Acetylcholine test: CAG met provocatietest

CNE Interventie Cardiologie 26-1-2016

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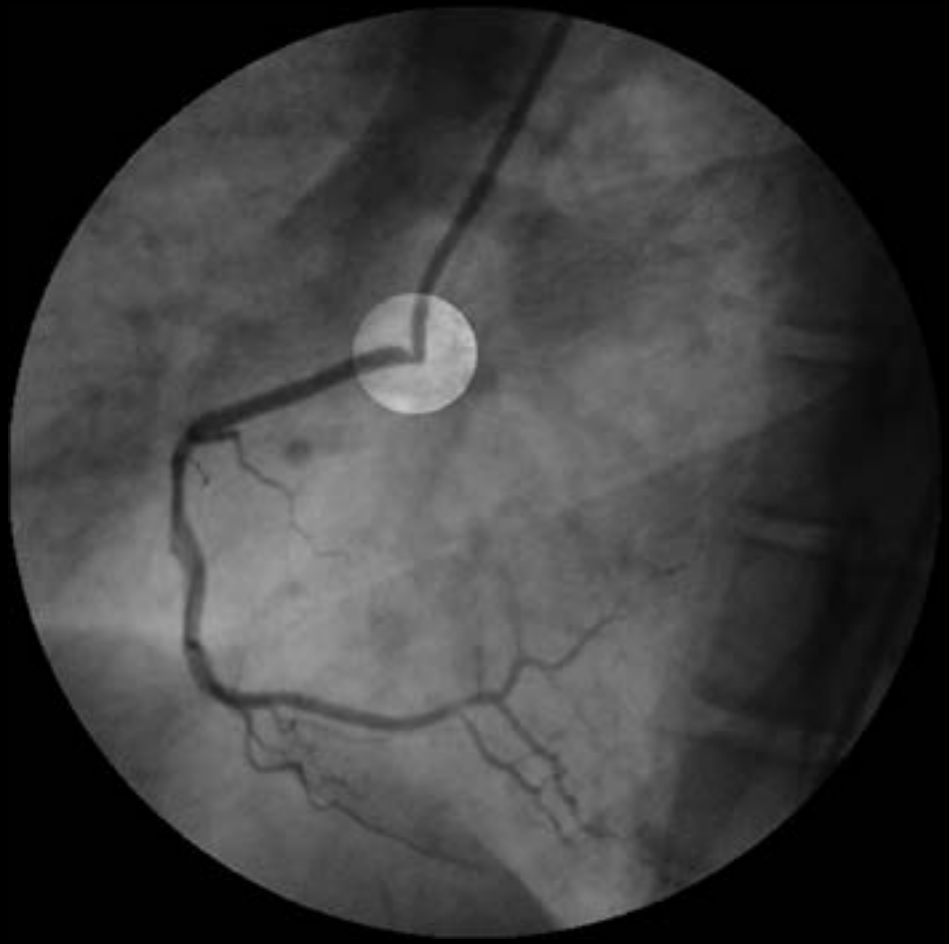
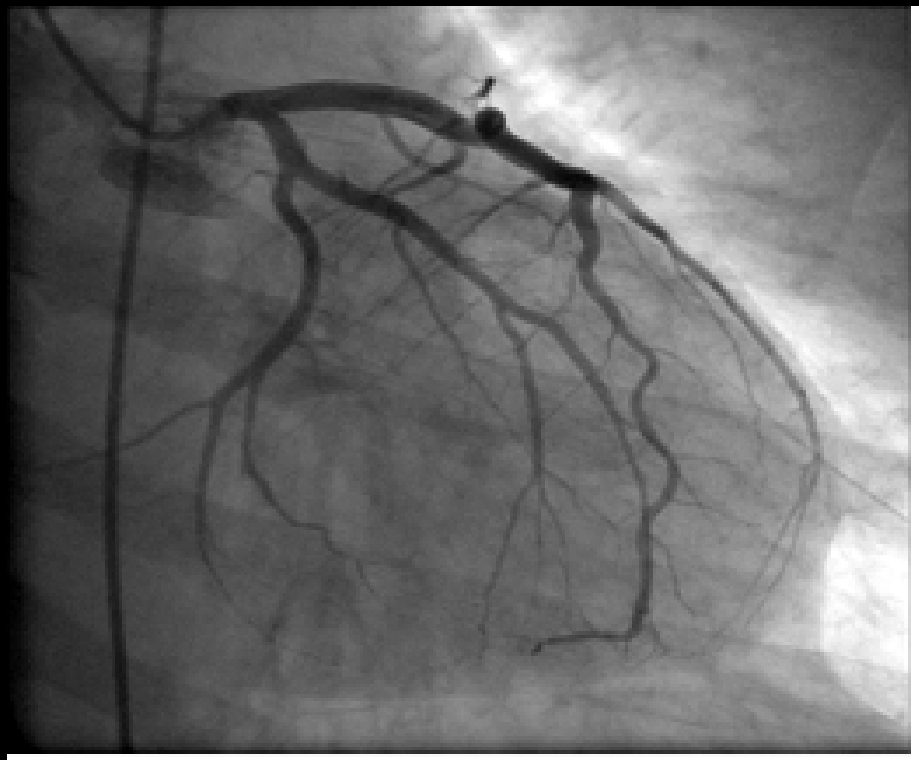
Disclosures and conflicts of interest

Geen

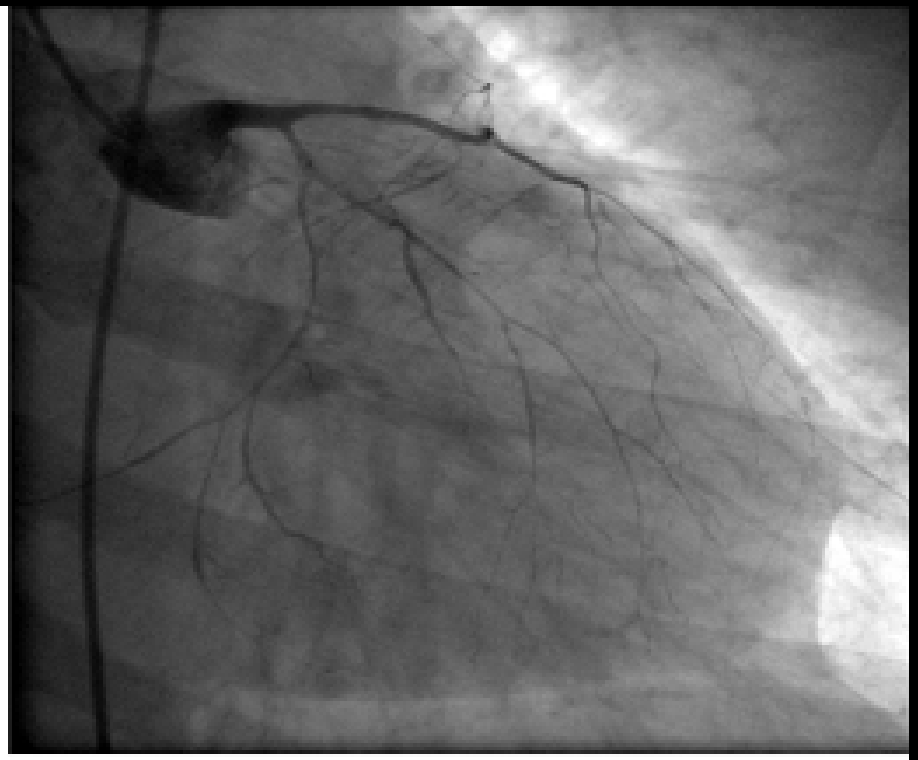
Coronaire spasme – Variant AP?



Ernstige vasospasme!

