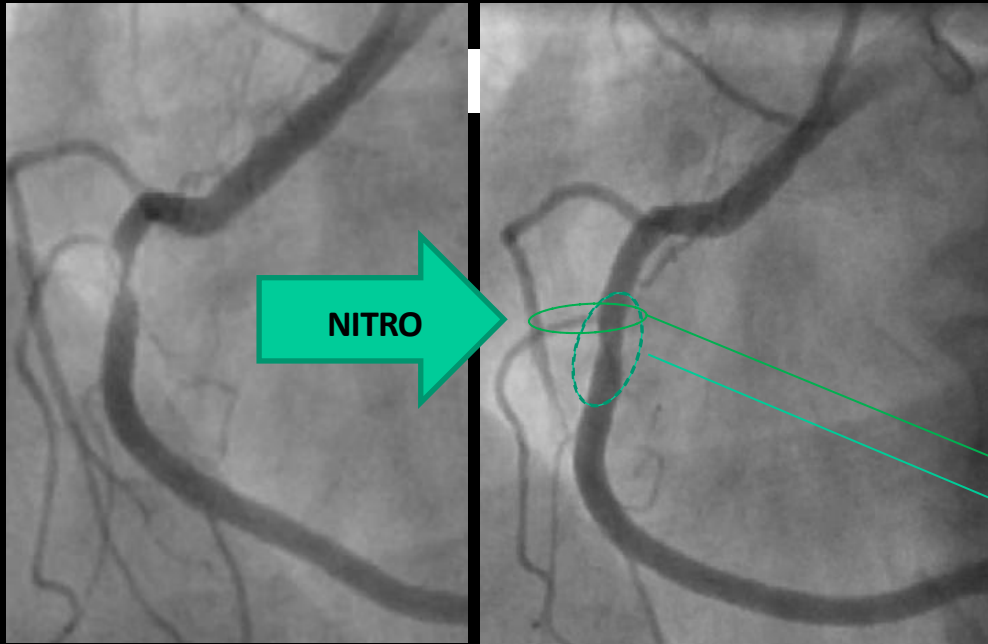
**OCT-defined Erosion:**  
Underlying visualized  
plaque with intact fibrous  
cap, lumen irregularity  
and thrombus

Luminal irregularity

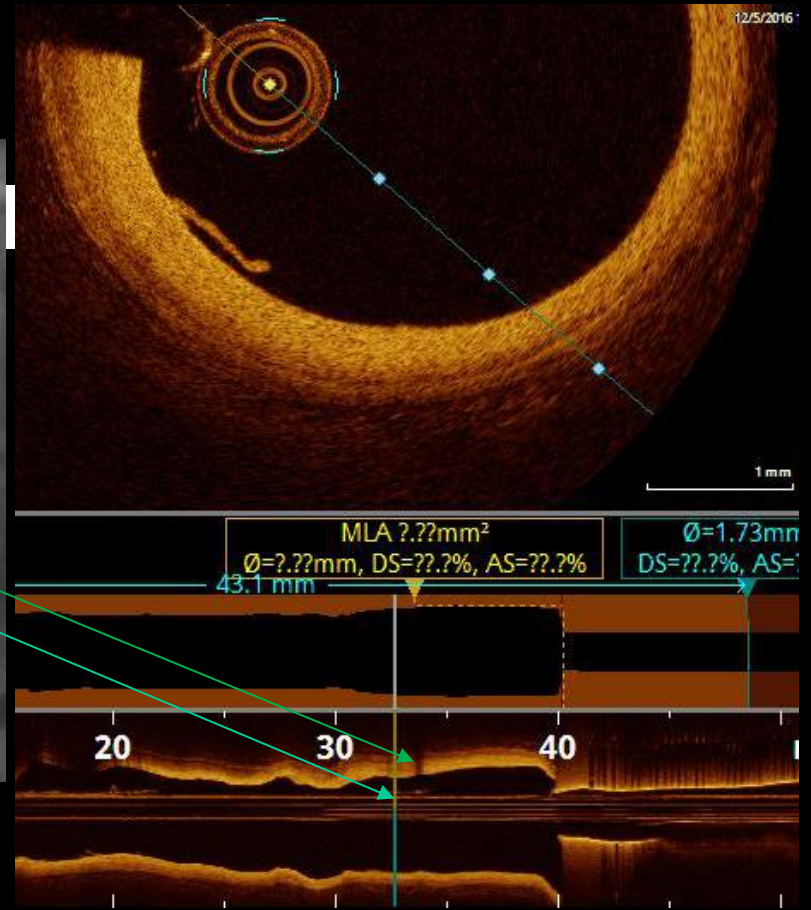
No luminal irregularity or  
thrombus

Each panel depicts the specific optical coherence tomography (OCT)-defined characteristics and findings.





