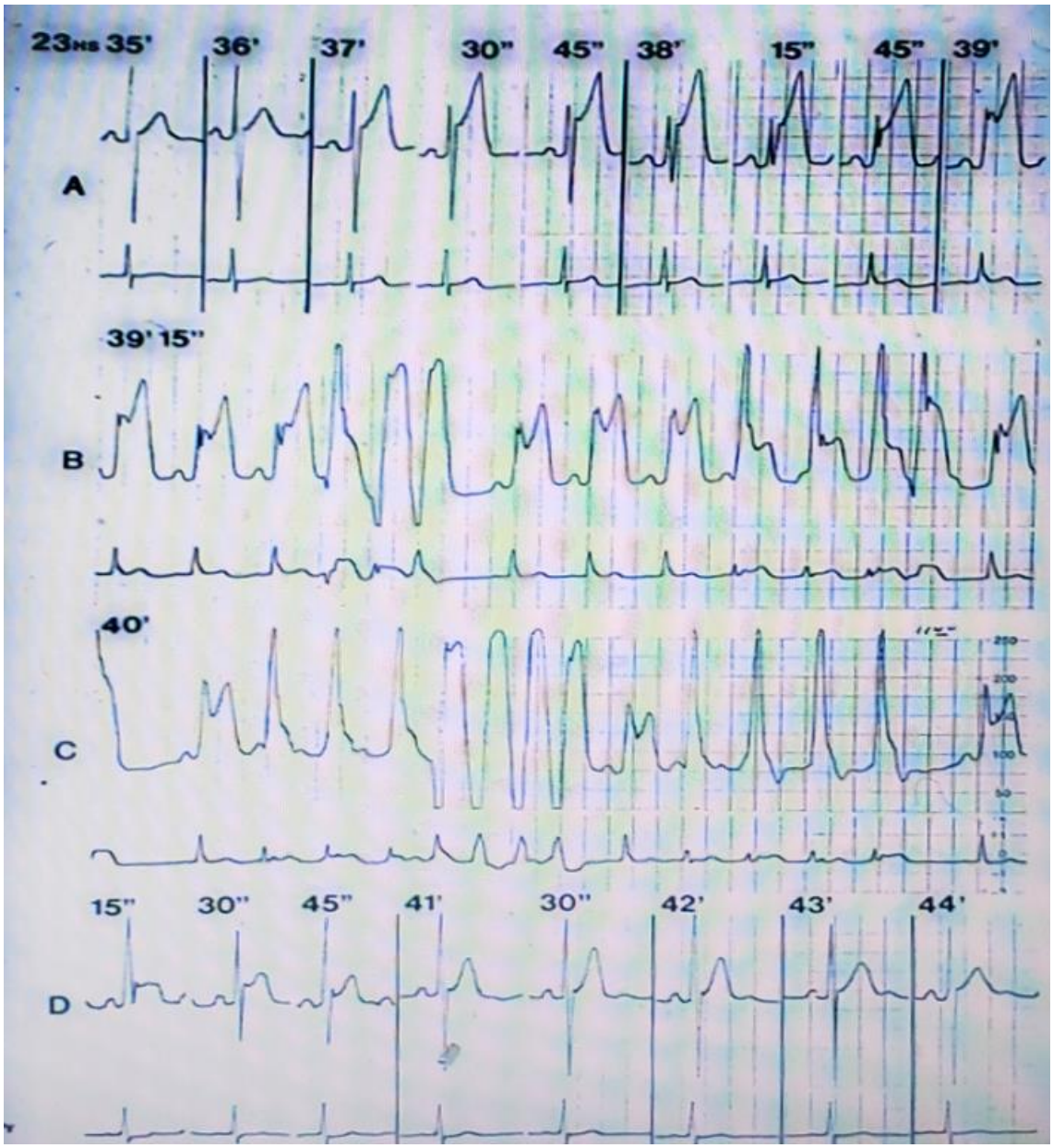
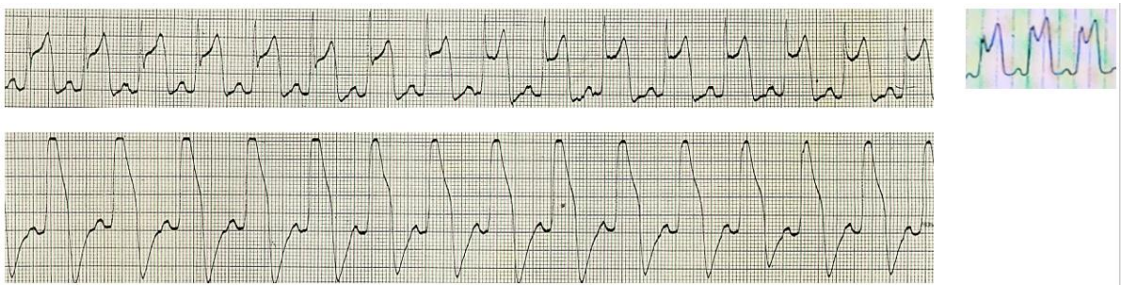
PRINZMETAL'S ANGINA CASE



Monitor Lead – Consecutive (Prof, Paul Levine case)

48 y.o. woman admitted as r/o MI with classic ischemic quality chest pain but occurring at rest; normal resting ECG. Premenopausal, nonsmoker, normal BP, neg. FH, Cholesterol 156, HDL 60c/o recurrent 8/10 crushing precordial chest pain



What should be done now?