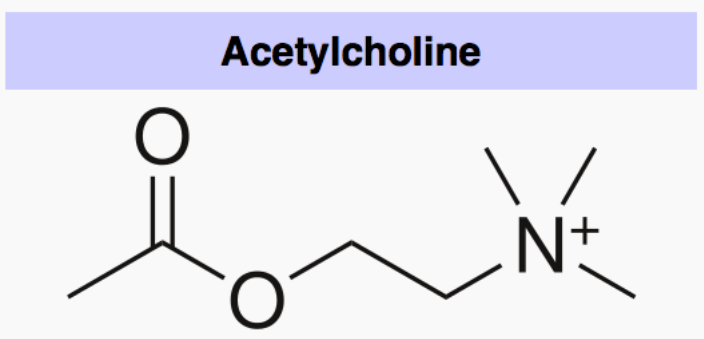


LAD Baseline: no pathologies, no culprit lesion

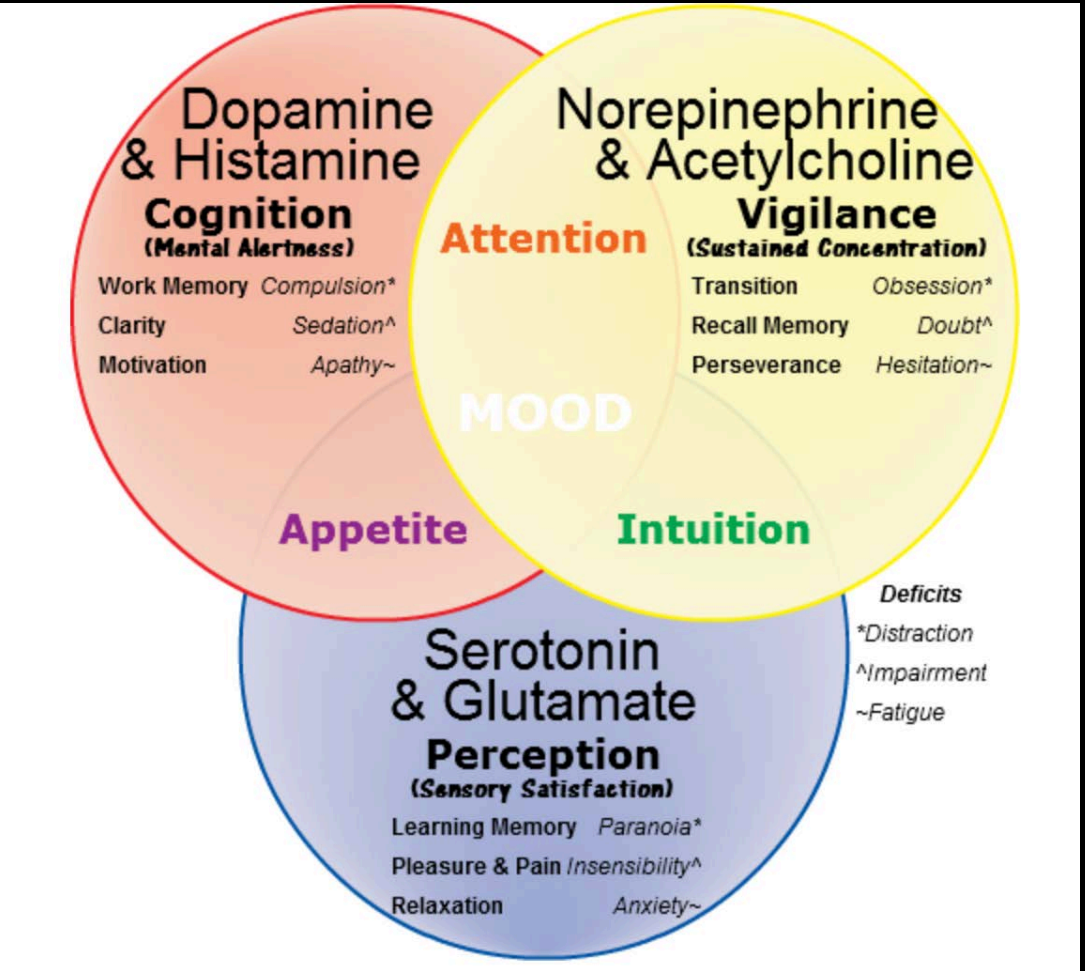


LAD after acetylcholine-infusion: epicardial spasm

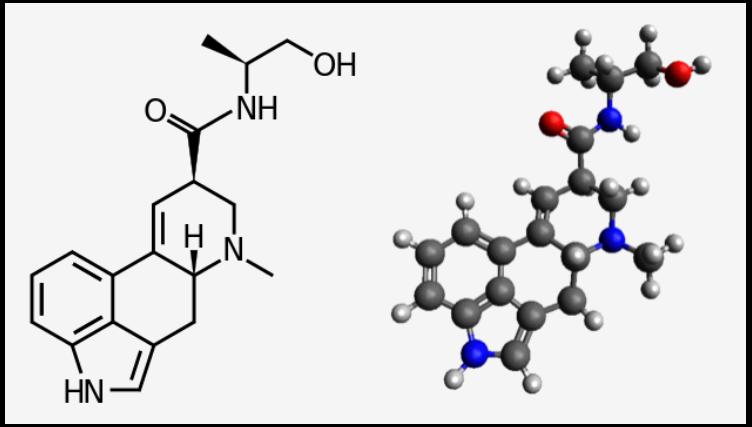
Acetylcholine



Werking via cholinerge muscarine receptoren.

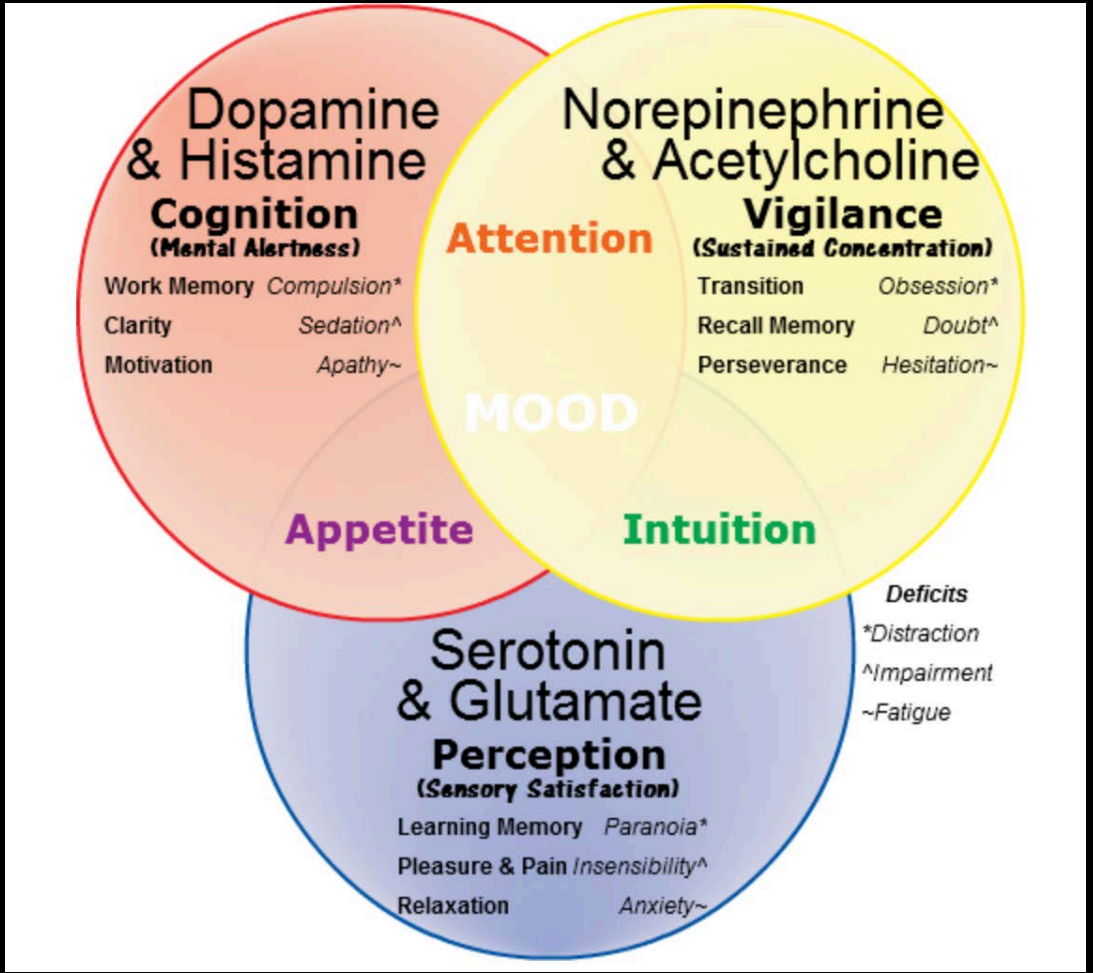


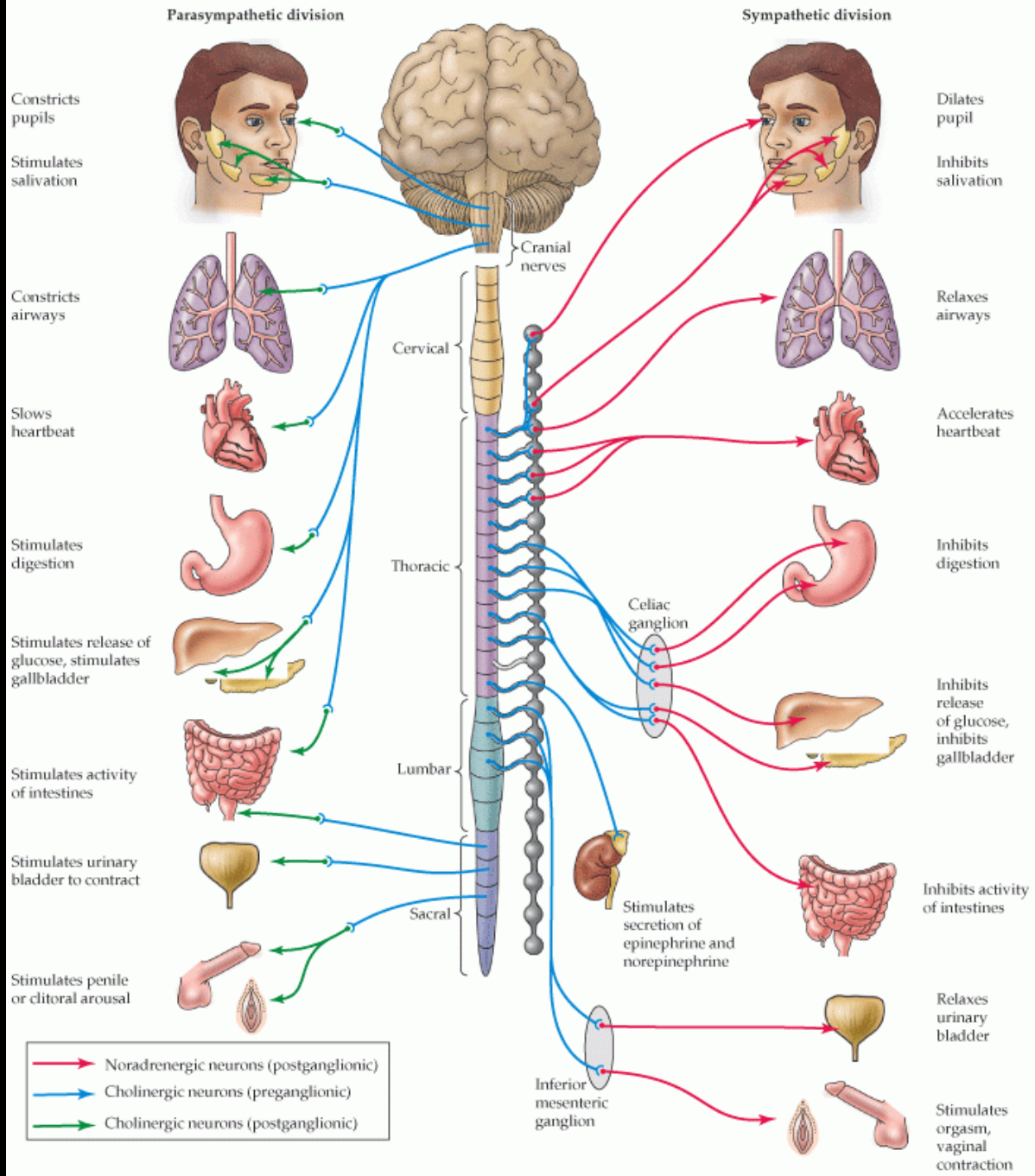
Ergonovine



Contractie glad spierweefsel via serotonerge receptoren

Bij i.v. toediening risico op Refractair spasme!