**NITRO**



# Message No. 3



**Les syndromes vasospastiques et microvasculaires échappent aux méthodes de dépistage habituelle – incluant l'imagerie et la coronarographie – le diagnostic vient souvent après des mois, voire des années de souffrance.**





## International standardization of diagnostic criteria for vasospastic angina

**Table 1** Coronary Artery Vasospastic Disorders  
Summit diagnostic criteria for vasospastic angina<sup>a</sup>

Vasospastic angina diagnostic criteria elements

- (1) *Nitrate-responsive angina*—during spontaneous episode, with at least one of the following:
  - (a) Rest angina—especially between night and early morning
  - (b) Marked diurnal variation in exercise tolerance—reduced in morning
  - (c) Hyperventilation can precipitate an episode
  - (d) Calcium channel blockers (but not  $\beta$ -blockers) suppress episodes
- (2) *Transient ischaemic ECG changes*—during spontaneous episode, including any of the following in at least two contiguous leads:
  - (a) ST segment elevation  $\geq 0.1$  mV
  - (b) ST segment depression  $\geq 0.1$  mV
  - (c) New negative U waves
- (3) *Coronary artery spasm*—defined as transient total or subtotal coronary artery occlusion ( $>90\%$  constriction) with angina and ischaemic ECG changes either spontaneously or in response to a provocative stimulus (typically acetylcholine, ergot, or hyperventilation)



**Table 4. Indications for Provocative Spasm Testing**

**Class I (Strong Indications)**

- History suspicious of VSA without documented spontaneous episode, especially if:
  - Nitrate-responsive rest angina, and/or
  - Marked diurnal variation in symptom onset/exercise tolerance, and/or
  - Rest angina without obstructive coronary artery disease
- Acute coronary syndrome presentation in the absence of a culprit lesion
- Unexplained resuscitated cardiac arrest
- Unexplained syncope with antecedent chest pain
- Recurrent rest angina following angiographically successful PCI