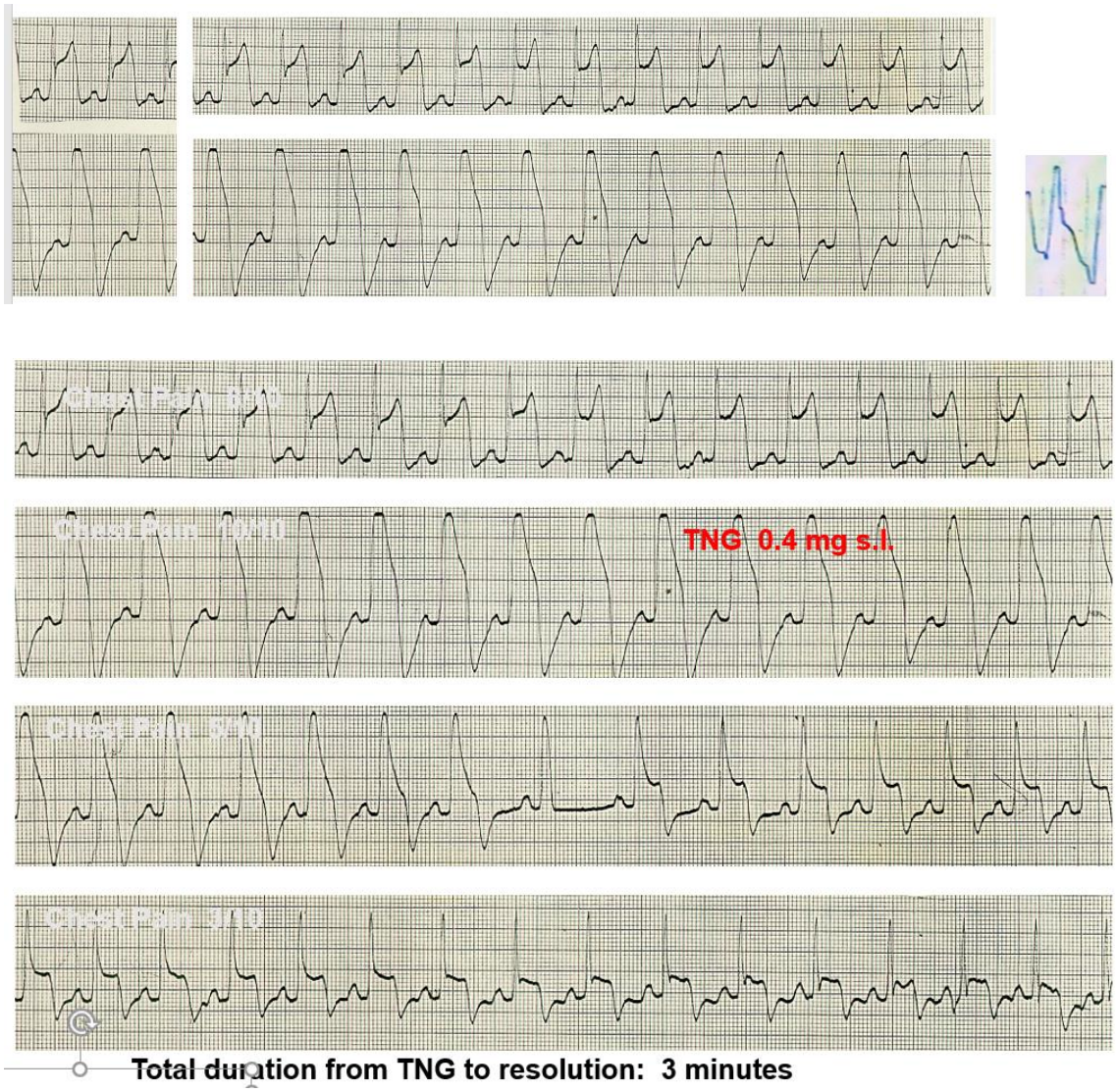
A. Emergency cardiac cath and PTCA

B. tPA (thrombolytic therapy)

C. Sublingual nitroglycerin

D. Morphine

Sequential rhythm strips from monitor

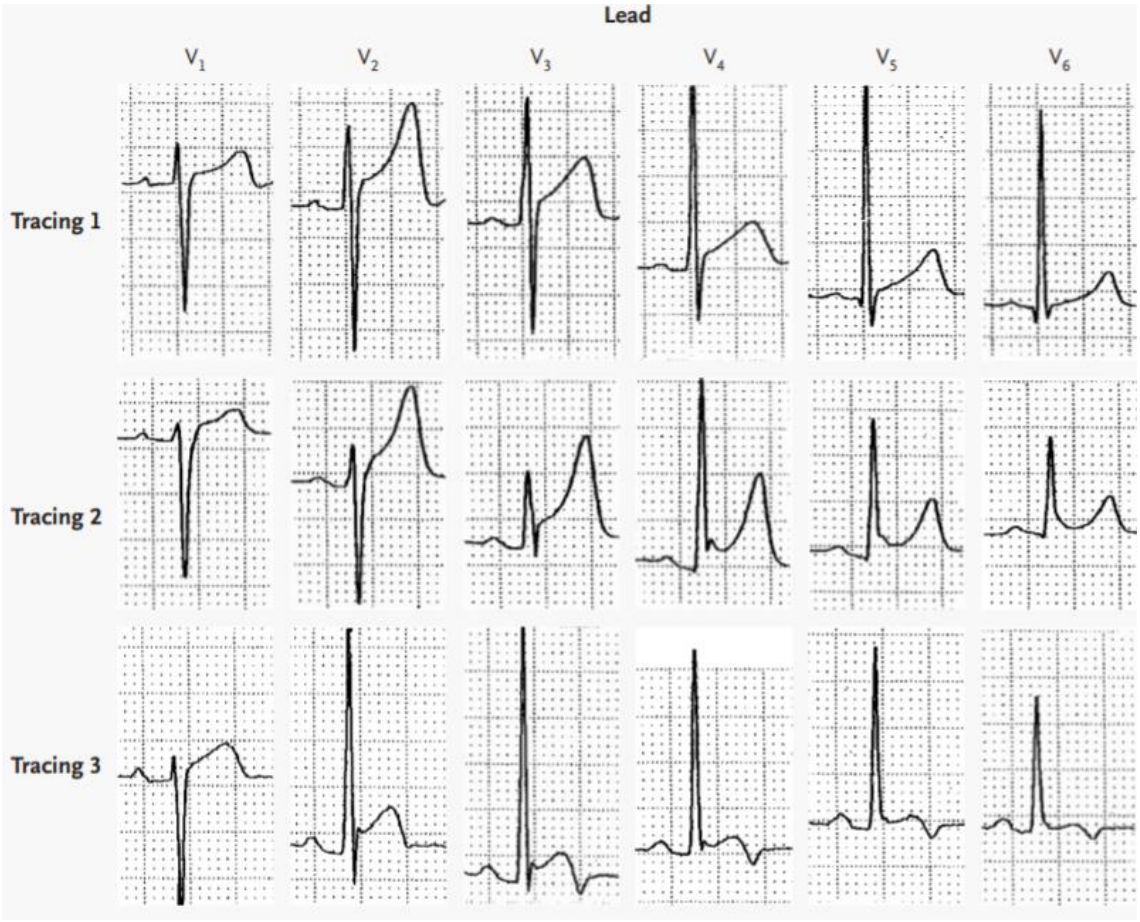


Diagnosis

- Prinzmetal's variant angina (coronary vasospasm)
- Cardiac catheterization
    - Normal LV function
    - Clean coronary arteries
    - LAD spasm induced with ergonovine
- Rx:
    - Sublingual TNG on prn basis
    - Nifedipine (Calcium Channel Blocker)

Causes of ST Segment elevation: ST-segment elevation in conditions other than acute myocardial infarction: the so-called ECG mimics of AMI

- Transmural ischemia/infarct
    - Infarct - will evolve Q waves, ST elevation, T inversion
    - Ischemia - will resolve, no permanent changes
- Epicardial irritation
    - Pericarditis
- Hyperkalemia
- Early repolarization pattern
- Brugada syndrome
- Brugada phenocopies
- Others