Parasympathetic division
Sympathetic division
Constricts pupils
Stimulates salivation
Constricts airways
Slows heartbeat
Stimulates digestion
Stimulates release of glucose, stimulates gallbladder
Stimulates activity of intestines
Stimulates urinary bladder to contract
Stimulates penile or clitoral arousal
Cranial nerves
Cervical
Thoracic
Lumbar
Sacral
Dilates pupil
Inhibits salivation
Relaxes airways
Accelerates heartbeat
Inhibits digestion
Celiac ganglion
Inhibits release of glucose, inhibits gallbladder
Inhibits activity of intestines
Stimulates secretion of epinephrine and norepinephrine
Relaxes urinary bladder
Inferior mesenteric ganglion
Stimulates orgasm, vaginal contraction
Noradrenergic neurons (postganglionic)
Cholinergic neurons (preganglionic)
Cholinergic neurons (postganglionic)

Angina Pectoris

Angina pectoris o.b.v. atheroscleros in epicardiale coronairen.

Variant angina pectoris – Prinzmetal Angina – coronair spasme

Microvasculaire dysfunctie – Cardiaal syndroom X

Angina Pectoris

1772: Eerste beschrijving van klassieke Angina Pectoris door William Heberden (GB).

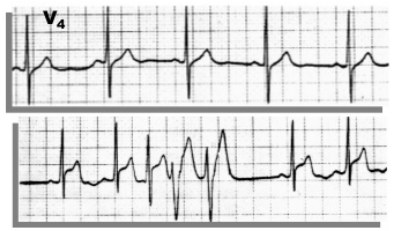

William Heberden
(1710 - 1801)

1959: Eerste beschrijving van Variant Angina Pectoris door Myron Prinzmetal (USA)

1959

Dr. Myron Prinzmetal

MYRON PRINZMETAL y cols., dirigen la atención hacia una forma inusual de angina que ellos denominan variante, en la que durante el evento ocurre elevación del segmento ST. La variante es atribuida a lesión subepicárdica, no relacionada a esfuerzo, cíclica con periodicidad diaria y horaria, y con tendencia a arritmias ventriculares graves.




(1908-1987)

1) Prinzmetal M, Kennamer R, Merliss R, Wada T, Bor N. Angina pectoris. A variant form of angina pectoris. Am J Med 1959;27:374.

Variant Angina Pectoris

AP door (hyper)contractie van gladspierweefsel i.p.v. stenose i.k.v. atherosclerose.

Symptomen typisch in rust i.p.v. inspanning, meestal ‘s nachts / vroege ochtend.

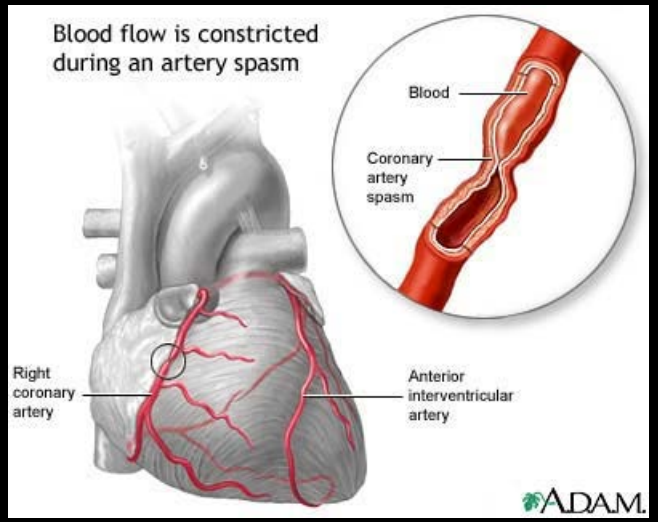
Vaak in cyclische aanvallen.

X-ECG meestal zonder ECG afwijkingen en/of klachten.

Bij ECG afwijkingen vaak ST-elevatie i.p.v. ST-depressie.

Snelle reactie op nitraten.

Diagnose per exclusionem



Mechanismen

Exact mechanisme onbekend!!!

Mogelijke mechanismen:

Acetylcholine komt vrij via parasympathische zenuwstelsel

- In gezond glad spierweefsel netto dilaterend effect.
- Balans tussen direct constructief effect vs. NO gemedieerde vasodilatatie
- Bij endotheelcel dysfunctie: minder productie van NO!

Thromboxane A2, vasoconstrictor geproduceerd door plaatjes.

- Gestoorde fibrinolysis t.g.v. gestoord lipidenspectrum, waardoor meer circulere

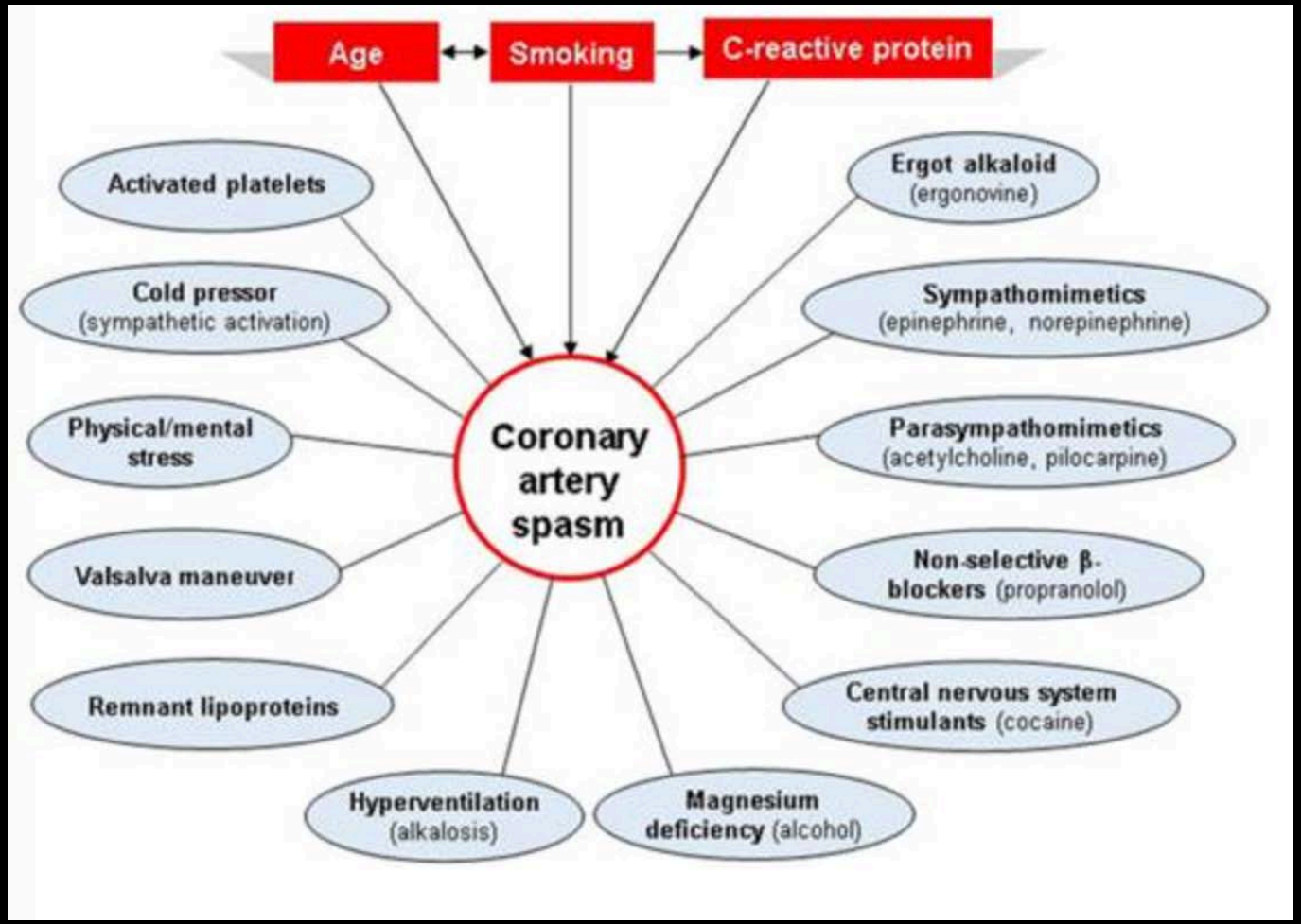
Verhoogde alpha-adrenerge receptor acitiviteit.

Mechanismen

Etiology	Mechanism	Comments
Autonomic nervous system	Frequent attacks at night when vagal tone is high Directly induced by catecholamines [60] or by stimuli (exercise, cold pressor test, cocaine, amphetamines) [70,114].	Night attacks frequently occur during rapid eye movement sleep, when a reduction in vagal activity is associated with an increase in adrenergic activity [26,27]. Spontaneous attacks are often preceded by a reduction of vagal activity [66], and followed by an increase in coronary levels of catecholamines [67].
Inflammation	Elevated peripheral white blood cell and monocyte counts, hs-CRP, interleukin-6, and adhesion molecules [16,50].	Inflammation is prevalent in CAS and atherosclerosis, it, therefore, may not constitute by itself a major direct cause.
Endothelial dysfunction	Acetylcholine, ergonovine, serotonin, or histamine, all of which are endothelium-dependent vasodilators, cause vasodilation by inducing nitric oxide release from the normal endothelium. While in the presence of endothelial dysfunction, they can induce CAS [27].	Endothelial dysfunction is not always present in CAS [86,87].
Smooth muscle cell hypercontractility	Rho-kinase activity is enhanced in coronary artery smooth muscle cells by inflammation in a porcine model [88-90]. Spontaneous CAS has been developed in K_{ATP} mutant or SUR2 K_{ATP} knockout mice [93,94]. Mice deficient in α_{1H} T-type calcium channel have reduced relaxation in response to acetylcholine [95].	Their relevance to CAS in humans remains to be elucidated.
Oxidative stress	NO could be degraded by oxygen free radicals [96-99]. Oxygen-reactive species have a detrimental effect on the vessel wall, leading to inflammation, endothelial damage [98] and vascular smooth muscle cell constriction [100]. In CAS, there are low plasma levels of vitamin E [101] and high plasma levels of thioredoxin [102].	It has been reported that there is no endothelial NO deficiency and dysfunction in patients with CAS [103].
Genetics	Mutation or polymorphism of the endothelial NO synthase gene [82,105,106] , polymorphism of paraoxonase I gene [107], polymorphisms for adrenergic and serotoninergic receptors [108,109], angiotensin-converting enzyme [110], and inflammatory cytokines [111,112] have been reported. In Japan, NADH/NADPH oxidase p22 phox gene is a susceptibility locus in men, while stromelysin-1 and interleukin-6 genes are susceptibility loci in women [113].	Studies of genetic mutations or polymorphisms in the pathogenesis of CAS have been inconsistent [104]. NO gene polymorphisms are found in only one-third of the patients [27]. Family history is not a risk factor for CAS [114].