**Class IIa (Good Indications)**

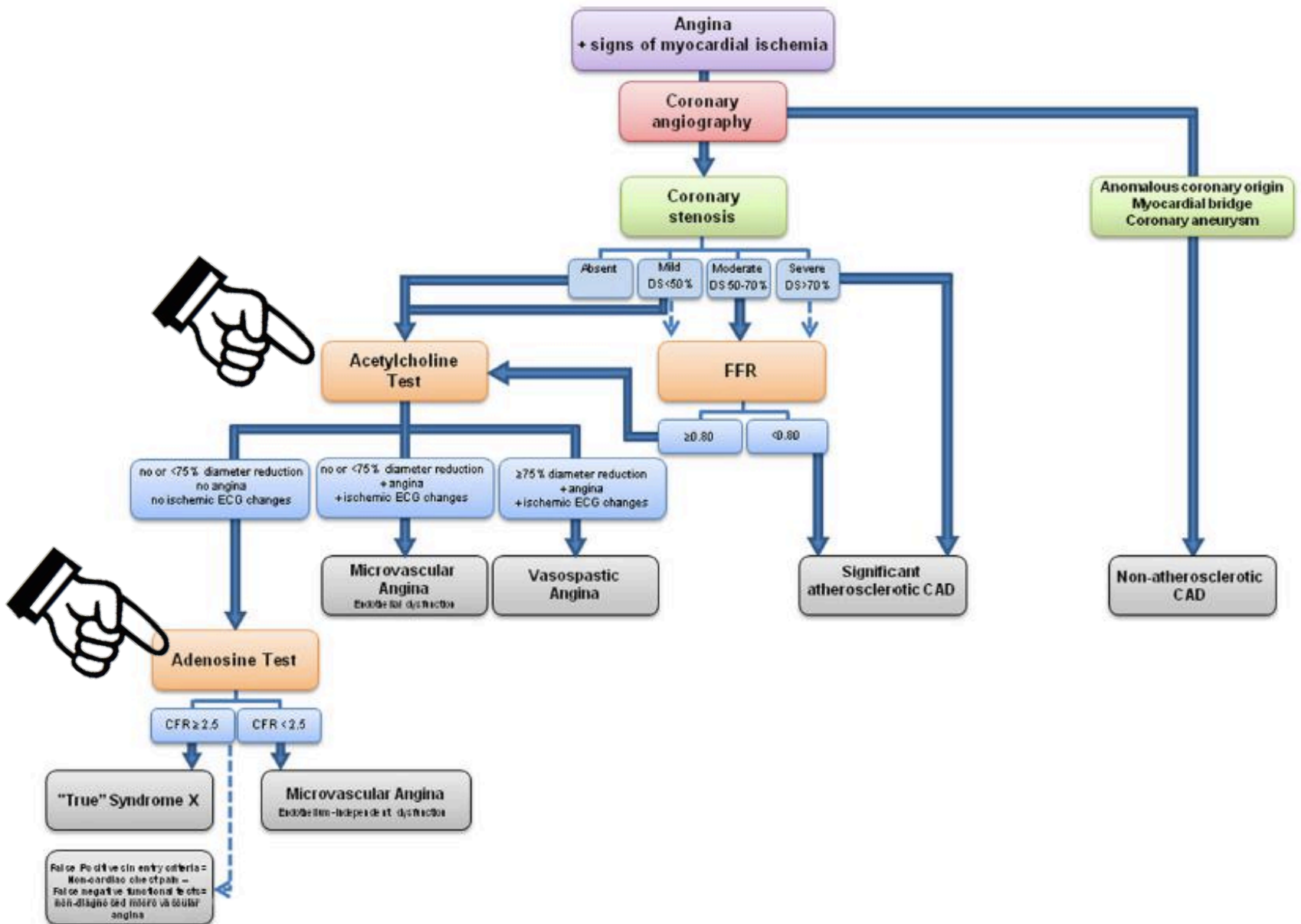
- Invasive testing for non-invasive diagnosed patients unresponsive to drug therapy

**Class IIb (Controversial Indications)**

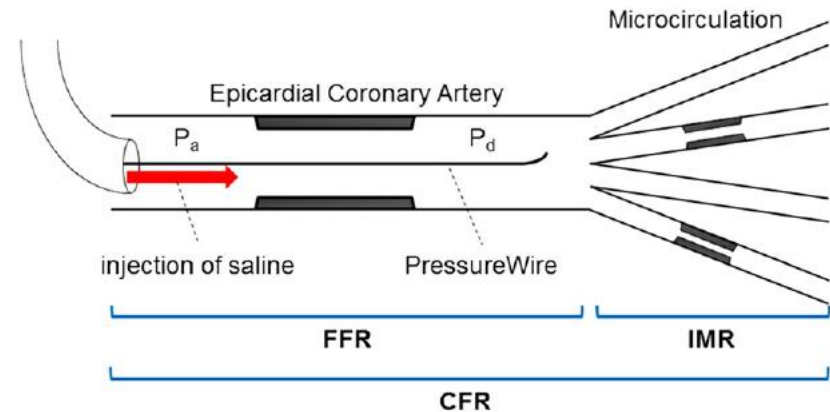
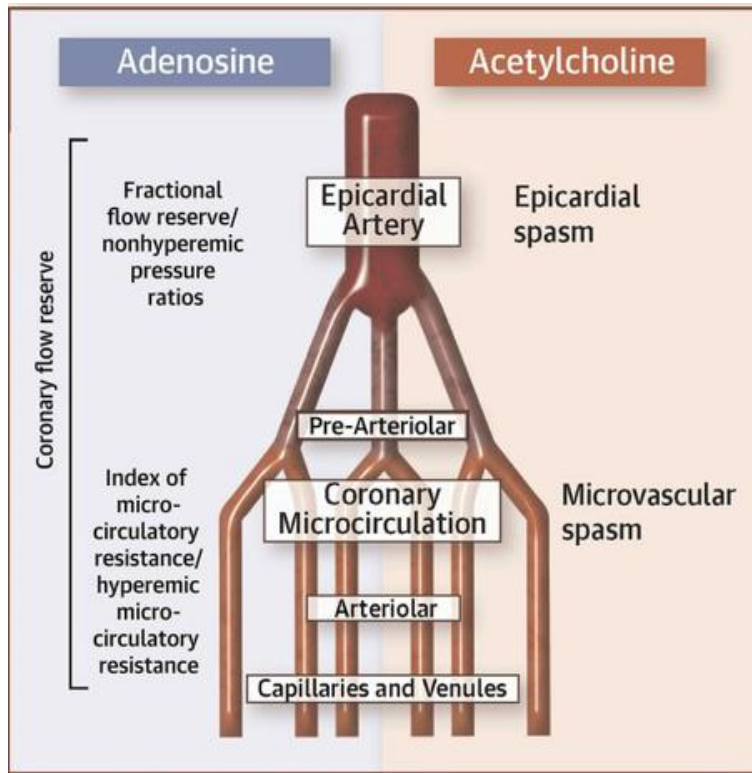
- Documented spontaneous episode of variant angina
- Invasive testing for non-invasive diagnosed patients responsive to drug therapy

