Case 29: Questions & Answers:

1. STEMI? Yes. Improved with NTG with prior similar resting CP complaints. Coronary angiography confirmatory for vasospastic angina, also known as Prinzmetal's angina.

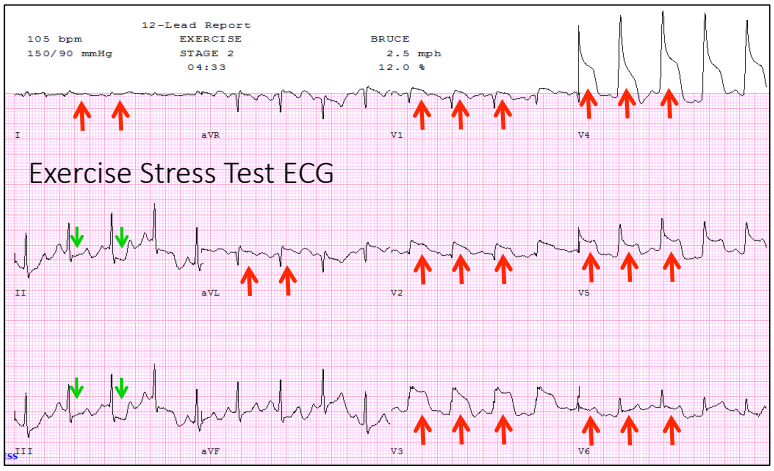
2. Territory? Anterolateral walls.

3. What is the Culprit Vessel? LAD segmental spasm.

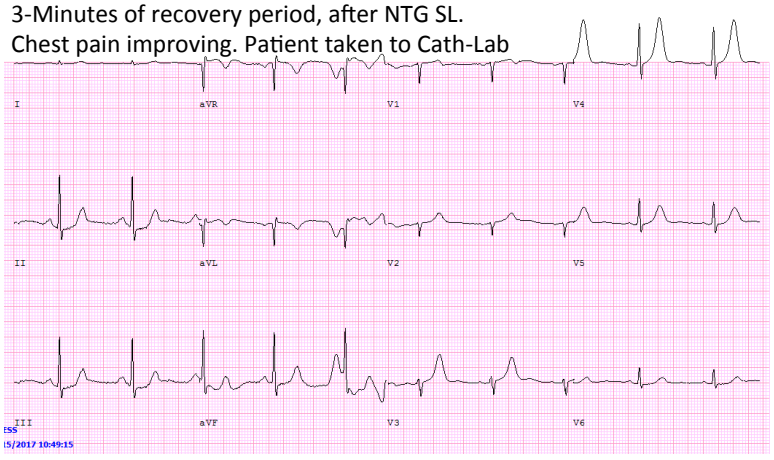
ECG findings:

- Exercise provoked ST segment elevations of injury upon V2-V6, L-1, and aVL (red arrows).
- Reciprocal ST segment depressions upon L-II, L-III and aVF (green arrows).
- STE suggestive of acute anterolateral STEMI versus vasospastic angina. Quick improvement with SL NTG and coronary angiography findings (see below) favor a Prinzmetal's angina.

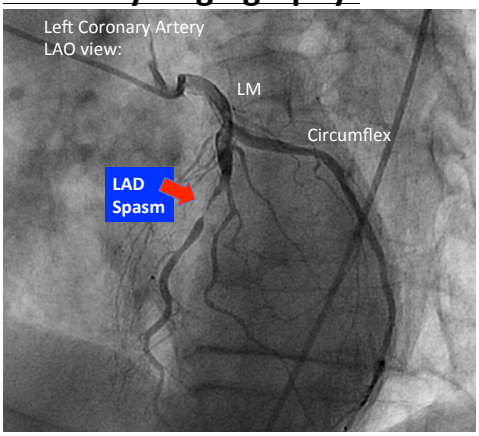
Exercise ECG:

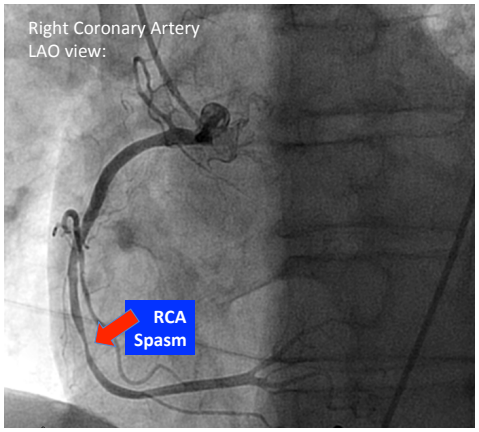


3-Minutes of recovery period, after NTG SL.
Chest pain improving. Patient taken to Cath-Lab