CAS, coronary artery spasm; hs-CRP, high-sensitivity C-reactive protein; NO, nitric oxide.

Mechanismen en uitlokkende factoren

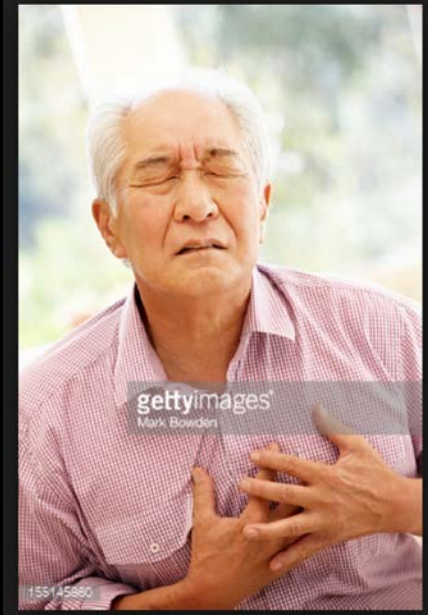


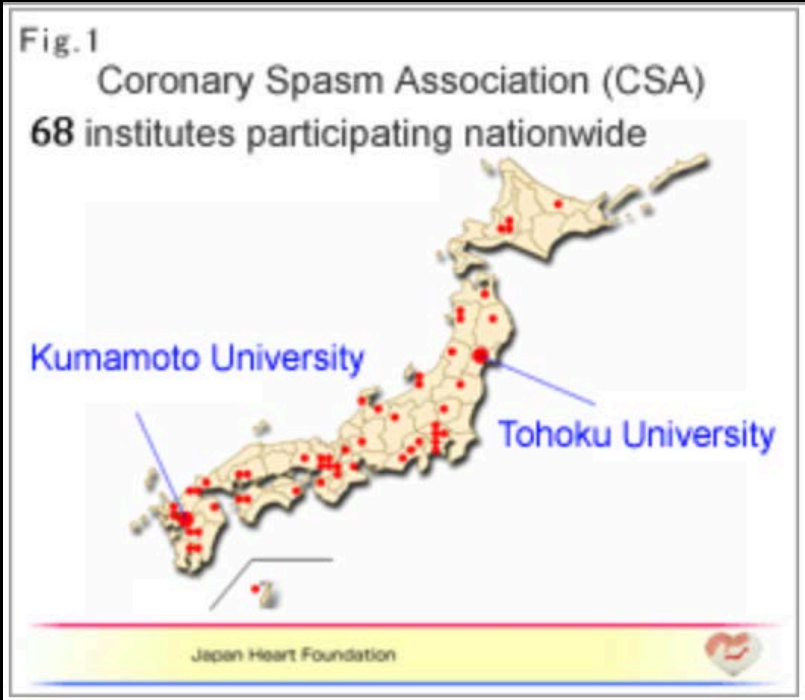
Incidentie bij CAG

USA: 2-3%

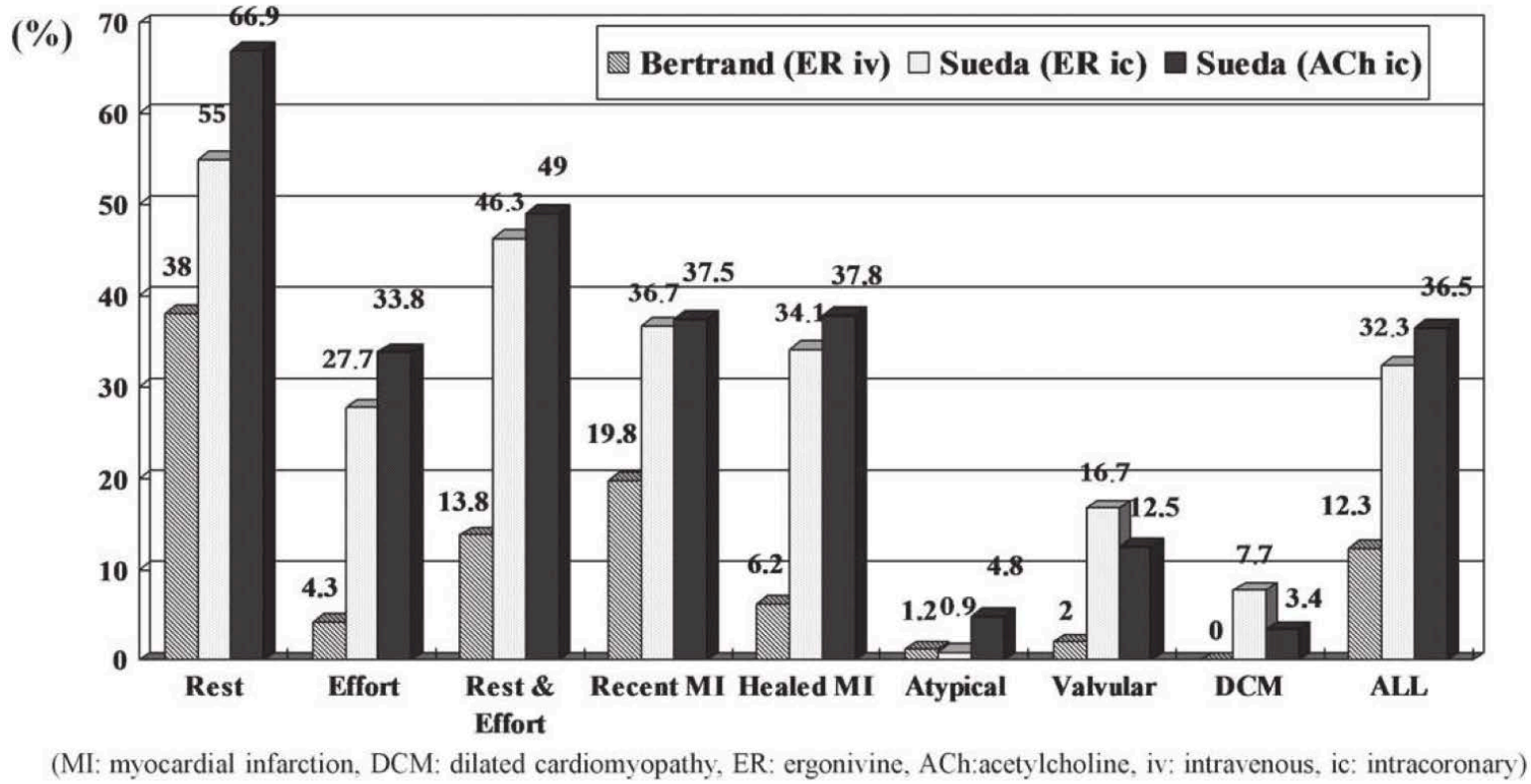
Italie: 10%

Japan: 20-30%





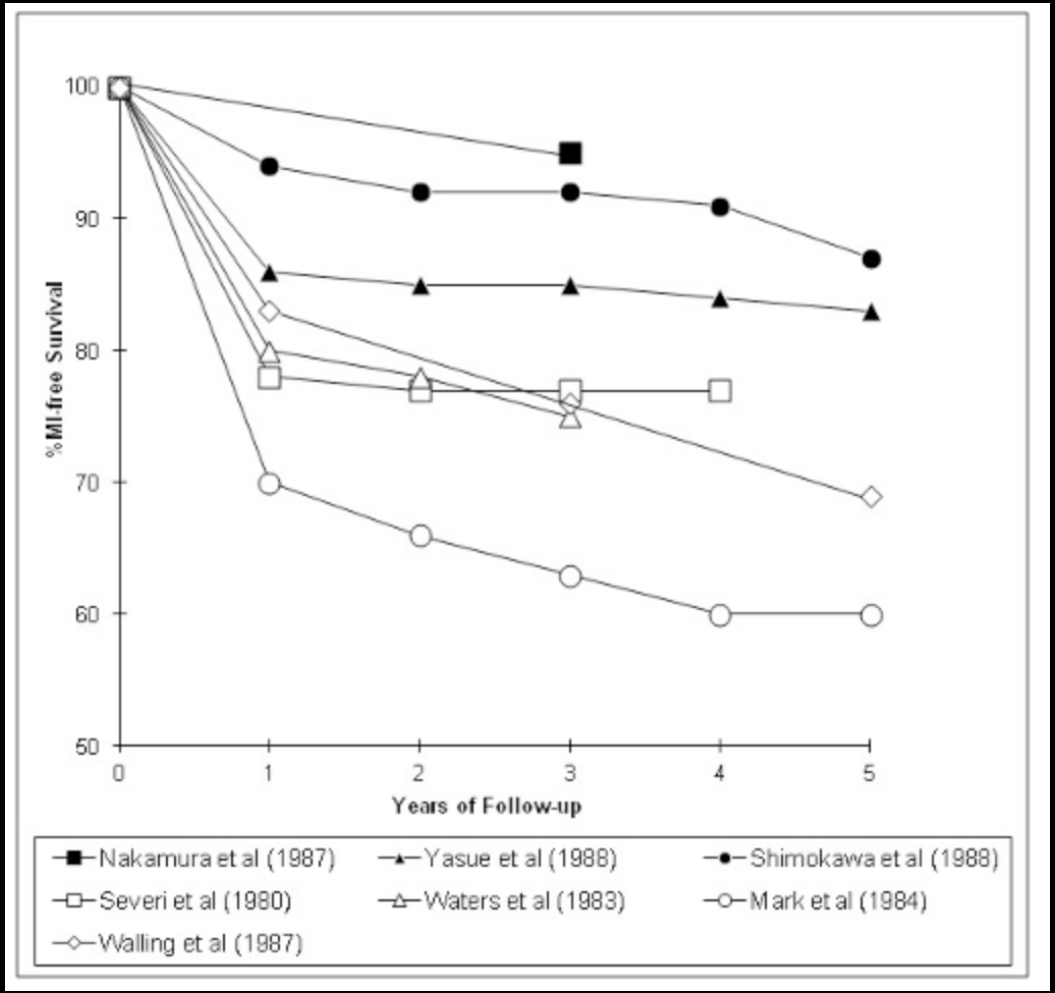
Incidentie verschillen Europa vs. Japan



(MI: myocardial infarction, DCM: dilated cardiomyopathy, ER: ergonivine, ACh:acetylcholine, iv: intravenous, ic: intracoronary)