**Class III (Contra-indications)**

- Emergent acute coronary syndrome
- Severe fixed multivessel CAD including left main coronary artery stenosis
- Severe myocardial dysfunction (Class IIb if symptoms suggestive of vasospasm)
- Patients without any symptoms suggestive of VSA



# Mechanisms of Coronary Microvascular Dysfunction

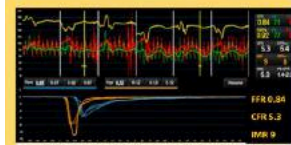


- **FFR** =  $P_d/P_a$  at maximal hyperemia
- **CFR** = hyperemic coronary flow  $\div$  resting coronary flow  
 =  $1/\text{hyperemic } T_{mn} \div 1/\text{resting } T_{mn}$   
 =  $\text{resting } T_{mn}/\text{hyperemic } T_{mn}$
- **IMR** =  $P_d$  at maximal hyperemia  $\div 1/\text{hyperemic } T_{mn}$   
 =  $P_d$  at maximal hyperemia  $\times$  hyperemic  $T_{mn}$

( $T_{mn}$ : an inverse correlate to absolute coronary flow)

# Diagnosis of Coronary Microvascular Dysfunction

## Vasospastic Angina



- Vasospastic Angina**
- 1 - Calcium channel blocker
  - 2 - Long-acting Nitrate
  - Avoid beta-blockers
  - Event prevention: ACEI, Statin
  - Lifestyle and cardiac rehabilitation

## Invasive Coronary Assessment in INOCA

- 1 Coronary Angiography**

  - Consider:
    - Obstructive CAD
    - Myocardial bridging
    - 'Flush' ostial branch occlusion
- 2 Guidewire (adenosine)**

Saline Bolus Pressure/Thermistor or Doppler wire

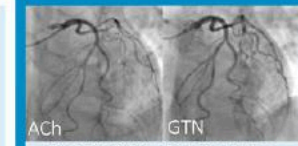
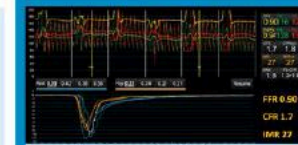
Coronary flow reserve - abnormal CFR  $\leq 2.0$   
Microvascular resistance - IMR  $\geq 25$  or HMR  $> 2.4$
- 3 Vasoreactivity (acetylcholine)**