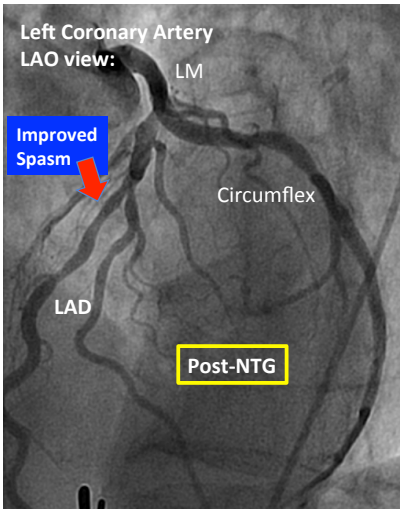


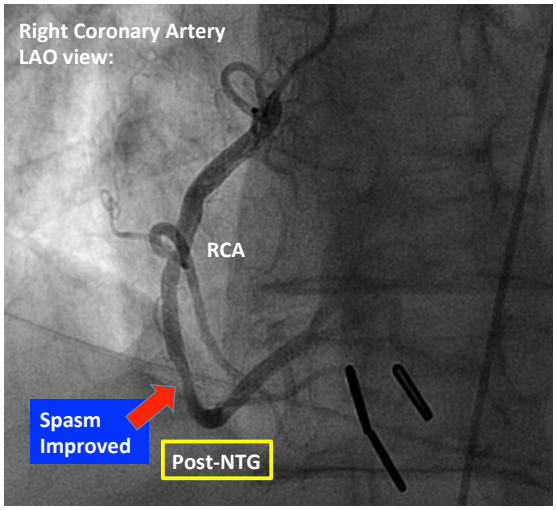
Coronary Angiography:





Post Nitrates



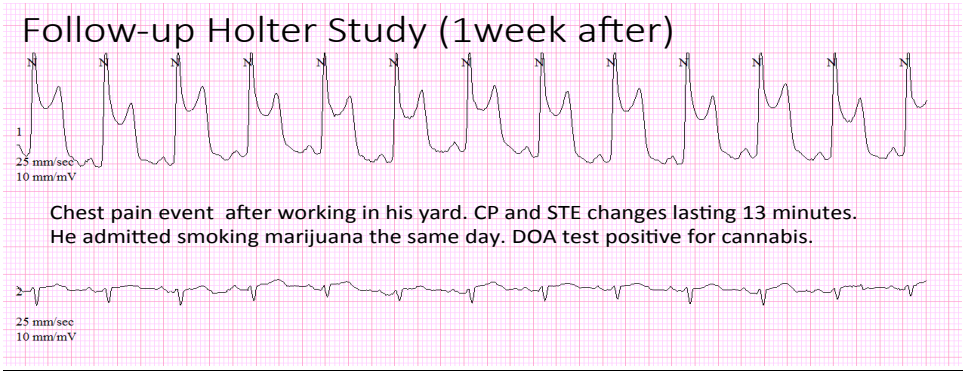


Laboratory Findings:

BARBITURATES	NEG		ng/mL
ETHANOL	NEG		mg/dL
COCAINE	NEG		ug/mL
BENZODIAZEPINES	NEG		ng/mL
CANNABINOIDS	>300.00		ng/mL
METHADONE	NEG		ng/ml
PROPOXYPHENE	NEG		ng/ml
PHENCYCLIDINE	NEG		ng/ml
AMPHETAMINES	NEG		ng/ml
OXYCODONE, URINE	NEG		ng/mL

Inpatient Care: Serial cardiac markers came negative for AMI. He was started on oral nitrates and calcium channel blockers and discharged home with instruction to quit marijuana use, and to avoid smoking or the use of alcohol. He was discharged with a scheduled holter study evaluation 1 week after discharge home.

Impression: Vasospastic angina with marijuana as active trigger.



Patient Outcome: The patient was hospitalized after the above abnormal holter study under cardiac telemetry care. His oral nitrate and calcium channel blocker dose were optimized and the patient was referred for substance abuse clinic. Prior to hospital disposition an exercise treadmill test was repeated with excellent tolerance and no ST elevations (coronary spasm) provoked.