Figure 2. Comparison of provoked spasm frequency of Bertrand et al and the authors of the current study. Abbreviations: ACh, acetylcholine; DCM, dilated cardiomyopathy; ER, ergonovine; ic, intracoronary; iv, intravenous; MI, myocardial infarction.

MI free survival



Ishii et al. JACC 2015

ABSTRACT

BACKGROUND Coronary artery spasm contributes to the pathogenesis of variant angina and ischemic heart disease and may play a role in the progression of atherosclerosis. It is unclear whether the location of spasm is related to outcome.

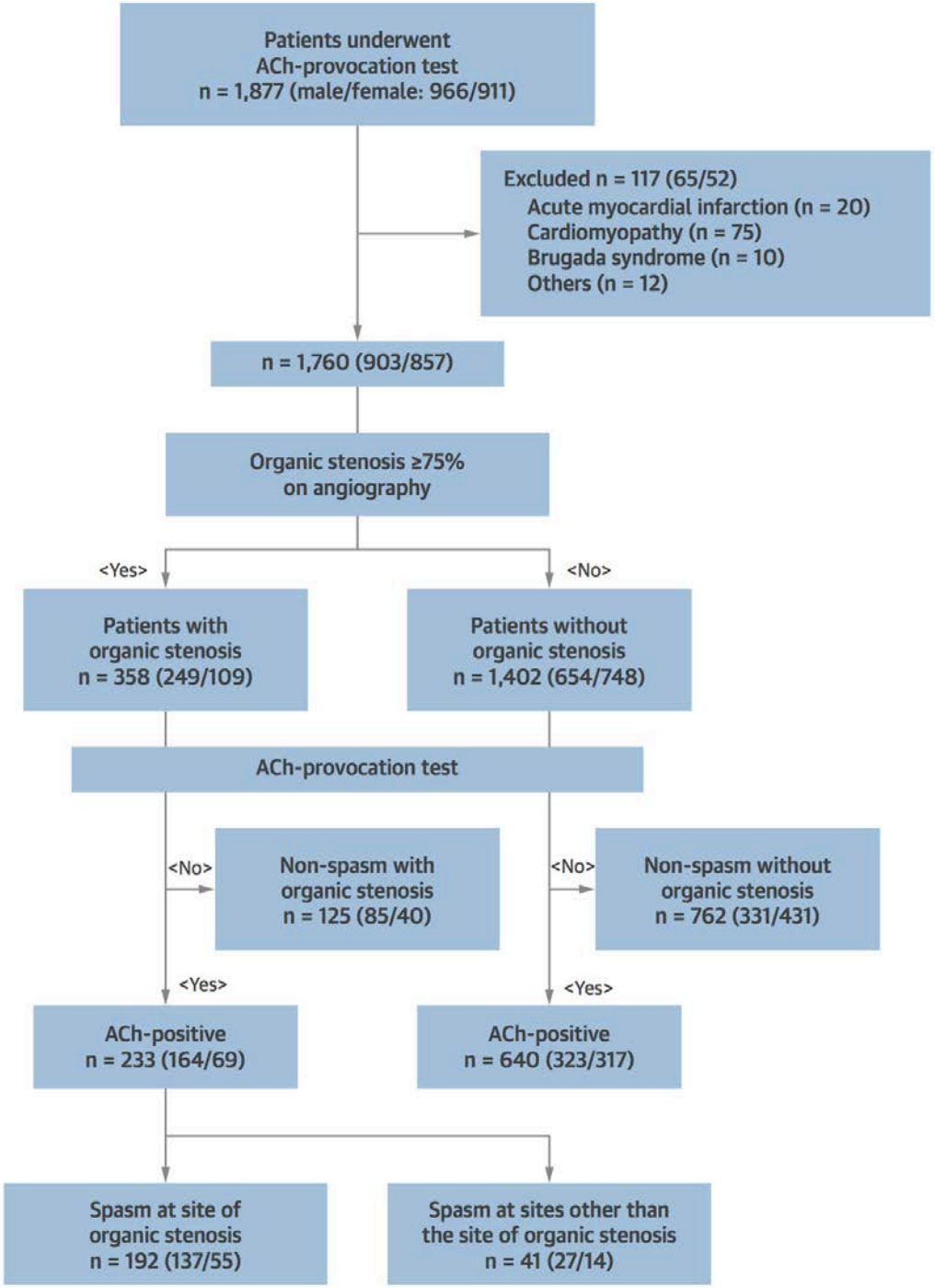
OBJECTIVES This study compared the clinical features and prognosis of patients with coronary spasm at the site of significant atherosclerotic stenosis with patients with spasm at sites without stenosis or nonsignificant stenosis.

METHODS This was a retrospective, observational study of 1,877 consecutive patients with typical or atypical angina-like chest pain undergoing acetylcholine (ACh)-provocation testing. A total of 1,760 patients were eligible for analysis. ACh-provoked coronary spasm and significant organic stenosis were observed in 873 and 358 patients, respectively.

RESULTS In patients with significant atherosclerotic stenosis, ACh-positive patients (n = 233) were younger and without diabetes mellitus compared with nonspasm patients (n = 125). In patients without organic stenosis, ACh-positive patients (n = 640) were older, had dyslipidemia, and were more likely to have a family history of ischemic heart disease than nonspasm patients (n = 762). Multiple logistic regression analysis identified ST-segment elevation during anginal attacks, organic stenosis of the left anterior descending artery, and multivessel spasm as correlates of spasm at sites of significant organic stenosis (n = 192). Multivariate analysis identified ACh-provoked spasm at the site of significant stenosis and use of nitrates as the 2 prognostic factors for major adverse cardiac events.

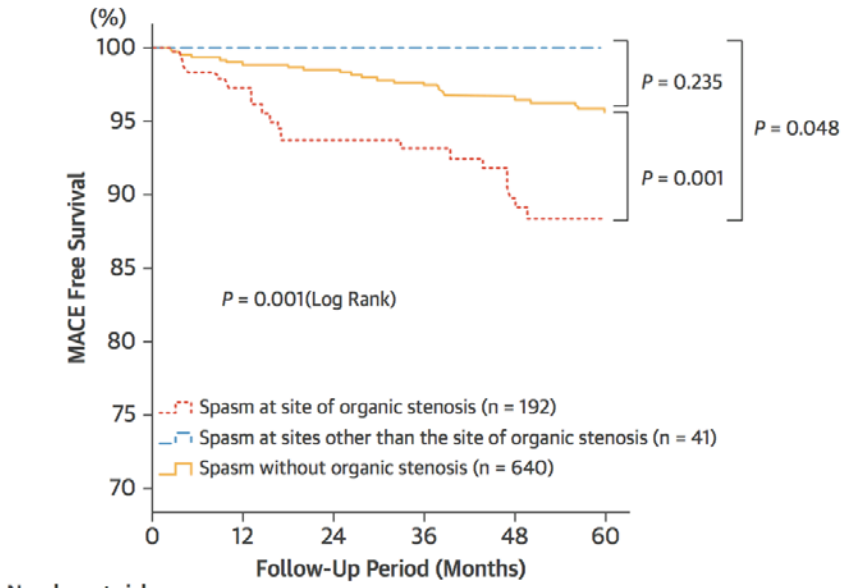
CONCLUSIONS The clinical features and prognosis of patients with ACh-provoked coronary spasm were different when it occurred at the site of significant atherosclerotic stenosis compared with patients with spasm elsewhere. Both spasm at the site of significant organic stenosis and nitrate use were significant predictors of major adverse cardiac events.

(J Am Coll Cardiol 2015;66:1105–15)


Patients underwent
ACh-provocation test
n = 1,877 (male/female: 966/911)
Excluded n = 117 (65/52)
Acute myocardial infarction (n = 20)
Cardiomyopathy (n = 75)
Brugada syndrome (n = 10)
Others (n = 12)
n = 1,760 (903/857)
Organic stenosis ≥75%
on angiography
<Yes>
<No>
Patients with
organic stenosis
n = 358 (249/109)
Patients without
organic stenosis
n = 1,402 (654/748)
ACh-provocation test
<No>
Non-spasm with
organic stenosis
n = 125 (85/40)
<No>
Non-spasm without
organic stenosis
n = 762 (331/431)
<Yes>
<Yes>
ACh-positive
n = 233 (164/69)
ACh-positive
n = 640 (323/317)
Spasm at site of
organic stenosis
n = 192 (137/55)
Spasm at sites other than
the site of organic stenosis
n = 41 (27/14)

Event free survival

FIGURE 2 MACE-Free Survival in Patients With Vasospastic Angina During Follow-Up



Number at risk

Spasm at site of organic stenosis	192	170	159	148	131	122
Spasm at sites other than the site of organic stenosis	41	38	35	29	24	21
Spasm without organic stenosis	640	589	569	520	474	441

Kaplan-Meier survival curve shows worse 5-year survival rates free from MACE in patients with spasm at site of organic stenosis (n = 192) compared with those with spasm at sites other than the site of organic stenosis (n = 41) and those with spasm but without organic stenosis (n = 640). MACE = major adverse cardiac event(s).