Acetylcholine incremental Doses & bolus Symptoms, ECG & angio

  - Epicardial vasospasm
  - Microvascular vasospasm
- 4 Diagnosis & Management**

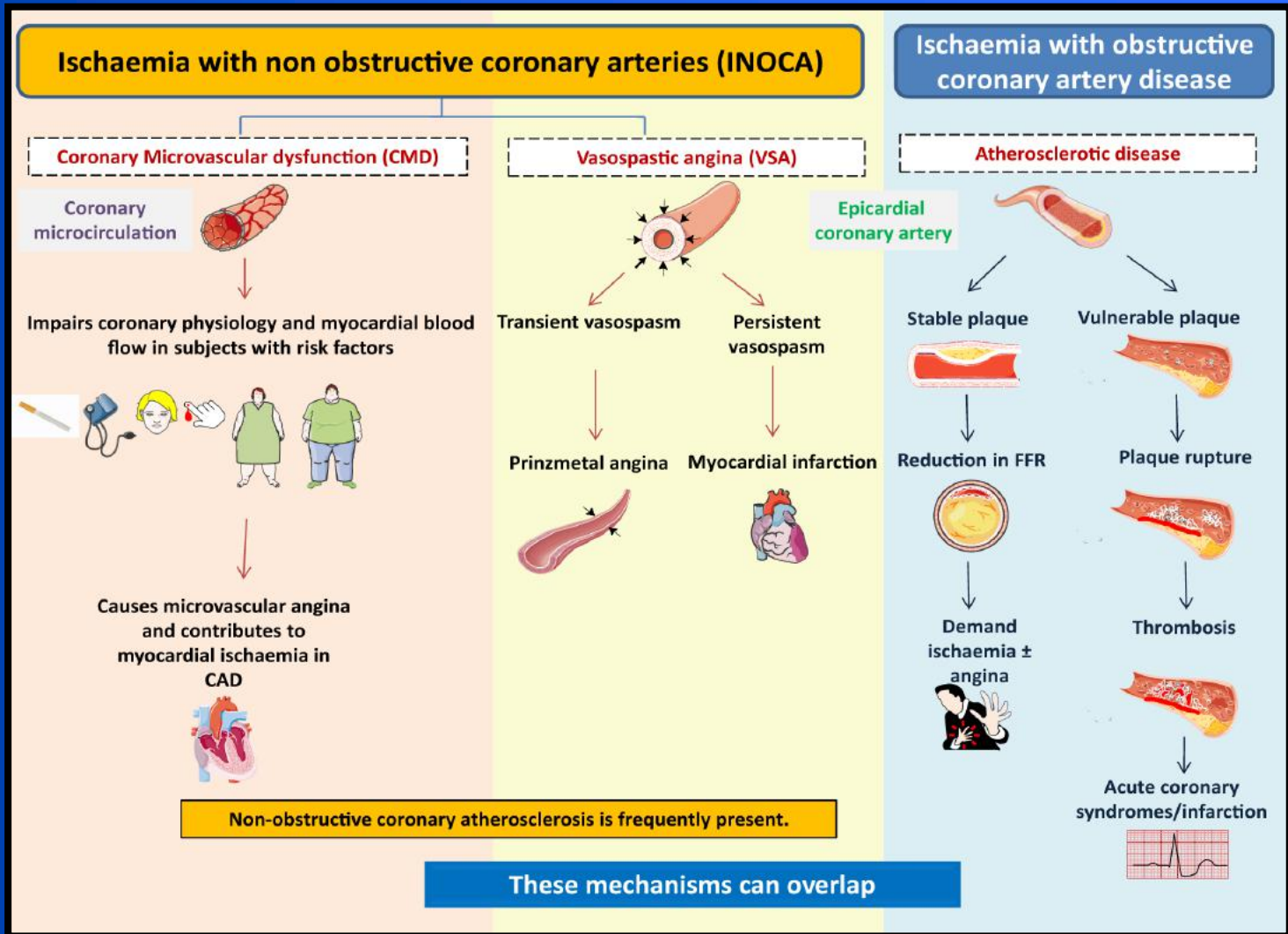
  1. Microvascular angina
  2. Vasospastic angina
  3. Mixed angina
  4. Non-Cardiac (normal IDP)

## Microvascular Angina



- Microvascular Angina**
- 1 - Beta-blocker
  - 2 - Calcium channel blocker
  - Avoid long acting nitrates
  - Event prevention: ACEI, Statin
  - Weight loss and cardiac rehabilitation





# Risque cardiovasculaire et traitement

- 1. Patients avec angine vasospastique ont une probabilité accrue (25%) de subir un infarctus du myocarde dans les 3 années suivant le diagnostic**
- 2. Patients avec dysfonction endothéliale ont un risque accru de 20% de subir un événement cardiaque adverse (décès, SCA, AVC, revascularisation) dans les 3 années suivant le diagnostic.**
- 3. Les patients avec angine vasospastique répondent en général très bien aux dérivés nitrés et à la double association des BCC dihydro- et non-dihydropyridine (eg. diltiazem et amlodipine).**
  - L'aspirine est controversée, mais devrait possiblement être arrêtée (sauf si indication de classe I ou IIa).**
  - Il convient de cesser tous dérivés des triptans, la cocaïne, les analogues des phénylpipéridines, le 5-FU... et possiblement les COX-2 inhibiteurs**
- 4. En plus de contrôle des facteurs de risque**