Teaching Points:

Prinzmetal's Angina (Vasospastic Angina) Review

Background:

- The diagnosis of coronary vasospastic angina is infrequently considered in patients with resting angina episodes.
- Resting chest pain is one of the most frequent symptoms of patients presenting to the emergency departments (ED), however, only 20-25% are finally diagnosed with an acute coronary syndrome (ACS).
- The principal cause of ACS is related to an acute atherosclerotic plaque that ruptures and leads to a thrombo-occlusive process and clinically presenting as unstable angina or an acute myocardial infarction (AMI).
- Although coronary artery spasm may result from plaque rupture with the liberation of vasoconstrictive substances, it may also result from a vasospastic syndrome that may lead to intense and sudden vasoconstriction of an epicardial coronary artery causing vessel occlusion or near occlusion.
- This vasospastic angina (VSA) syndrome was first described in 1959 by Prinzmetal et al in 32 cases of angina occurring at rest, reporting that the clinical characteristics of these patients differed to those with classical angina of effort related to obstructive CAD, therefore also recognized as variant or Prinzmetal's angina.
- Variant angina events usually occur spontaneously and are characterized by *hallmark features:*
    1. Recurrent episodes at rest, often occurring in the early morning hours, associated with
    2. Transient ST-segment elevations and

3. Prompt resolution with short-acting nitrates.

- The importance of recognizing and diagnosing VSA relates to:
  1. Its association to major adverse events including syncope, AMI, cardiac arrhythmias and sudden cardiac death, which may occur before the diagnosis of VSA is considered.
  2. The potential to prevent these adverse events by avoiding the use of potential precipitants for coronary artery spasm (e.g. vasoconstrictors) and the use of established effective therapies (nitrates and calcium channel blockers).

Pathophysiology & Pathogenesis:

- Coronary angiography, performed during spontaneous angina attacks, has demonstrated that coronary spasm is the usual cause of variant angina.
- Spasms may occur in either angiographically normal or diseased vessels, frequently associated to coronary plaques that may be either non-obstructive or obstructive.
- Usually occurring at a localized coronary segment (focal spasm) or may occur on 2 or more segments of the same (multifocal spasm) or of different (multivessel spasm) epicardial coronary arteries or may also involve diffuse coronary extension or microvascular spasm.
- The exact underlying pathology predisposing to spasm is not clearly understood.
- The probable underlying defect is the presence of endothelium dysfunction (ED) that exposes the medial smooth muscle to vasoconstrictors (favored over vasodilators).
- ED can also impair coronary flow-dependent vasodilatation owing to the decreased production and release of nitric oxide.
- There is also evidence of involvement of the autonomic nervous system, with reduced parasympathetic tone and enhanced reactivity of the alpha-adrenergic vascular receptors.
- Except for cigarette smoking, the conventional atherosclerotic risk factors do not appear to predispose patients to variant angina.

Epidemiology:

- The actual prevalence of vasospastic angina in the general population remains largely unknown, primarily related to diagnostic challenges.
- It appears to be more frequent in individuals from Japan compared to Caucasian populations.
- It afflicts younger patients and females more than males.
- The diagnosis is more often made in individuals less than 50 years of age than in older people.

Diagnosis:

- Key for the diagnosis is the documentation of ST-segment elevation in a patient during transient chest discomfort and resolves when the chest discomfort subsides.
- STE implies transmural focal ischemia associated with a complete epicardial coronary occlusion in the absence of collateral circulation
- Typically, NTG is exquisitely effective in relieving the spasm.
- **COVADIS Diagnostic Criteria for Vasospastic Angina* (table-1):**

  The Coronary Vasomotion Disorder International Study Group (COVADIS) was established to develop international standards for diagnostic criteria for VSA (published on 2015).

Table I Coronary Artery Vasospastic Disorders Summit diagnostic criteria for vasospastic angina[a]

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 β-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 ≥0.1 mV
   (b) ST segment depression ≥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)

[a]'Definitive vasospastic angina' is diagnosed if nitrate-responsive angina is evident during spontaneous episodes and either the transient ischaemic ECG changes during the spontaneous episodes or coronary artery spasm criteria are fulfilled. 'Suspected vasospastic angina' is diagnosed if nitrate-responsive angina is evident during spontaneous episodes but transient ischaemic ECG changes are equivocal or unavailable and coronary artery spasm criteria are equivocal.

- Episodes of VSA often occur in clusters, with prolonged asymptomatic periods of weeks to months.
- In many cases, coronary artery vasospasm can occur spontaneously without an identifiable cause. Attacks can be precipitated by an emotional stress, hyperventilation, exercise, or exposure to cold.
- Other triggers of spasm in susceptible patients include cocaine, amphetamine, alcohol, cigarette smoking, cannabis, hypomagnesemia, vitamin E deficiency, insulin resistance, or administration of sumatriptan and ergotamine (migraine treatment).
- Exercise does not usually provoke an episode of spasm. However, among patients who are very symptomatic during a "hot phase" of the condition, characterized by more frequent and intense episodes, spasm may be triggered by the elevated catecholamines associated with exercise.
- A circadian variation in angina episodes is most often seen, more commonly occurring in the early morning.
- In addition to helping with the diagnosis, ***ambulatory monitoring*** should be performed to assess the efficacy of therapy, given that asymptomatic episodes are common and sometimes associated with significant arrhythmias. In one report using 24-hour ambulatory ECG monitoring, 79% of episodes were asymptomatic.
- Most patients with vasospastic angina will have a normal ***noninvasive stress test.*** However, exercise-induced spasm with ST-segment elevation has been reported to occur in 10 to 30 percent of patients with vasospastic angina, particularly during the "hot phase" of this condition.
- For most patients presenting with angina chest pain (including those with episodes predominantly at rest) and no transient ischemic ST changes on ECG, it is recommend evaluating for fixed obstructive coronary artery disease prior to an evaluation directed at vasospastic angina. If significant fixed obstructive disease is reasonably excluded, the diagnosis of vasospastic angina can be pursued.