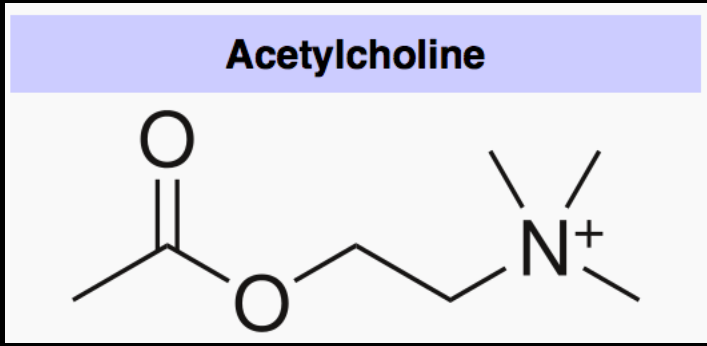
Acetylcholine test

Contra-indicaties:

- HS stenose > 50%
- Ernstig drievatslijden of twee vatslijden met CTO
- Hartfalen NYHA III of IV
- Ernstig asthma

Voorbereiding:

- Defibrillatie plakkers
- Tijdelijke pacemaker draad
- Nitro i.c.



Toediening Acetylcholine:

Bolus gedurende 20 seconden met 3 min interval

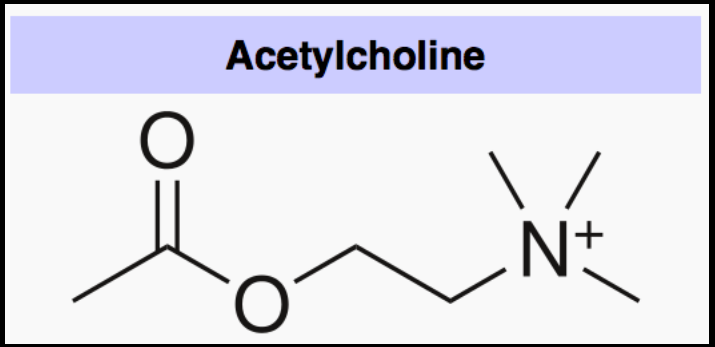
RCA: 20 ug – 50 ug (max. 80 ug)

CA: 20 ug – 50 ug – 100 ug (max. 200 ug)

Acetylcholine test

Criteria positieve ACh test (AJC 2008):

- **Tijdelijke transluminale vernauwing ≥ 90%**
- **ECG veranderingen wijzend op ischemie**



Diagnose Variant AP

90% sensitivity and 99% specificity bij:

- **Positieve Acethylcholine test +**
- **Klinische criteria Prinzmetal**
  - The angina did not occur with exertion and exercise - stress tests were typically negative.
  - During pain, ST segment elevation rather than depression occurred
  - The angina episodes often recurred at the same time, frequently awaking the patient from sleep
  - The episodes may be associated with arrhythmias or progress on to myocardial infarction

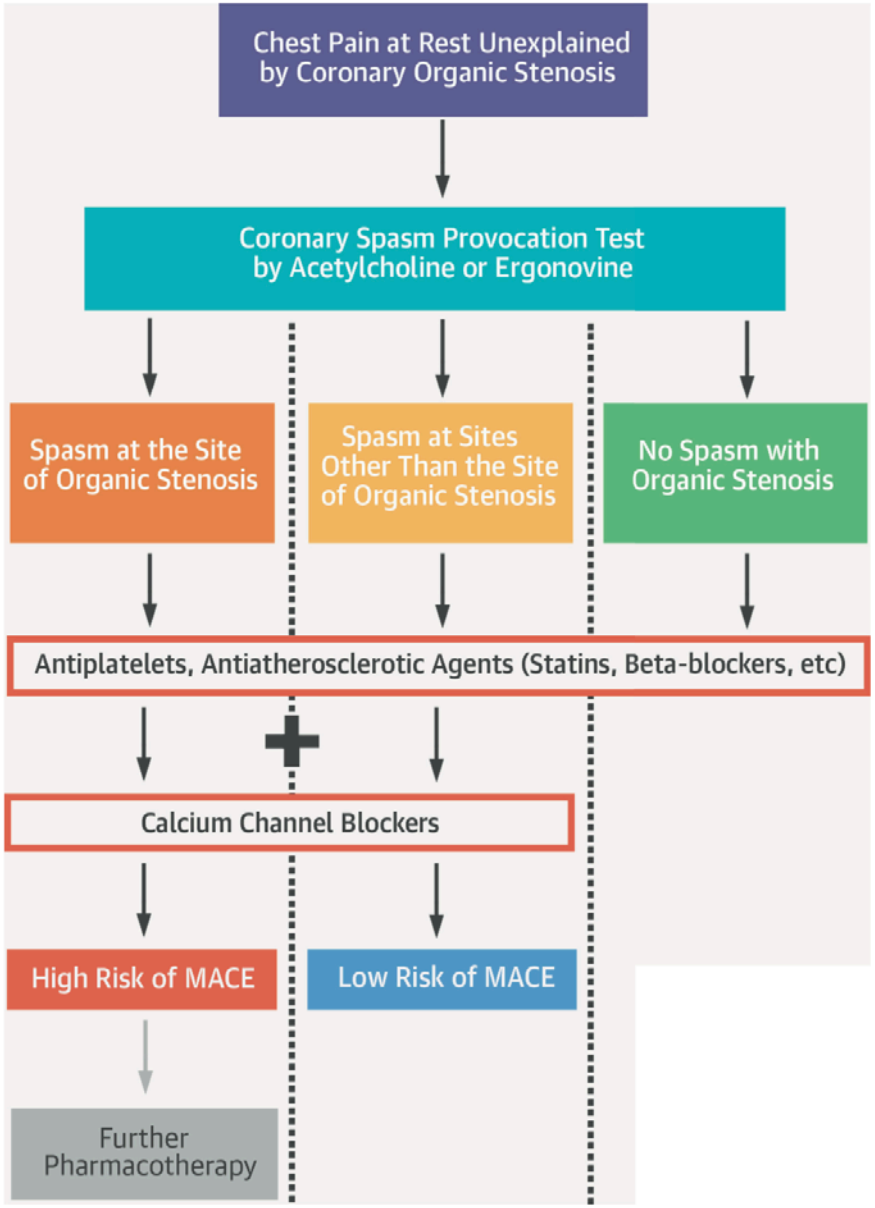
Complicaties Spasme Provocatie test

Table 1. Serious Major Complications Among Past Studies

	Pharmacologic Agents	No. of Patients	VF	VT, (sustained VT)	Bradycardia	Shock	Tamponade	AMI	DC	CABG	Death	Serious Major Complications, n (%)
Buxton (1980)	ER IV	106	2	1 (1)	2	5	0	0	0	1	3	5 (4.72)
Bertrand (1982)	Methyl ER IV	1089	4	1 (1)	2	—	0	0	4	0	0	5 (0.46)
Harding (1992)	ER IV	3447	(7)	(7)	—	—	—	4	—	0	0	11 (0.03)
Ong (2014)	ACh IC	847	0	1 (0)	6	—	0	0	0	0	0	0 (0)
Sueda (1999)	ACh IC	715	0	7 (1)	—	2	1	0	1	0	0	4 (0.56)

Abbreviations: ACh, acetylcholine; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; DC, direct current; ER, ergonovine; IC, intracoronary; IV, intravenous; VF, ventricular fibrillation; VT, ventricular tachycardia.

CENTRAL ILLUSTRATION **Diagnostic, Prognostic, and Pharmacotherapeutic Approaches to Spasm at Site of Stenosis**



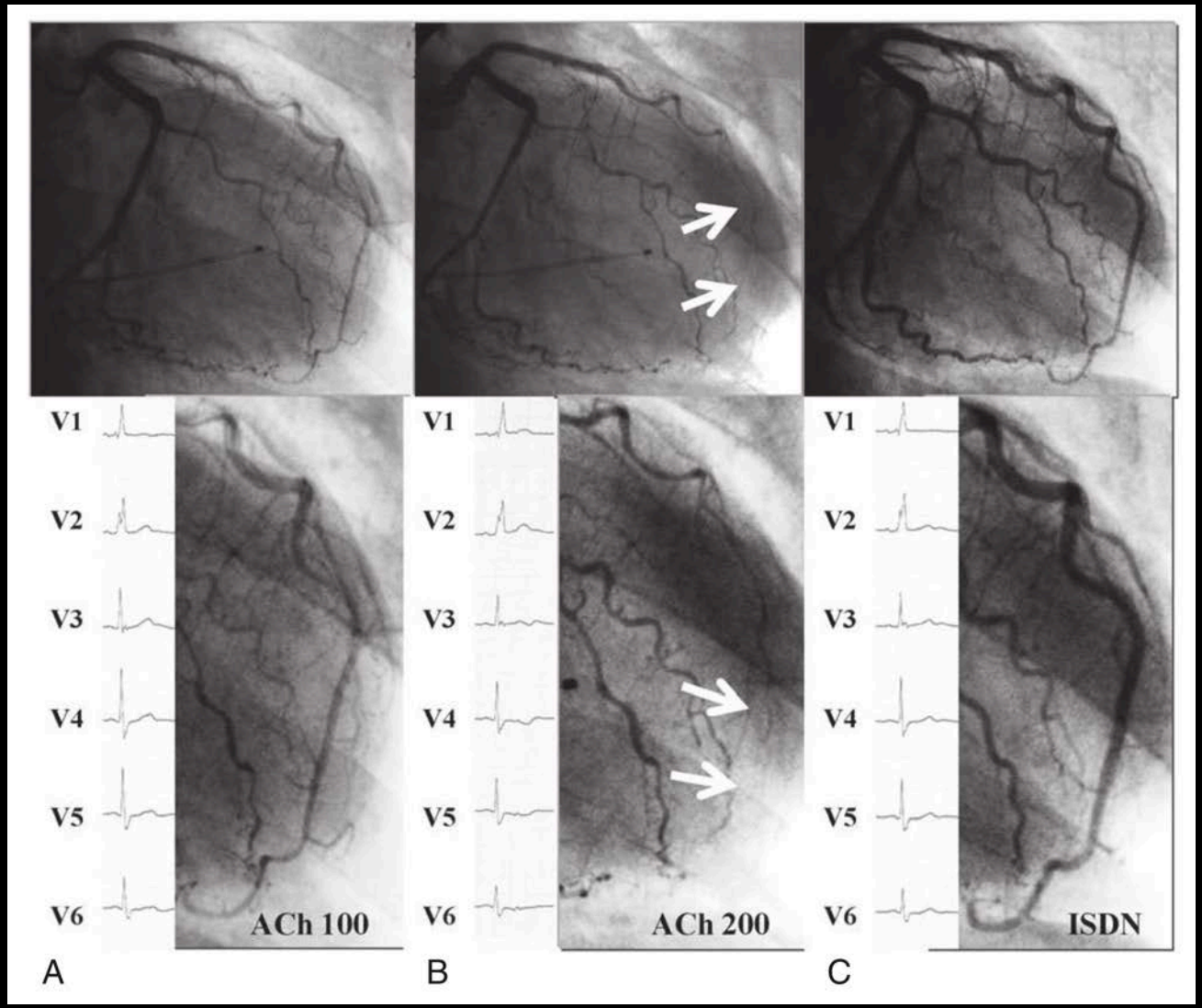
Ishii, M. et al. J Am Coll Cardiol. 2015; 66(10):1105-15.