# Message No. 4



**L'ignorance des symptômes d'un patient avec douleur cardiaque, angine et coronaire normale peut mettre en danger la vie et la qualité de vie des patients.**

# Mental stress-induced myocardial ischemia

Syndrome cœur sensible

Viscosité

Dysfonction microvasculaire

Douleur cardiaque

Simulation

Hémoglobinopathie

Cardiomyopathie infiltrative

Embolie coronaire

Fistules coronaires

**CORONAIRES NORMALES**

Syndrome Y  
Syndrome X



# Ischémie myocardique induite par le stress mental

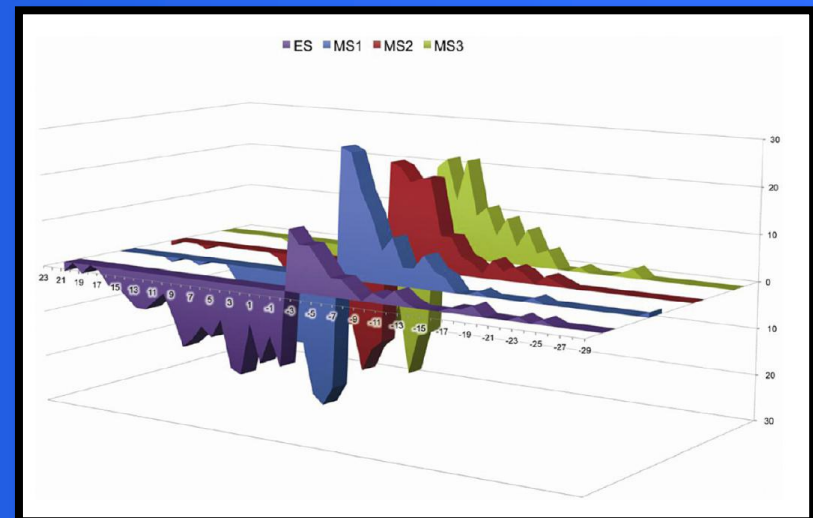
**La réponse hémodynamique au stress mental diffère fondamentalement de celle induite par le stress en ceci que le stress mental n'entraîne qu'une légère augmentation de la fréquence cardiaque et de la pression artérielle**



# Stress mental

Any of the following, occurring during the mental stress tasks

1. Détérioration de la contractilité cardiaque régionale
2. Reduction de la FEVG  $\geq 8\%$  et
3. Déviation ( $\downarrow$  ou  $\uparrow$ ) of segment ST à ECG in  $\geq 2$  dérivations



# **Mental stress-induced myocardial ischemia (MSIMI)**

- **The Hemodynamic responses to mental stress differ fundamentally from exercise-induced stress, in that mental stress causes little increase in heart rate and a lower-grade increase in systolic blood pressure relative to physical stress**



# **Mental stress-induced myocardial ischemia (MSIMI)**

- **Typically without pain and occurs at lower levels of O<sup>2</sup> demand than ischemia induced by exercise.**
- **Generally not related to the extent of CAD**
- **Stress-induced hemodynamic changes (↑ in systemic vascular resistance, coronary artery vasoconstriction, and microvascular changes) may all contribute to the pattern of ischemia.**

# **MSIMI stressing**

**Any of the following, occurring during the mental stress tasks**

- 1. New or worsening of wall motion abnormality;**
- 2. Reduction of LVEF  $\geq 8\%$  and/or**
- 3. Deviation ( $\downarrow$  or  $\uparrow$ ) of ST segment of ECG in  $\geq 2$  leads lasting for  $\geq 3$  consecutive beats**

## REMIT Trial

Identify adult patients with clinically documented coronary disease

Laboratory mental stress & exercise test; Platelet study, etc

Patients who develop MSIMI

Escitalopram  
5-20 mg/day

6 weeks

Placebo  
Matched dosing

Repeat same baseline tests

Primary Endpoint: MSIMI

Secondary Endpoints:

Platelet activity

CV reactivity during mental stress testing

Depressive and/or anxiety symptoms, hostility, General well being

Long-term fatal and non-fatal cardiovascular events

Study design.