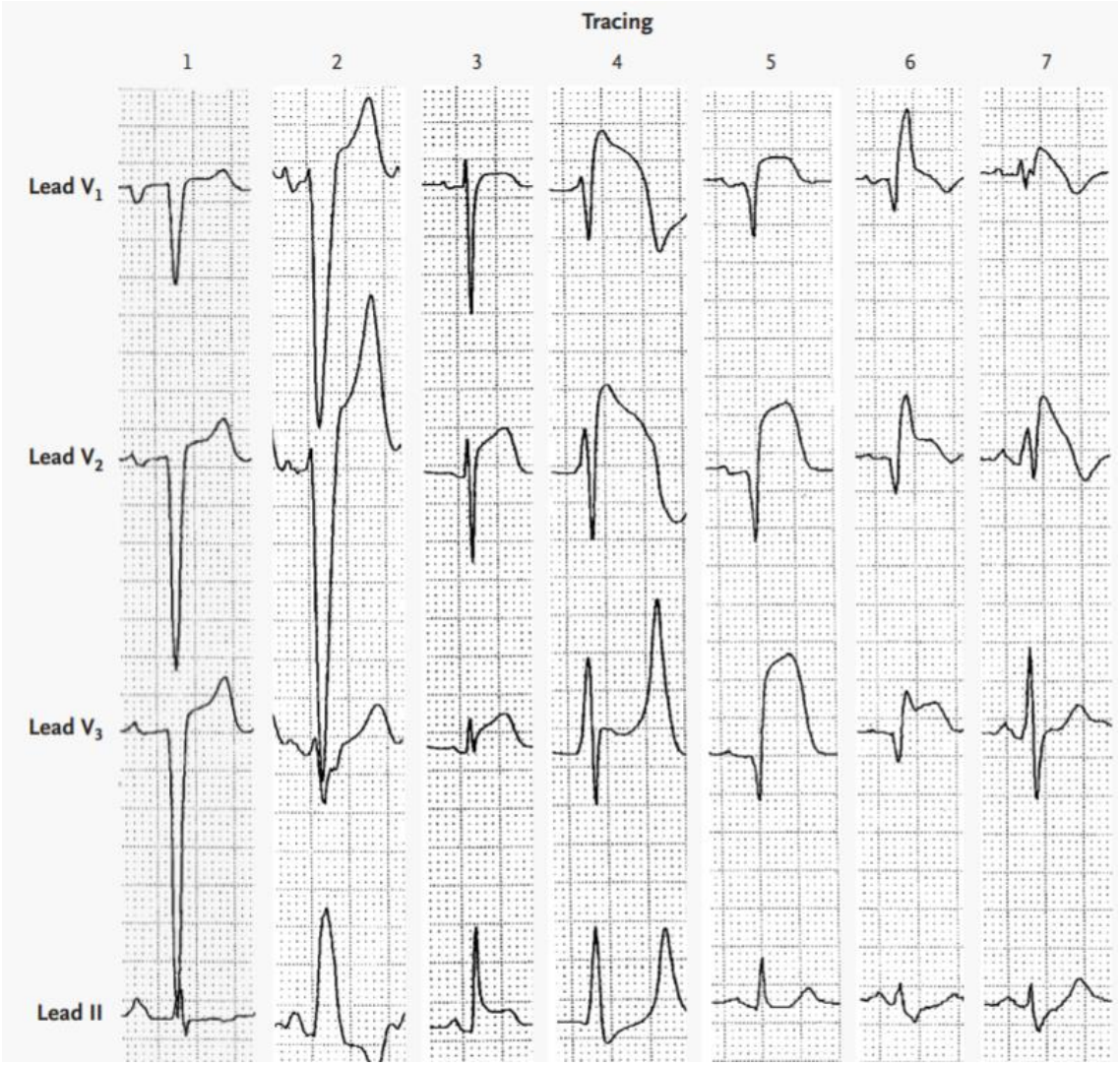


Electrocardiograms showing normal ST-segment elevation and normal variants.

I. Tracing 1 shows normal ST-segment elevation. Approximately 90% of healthy young men have ST-segment elevation of 1 to 3 mm in one or more precordial leads. The ST segment is concave.

II. Tracing 2 shows the early-repolarization pattern, with a notch at the J point in V4. The ST segment is concave, and the T waves are relatively tall.

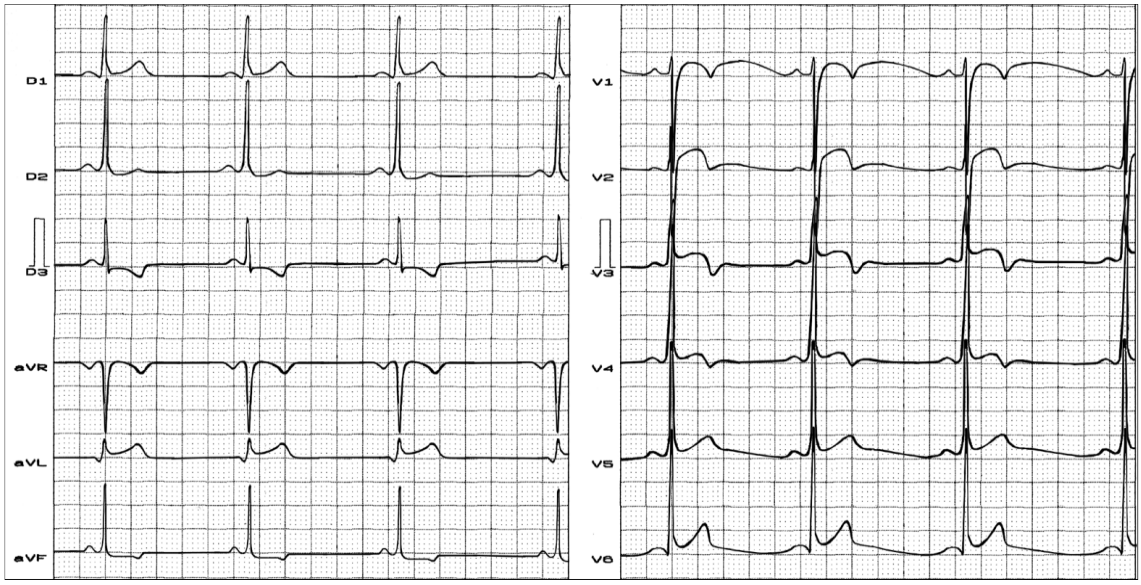
III. Tracing 3 shows a normal variant that is characterized by terminal T-wave inversion. The QT interval tends to be short, and the ST segment is coved.



Electrocardiograms Showing ST-Segment Elevation in Various Conditions.

1. Tracing 1 is from a patient with left ventricular hypertrophy
2. Tracing 2 is from a patient with left bundle-branch block.
3. Tracing 3 from a patient with acute pericarditis, is the only tracing with ST-segment elevation in both precordial leads and lead II and PR-segment depression.
4. Tracing 4 shows a pseudoinfarction pattern in a patient with hyperkalemia. The T wave in V3 is tall, narrow, pointed, and tented.
5. Tracing 5 from a patient with acute anteroseptal infarction.
6. Tracing 6 from a patient with acute anteroseptal infarction and right bundle-branch block, include the remaining R' wave and the distinct transition between the downstroke of R' and the beginning of the ST segment.

7. Tracing 7 from a patient with the type 1 Brugada pattern , shows rSR' and ST-segment elevation limited to V1 and V2. The ST segment begins from the top of the R' and is downsloping. Type-1 ECG Brugada pattern: J point and ST segment elevation ≥2 mm, with upper convexity(1A) or descending oblique rectilinear(1B) and negative symmetrical T wave in at least one right precordial leads (V1-V2 or V1-V3) and/or high right precordial leads V_{1H}, V_{2H} and V_{3H}.



Clinical diagnosis: healthy patient. Tracing obtained in a periodical evaluation.