For patients with known coronary stenosis of otherwise uncertain physiological significance who are considered for revascularization, the acetylcholine-provocation test provides for a full assessment of the site and mode of coronary spasm. Severity of spasm helps guide optimal pharmacotherapy. MACE = major adverse cardiac event(s).

Case 1

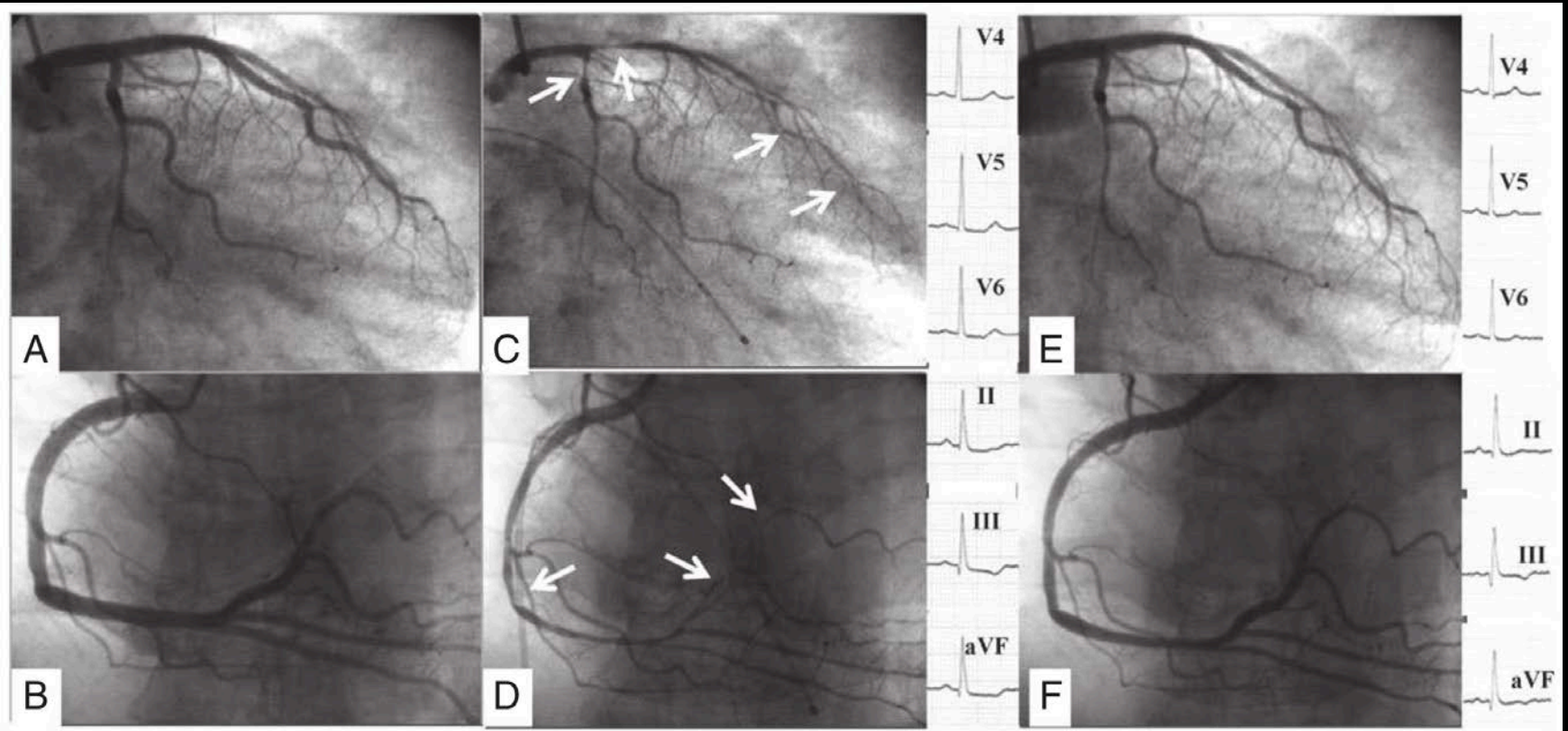
84 jarige man.

AP in rust sinds 6 mnd.



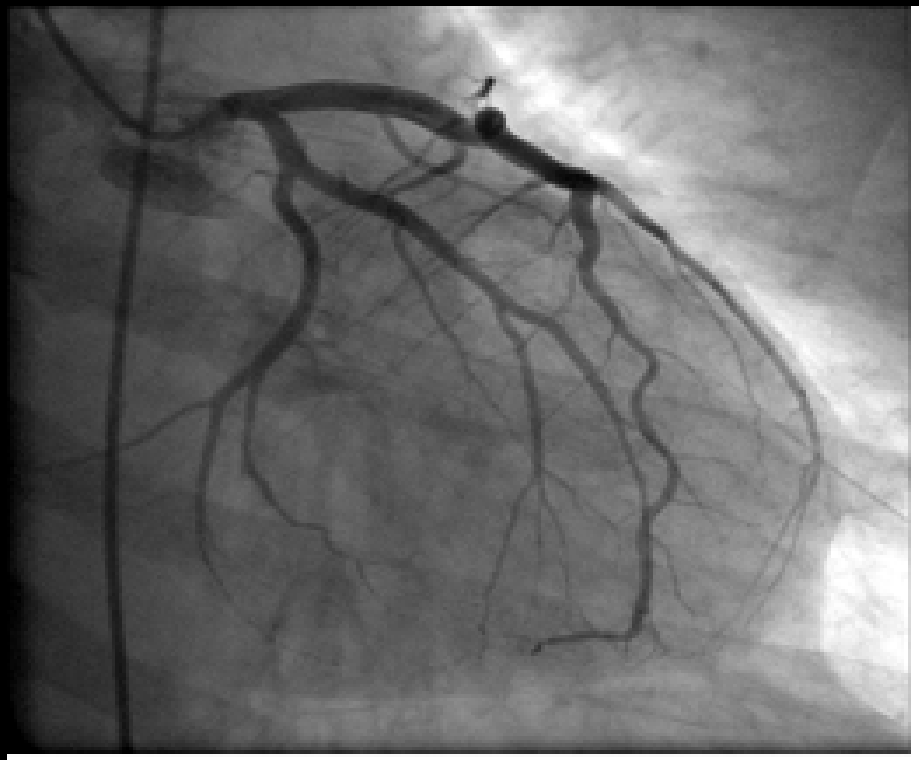
Case 2

70 jarige vrouw. AP in rust ‘s nachts en vroege ochtend.

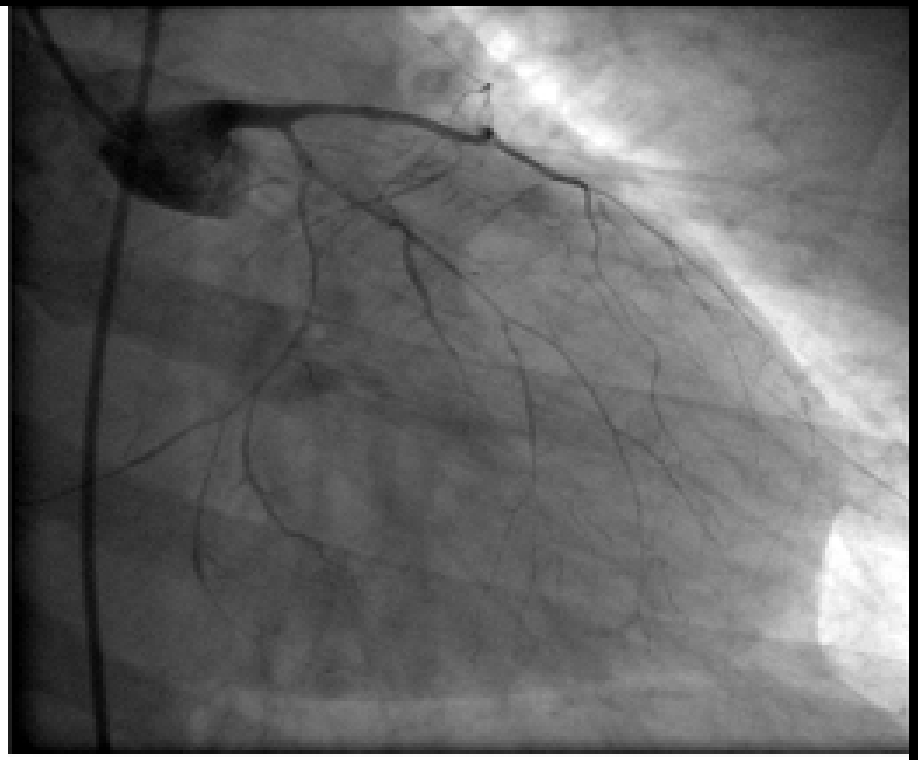


(a, b: after nitrate, c: ACh 100 µg in LCA, d: ACh 50 µg in RCA, e: ER 64 µg in LCA, f: ER 40 µg in RCA)