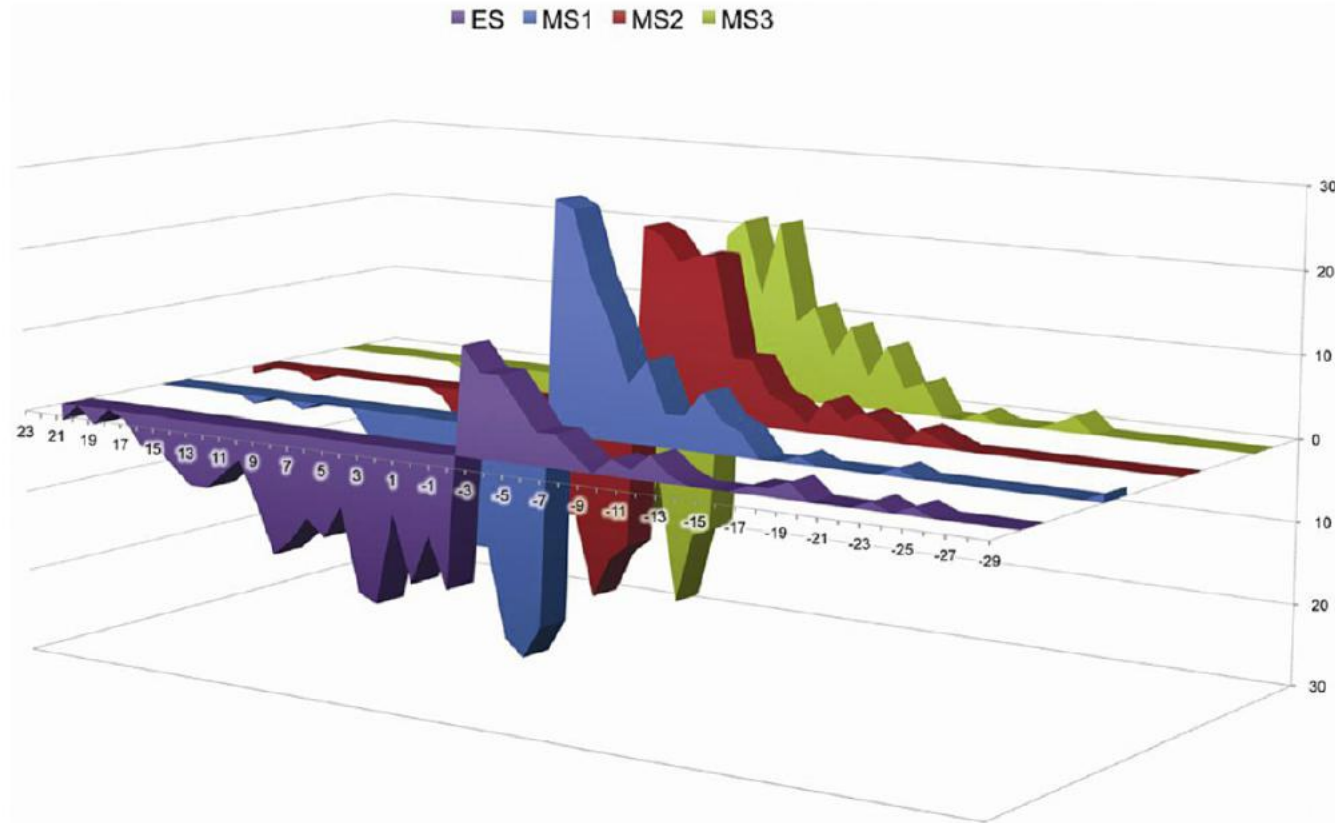
**Table 1** Left Ventricular Responses and Electrocardiographic Ischemic Change to MS and ES (n = 290)

	MS			ES
WMA	36.21			21.60
EF drop $\geq 8$	18.05			4.96
EF drop $\geq 5$	35.71			8.78
Ischemic ECG	0			17.93
Overall stress-induced ischemia*	43.45 (MSIMI)			33.79 (ESIMI)

	MS1	MS2	MS3	ES
$\Delta$ WMSI†	0.029 $\pm$ 0.09 (-0.19, 0, 0.50)	0.047 $\pm$ 0.12 (-0.29, 0, 0.88)	0.059 $\pm$ 0.15 (-0.375, 0, 1.0)	0.037 $\pm$ 0.22 (-1.0, 0, 1.31)
$\Delta$ LVEF†	-0.28 $\pm$ 5.10 (-29.0, 0, 17.0)	-0.58 $\pm$ 5.60 (-17.0, -1.0, 23.0)	-0.33 $\pm$ 5.93 (-20.0, 0, 15.0)	4.48 $\pm$ 7.75 (-24.0, 4.0, 23.0)