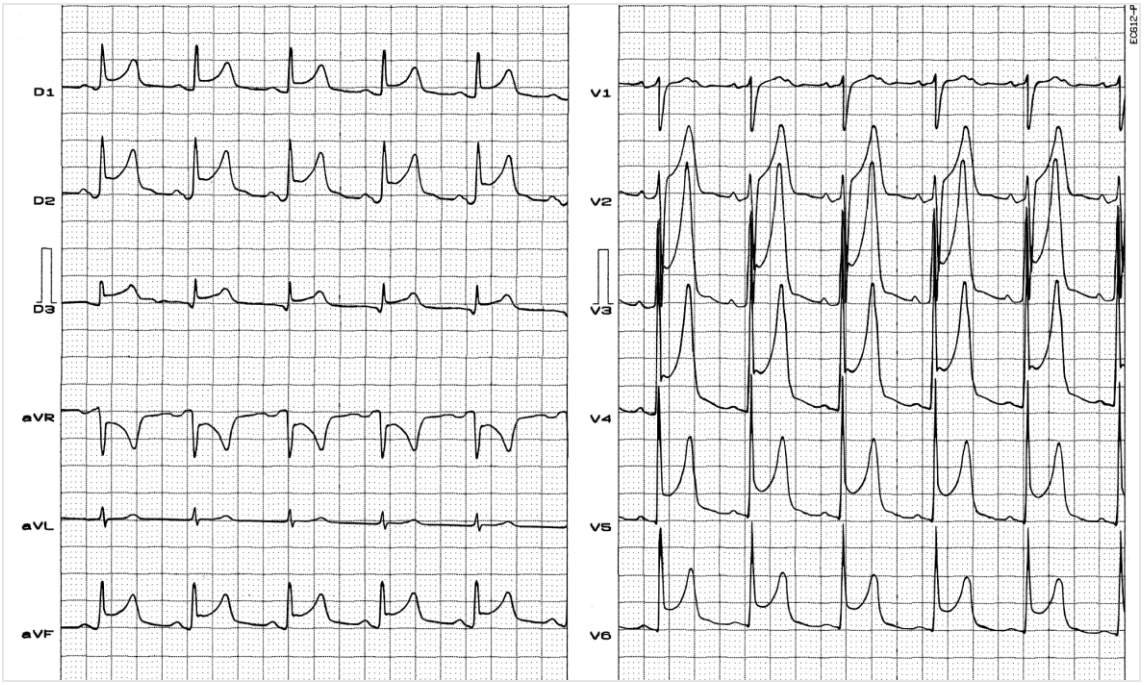
ECG diagnosis: sinus bradycardia, respiratory sinus arrhythmia or phasic sinus arrhythmia. Positive voltage criterion for LVE. SV_1 or V_2+RV_5 or V_6 >35 mm (Index of Sokolow Lyon). ST segment elevation from V_2 to V_6 and with negative T from V_1 to V_4. Early repolarization, pattern of pseudo injury and anterior subepicardial ischemia. Normal chest X-rays and echocardiogram. Pattern of pseudo epicardial injury and ischemia in anterior wall in an athlete, professional player of basketball with normal heart.

Electrocardiographic characteristics of “benign” early Repolarization Pattern

1. HR: frequent characteristic sinus bradycardia
2. Respiratory sinus arrhythmia is effectively benign, meaning that it is not harmful. It occurs when a person's heart rate relates to their breathing cycle. In other words, when the person breathes in, their heart rate increases, and when they breathe out, the rate decreases.

3. Axes of QRS, ST segment and T wave, oriented in the same direction in the frontal plane;
4. Deep and narrow Q waves followed by R wave of great voltage in left precordial leads;
5. Notch or slurring of R wave descending branch (J-wave) possible but not obligatory;
6. Transition area in precordial leads of sudden occurrence;
7. J point and ST segment elevation, usually < 2 mm (exceptionally it may be > 5 mm) of superior concavity in middle and/or left precordial leads and possibly in inferior leads;
8. Possible reduction in J point and ST segment elevation by sympathetic action and sympathomimetic drugs;
9. Absence of reciprocal or mirror image (exception in VR lead);
10. Symmetrical or pseudo symmetrical T waves, with great width and polarity matching QRS;
11. The ERP consists of J-point and convex ST segment elevation, often with a notch at the intersection of the two.(Patton KK, et al 2016 et al) It is frequently seen in athletes, up to 35% in one study,(Noseworthy PA, et al.2011.) and is more common in those who are younger, male or of African-Caribbean descent(Junttila MJ, et al. 2011.) While the ERP has been associated with SCA in the general population, especially if present in the inferior leads, it is enhanced by exercise training and there are no data suggesting an increased risk of SCA in young athletes. No secondary evaluation is needed for these athletes.