- Three ***provocative tests*** (ergonovine, acetylcholine, and hyperventilation) can be performed in the catheterization laboratory in an attempt to confirm the diagnosis. These tests are done only when the diagnosis of vasospastic angina is suspected, but not firmly established. At present, pharmacologic provocative testing is not frequently performed and should be employed only by experienced teams. Table-2 describes **COVADIS** recommendation regarding provocative spasm testing ranked in categories according to risk and benefits of the study according to the patient. (Reference-2)

Table 2 Indications for provocative coronary artery spasm testing

Class I (strong indications)
- History suspicious of VSA without documented 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
  - Unresponsive to empiric therapy
- 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
- Documented spontaneous episode of VSA to determine the 'site and mode' of spasm

Class IIb (controversial indications).
- Invasive testing for non-invasive diagnosed patients responsive to drug therapy

Class III (contra-indications)
- Emergent acute coronary syndrome
- Severe fixed multi-vessel coronary artery disease including left main stenosis
- Severe myocardial dysfunction (Class IIb if symptoms suggestive of vasospasm)
- Patients without any symptoms suggestive of VSA

- Testing for vasospastic angina with ***hyperventilation*** has been evaluated in studies of ***electrocardiogram monitored*** patients and had a high specificity (100 percent) in one study and a sensitivity ranging between 55 and 95 percent, depending on the frequency of daily attacks. Hyperventilation is rarely used as a provocative test during coronary arteriography.

Management:

- Most attacks of angina resolve spontaneously without evidence of MI. However, a prolonged vasospasm may result in complications such as MI, syncope, high degree of AV block, life-threatening ventricular tachycardia or SCD.
- Treatment of vasospastic angina reduces the frequency of symptomatic episodes and appears to decrease the frequency of serious complications.
- Although episodes may terminate spontaneously, a sublingual nitrate is effective in reducing the duration of each episode. It is recommended that patients use sublingual nitrates with the onset of each episode, both to decrease the duration of symptoms and ischemia.

- Patients with frequent or prolonged episodes (>10min) should be instructed to visit the hospital for admission, close ECG monitoring, intravenous nitrates and intensification of therapy.
- Calcium channel blockers (nifedipine, diltiazem, and verapamil) are the first-line therapy for vasospastic angina. These agents prevent vasoconstriction and promote vasodilation in the coronary vasculature, thereby alleviating symptoms.
- One study demonstrated that the use of calcium channel blocker therapy was an independent predictor of myocardial infarct-free survival in vasospastic angina patients. Beginning with a calcium channel blocker as a first line therapy is recommended since it is effective in alleviating symptoms in over 90 percent of patients in an observational study.
- The long-acting nitrates are also effective in alleviating symptoms, but the occurrence of nitrate tolerance makes them a less desirable first-line approach.
- Treatment with alpha-receptor blocker may be of some benefit when incomplete response is obtained to calcium channel blockers and nitrates.
- Irrespective of therapy chosen, it is important to document suppression of both symptomatic and asymptomatic episodes with ambulatory electrocardiographic monitoring, given the frequency of the latter.
- Persistence of asymptomatic episodes should lead to an intensification of therapy if possible, in an attempt to lower the risk of ventricular arrhythmias.
- Statins have been shown to be effective in preventing coronary spasm and may exert their benefits via endothelial nitric oxide or direct effects on the vascular smooth muscle.
- Nonselective beta-blockers can exacerbate vasospasm and should be avoided.

Prognosis

- In general, the long-term prognosis of patients with vasospastic angina is good, particularly in patients receiving medical therapy.
- Infarct-free survival ranged between 60-95% at five years.
- Independent predictors of worse prognosis include the presence of obstructive CAD, no treatment with calcium channel blockers, and multivessel spasm.

References

1. Amsterdam E, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes.
2. Beltrame J, et al. International standardization of diagnostic criteria for vasospastic angina. Eur Heart J 2015

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