# Distribution of $\Delta$ LVEF During Mental and Exercise Test





**Table 1.** Baseline Demographic and Clinical Characteristics

Characteristic	No. (%)		
	Escitalopram (n = 64)	Placebo (n = 63)	Total (N = 127)
Age, mean (SD), y <sup>a</sup>	66.5 (9.3)	61.4 (11.5)	64.0 (10.7)
White race	53 (82.8)	47 (74.6)	100 (78.7)
Women	11 (17.2)	15 (23.8)	26 (20.5)
Living alone	14 (21.9)	13 (20.6)	27 (21.3)
Unmarried	18 (28.1)	22 (34.9)	40 (31.5)
Smoking			
Current	13 (20.3)	8 (12.7)	21 (16.5)
Past	27 (42.2)	35 (55.6)	62 (48.8)
Never	24 (37.5)	20 (31.8)	44 (34.6)
Medications at baseline, No./total (%)			
Aspirin	60/63 (95.2)	61 (96.8)	121/126 (96.0)
Other antiplatelet agent	28/63 (44.4)	29 (46.0)	57/126 (45.2)
ACE inhibitor	40/63 (63.5)	39 (61.9)	79/126 (62.7)
ARB	11/63 (17.5)	10 (15.9)	21/126 (16.7)
$\beta$ -Blocker	55/63 (87.3)	54 (85.7)	109/126 (86.5)
Calcium channel blocker	14/63 (22.2)	11 (17.5)	25/126 (19.8)
Lipid-lowering agent, No./total (%)			
Statin	62/63 (98.4)	57/62 (91.9)	119/125 (95.2)
Other	17/63 (27.0)	9/61 (14.8)	26/124 (21.0)
Chest pain			
At rest	5 (7.8)	3 (4.8)	8 (6.3)
On exertion	9 (14.1)	7 (11.1)	16 (12.6)
Diseased coronary arteries, No./total (%) <sup>b</sup>			
1	22/63 (34.9)	26/63 (41.3)	48/126 (38.1)
2	9/63 (14.3)	12/63 (19.0)	21/126 (16.7)
3	19/63 (30.2)	17/63 (27.0)	36/63 (28.6)
4	13/63 (20.6)	8/63 (12.7)	21/63 (16.7)
Myocardial infarction, No./total (%)			
Yes	30 (46.9)	30 (47.6)	60 (47.2)
No	34 (53.1)	32 (50.8)	66 (52.0)
Uncertain	0	1 (1.6)	1 (0.8)
Prior CABG surgery	31 (48.4)	31 (49.2)	62 (48.8)
Prior PTCA/stenting	37 (57.8)	39 (61.9)	76 (59.8)
History of diabetes mellitus	21 (32.8)	14 (22.2)	35 (27.6)
Hypertension	50 (78.1)	48 (76.2)	98 (77.2)
Hyperlipidemia	62 (96.9)	57 (90.5)	119 (93.7)
Heart failure	2 (3.1)	5 (7.9)	7 (5.5)
NYHA class, No./total (%)			
I	60 (93.8)	57/62 (91.9)	117/126 (92.9)
II	3 (4.7)	4/62 (6.4)	7/126 (5.6)
III	1 (1.6)	1/62 (1.6)	2/126 (1.6)
History of depression	11 (17.2)	10 (15.9)	21 (16.5)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery by-pass graft; NYHA, New York Heart Association; PTCA, percutaneous coronary angiography.

<sup>a</sup> $P = .01$ .

<sup>b</sup>Significant coronary stenosis ( $\geq 70\%$ ) or status post revascularization in the 4 epicardial coronary arteries (left main, left anterior descending, left circumflex, and right coronary) documented prior to enrollment.

# Escitalopram in MSIMI

- How do SSIRs prevent ischemia is not entirely clear, but it has been hypothesized that they may prevent the microcirculatory dysfunction triggered by an inappropriate response to stress of the central nervous system and of the hypothalamic-pituitary-adrenal axis system.
- SSRI in general and escitalopram in specific may address ischemia through mechanisms that cannot be modified by conventional antiischemic agents