Acute pericarditis

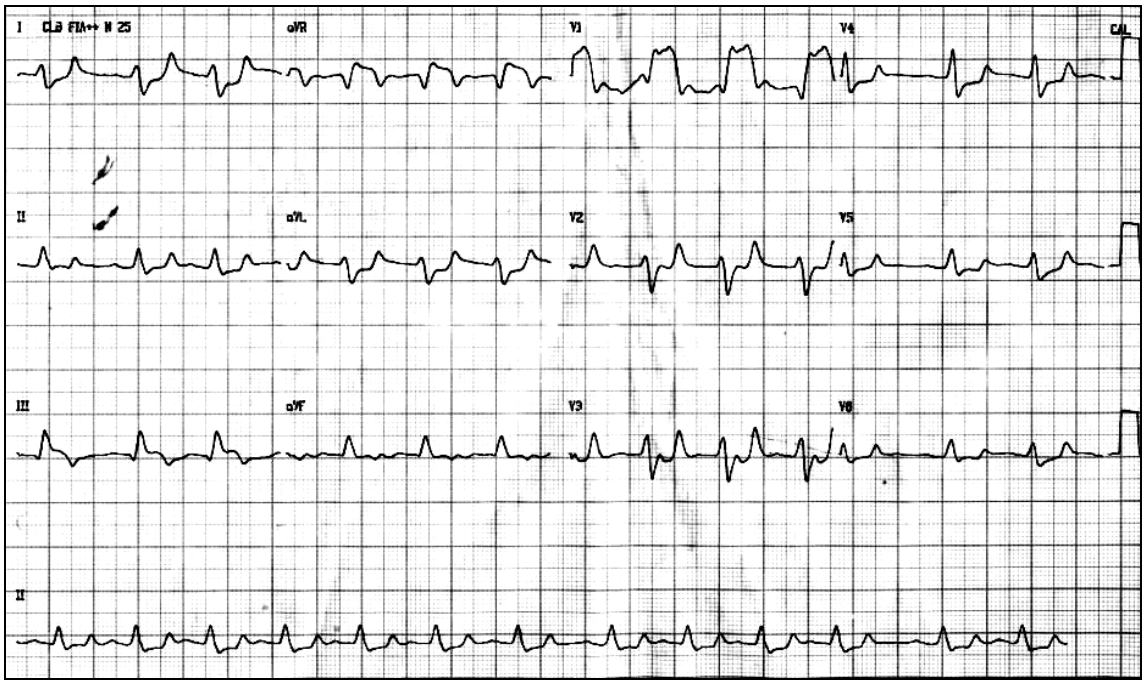


Acute pericarditis with significant and diffuse ST segment elevation.

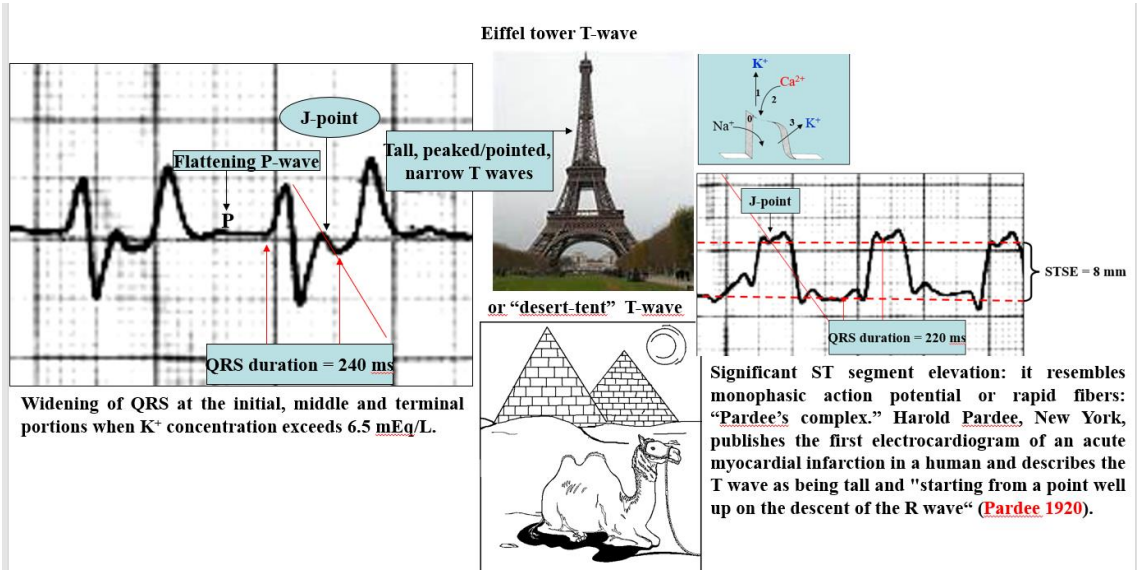
Simulation of electrocardiographic manifestation of STEMI: Severe hyperkalemia key for diagnosis

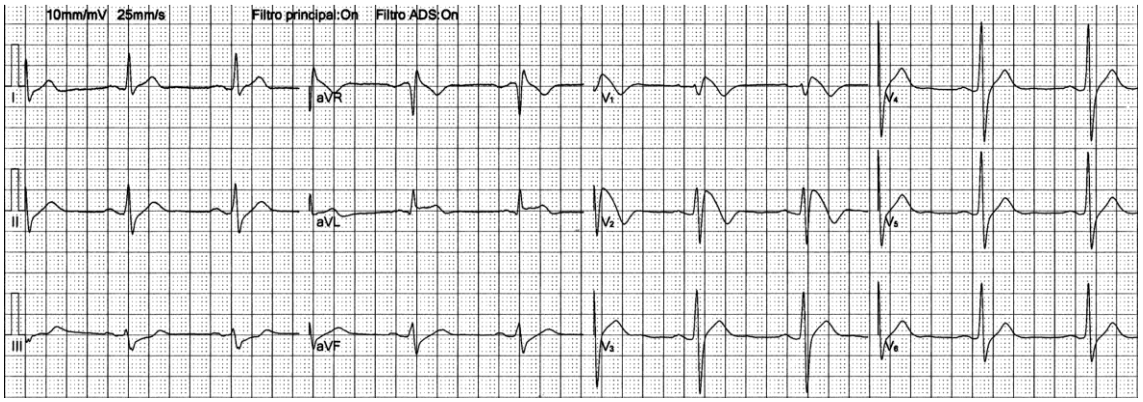
65-year-old man, white, businessman, suffers from hypertension and long-standing type 2 diabetes. He was admitted to ER complaining of chest discomfort that started one hour ago. The admission ECG is shown attached. The strategy was primary PCI for ST-SEMI because patients with ST-SEMI benefit from prompt reperfusion therapy. Additionally, the patient had testicular seminoma, widespread metastasis, and renal failure exacerbated by cardiac catheterization, and probably by high blood pressure and diabetes mellitus. There was some initial improvement after dialysis but unfortunately as a consequence of the underlying disease he died. Questions: What is the electrocardiographic diagnosis? Culprit artery? What would you expect to find in the catheterization?