Case 3



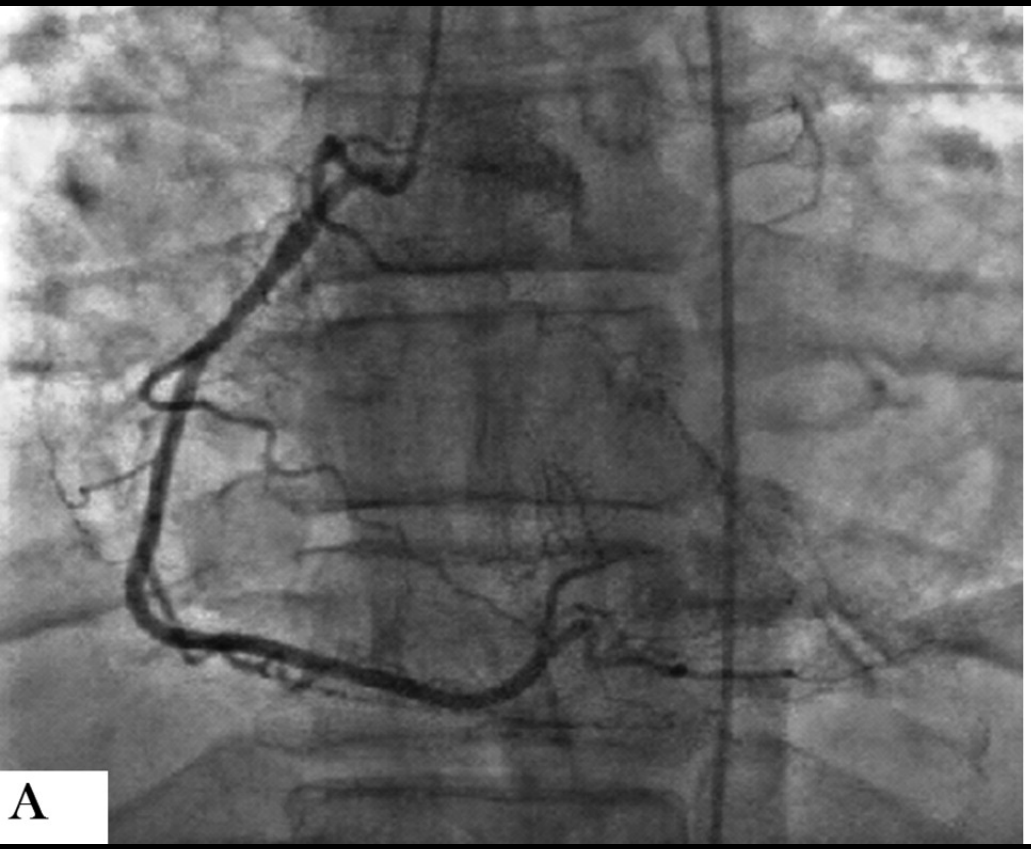
LAD Baseline: no pathologies, no culprit lesion

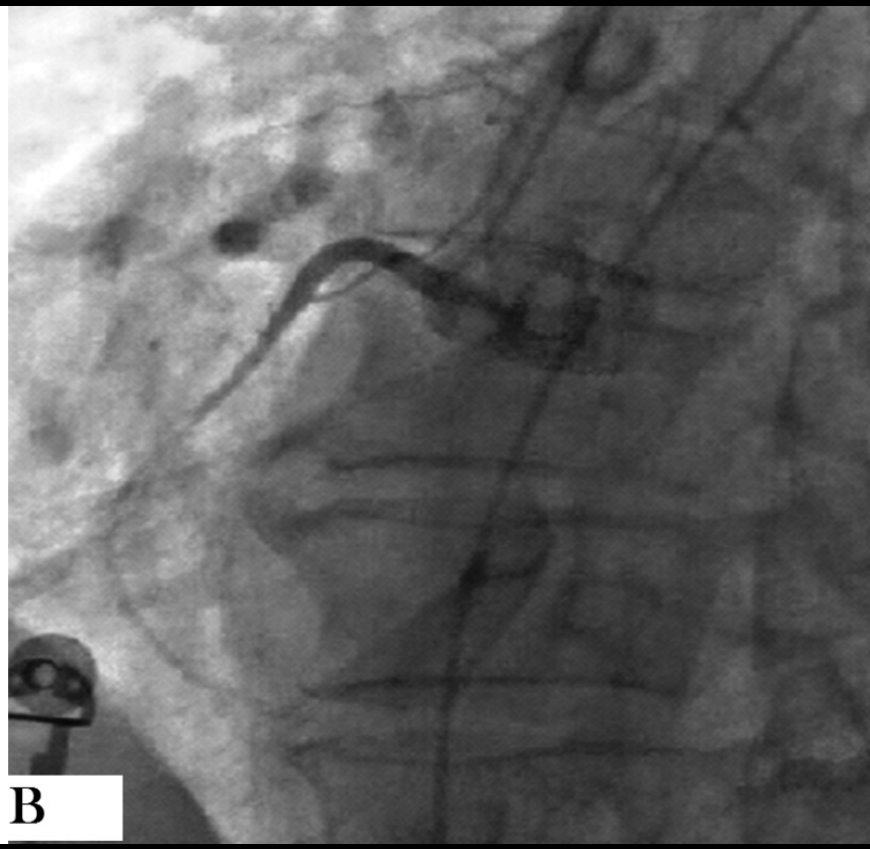


LAD after acetylcholine-infusion: epicardial spasm

Case 4

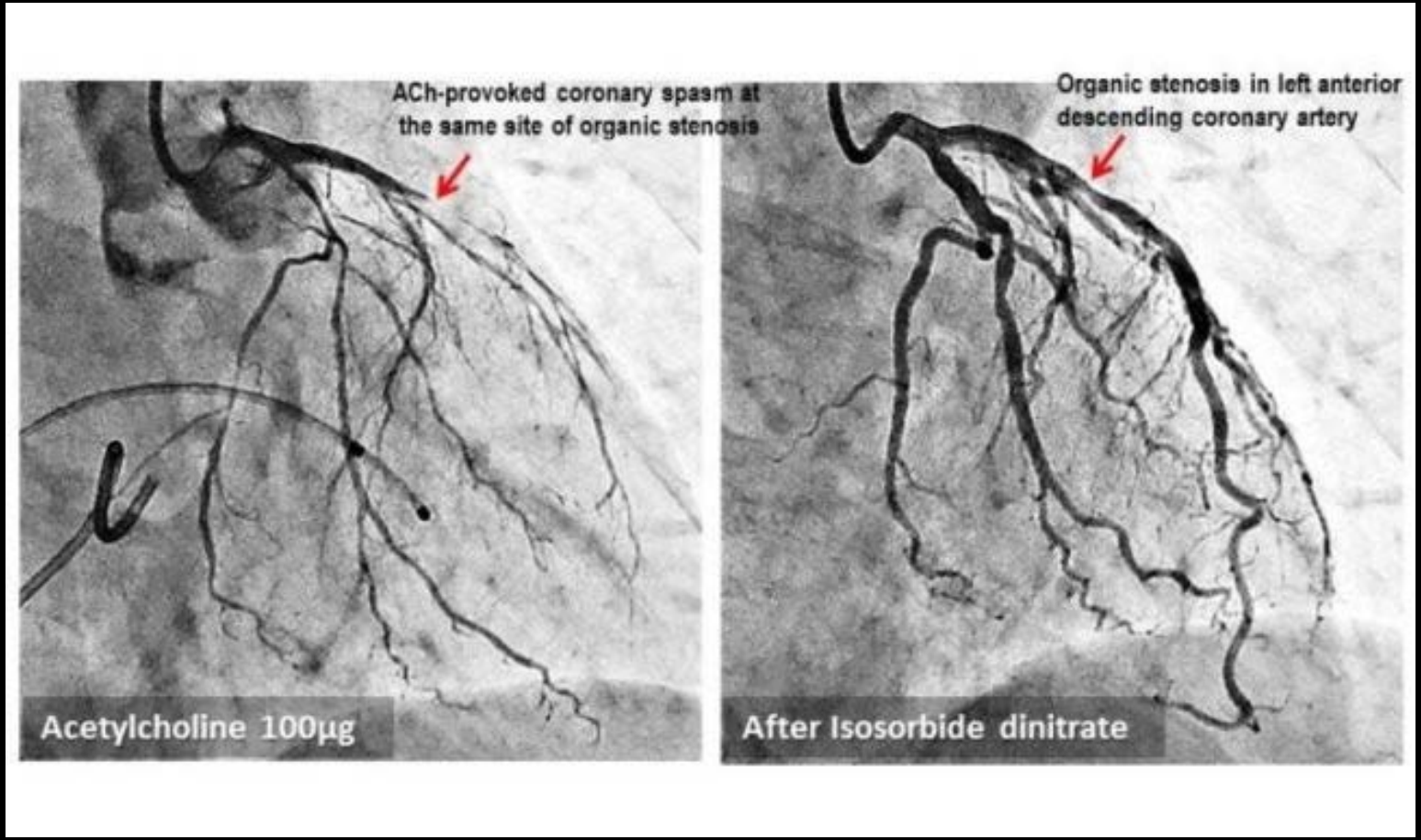
62 jarige vrouw. AP in rust. RF: DM en dyslipidemie.





Case 5

55 jarige man. AP in rust en bij inspanning. RF: dyslipidemie, roken.



https://www.youtube.com/watch?v=paTSAVD5fgE

Professor Udo Sechtem - Stuttgart

Dank voor uw aandacht