Serum $K^+ = 7.9$

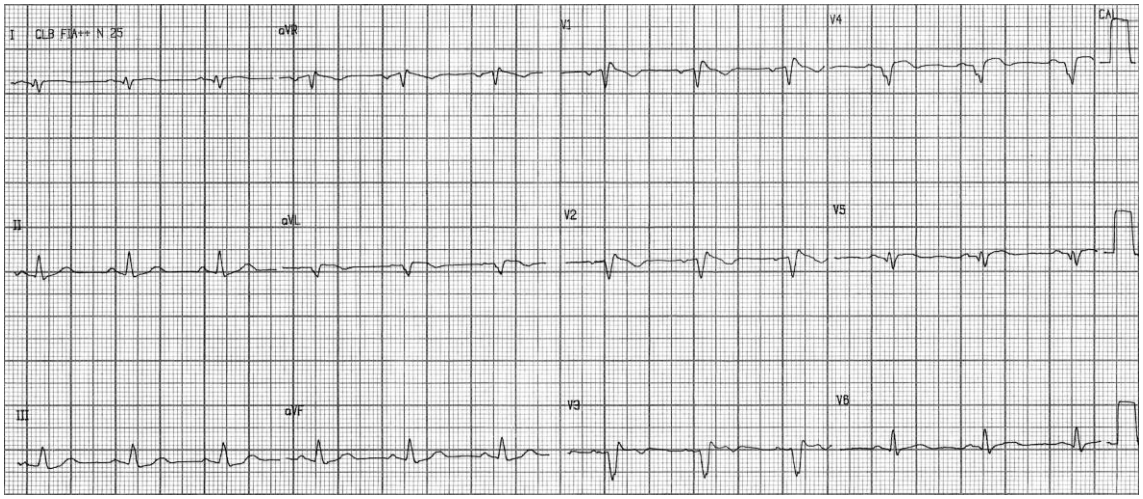


Courtesy Dr Raimundo Barbosa-Barros.

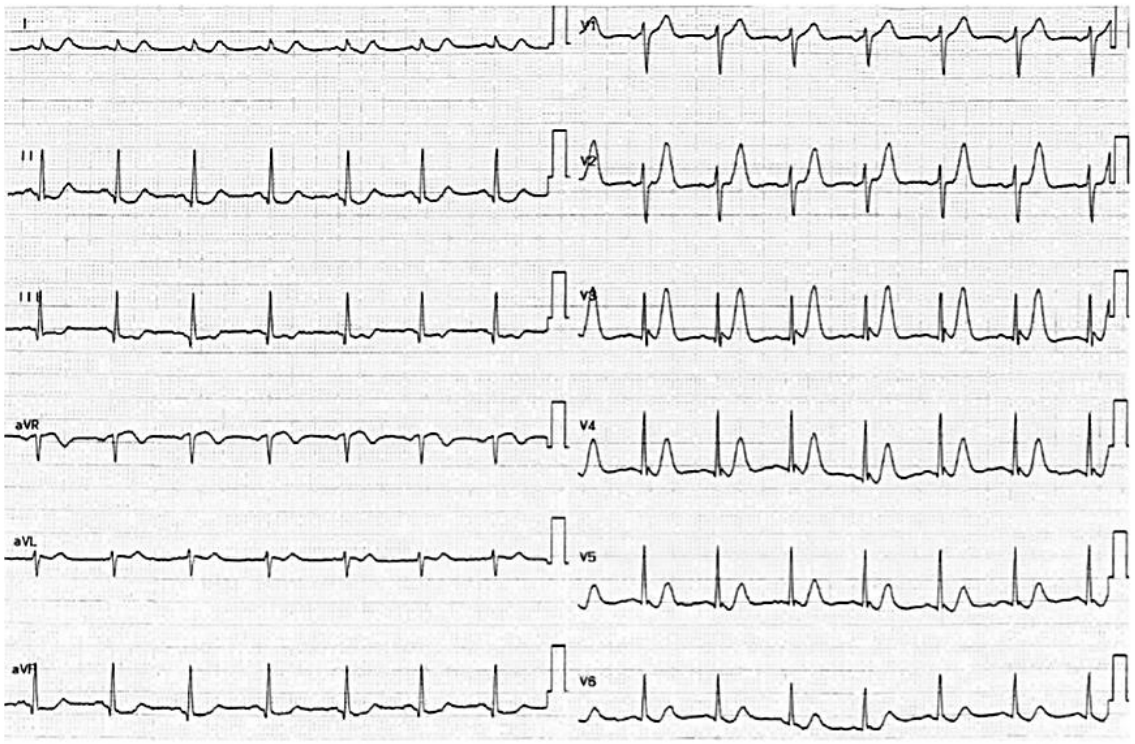




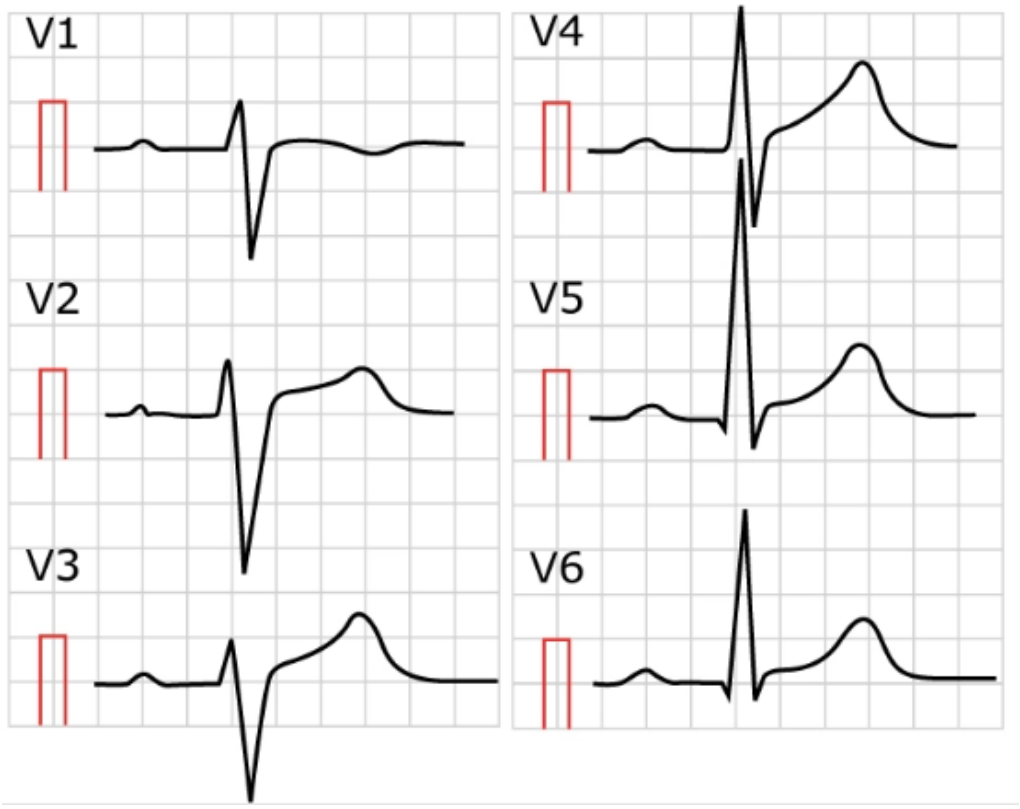
Typical Brugada type 1 ECG pattern



Brugada phenocopy secondary critical LAD obstruction: Type 1 AMI



ECG shows hyperacute T waves in leads V1 to V4 and 0.5-mm ST-segment elevation in aVR. Initial echocardiographic images show hypokinetic anterior and anteroseptal walls and anterior and septal apical segments consistent with acute occlusion of the LAD coronary artery. Based on echocardiographic findings, the patient was taken immediately to PCI. Angiography confirmed a proximal LAD critical stenosis, and the patient underwent angioplasty and a drug-eluting stent placement. After the procedure, the patient was taken to the ICU, where he had an uneventful recovery and was discharged home 2 days after.



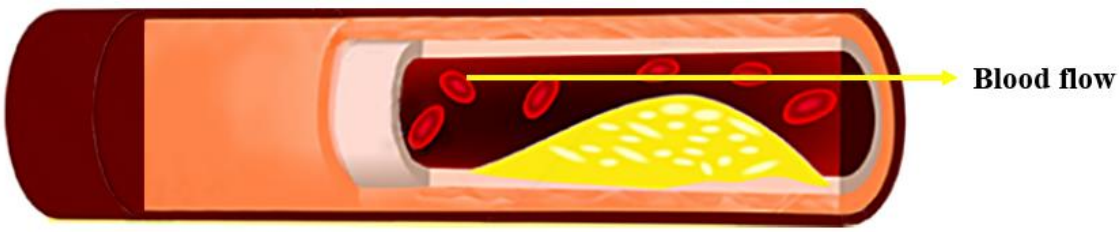
Male/female pattern also called "Normal ST segment elevation"

Male/female pattern is by far the most common type of ST segment elevation, It is completely benign and no study to date has associated this pattern with any increased risk of cardiovascular or all cause mortality. The prevalence has been examined thoroughly in males(particularity in US arm), which is why it is usually referred to as male pattern,, but it is also common in females. Nevertheless, studies show that among males aged 16 to 58 years, roughly 90% display ≥1mm ST segment elevation ≥1mm chest leads. The prevalence declines to 30% among males aged 70 years or above. In females, on the other hand, the prevalence is steady throughout the age span, being approximately 20%. It is blatant, but far too common mistake(even among cardiologist and electrophysiologists) to confuse male/female pattern with early repolarization.(Surawicz B1, Parikh SR. Prevalence of male and female patterns of early ventricular repolarization in the normal ECG of males and females from childhood to old age. J Am Coll Cardiol. 2002 Nov 20;40(10):1870-6. DOI: 10.1016/s0735-1097(02)02492-0)

Current classification of myocardial infarction

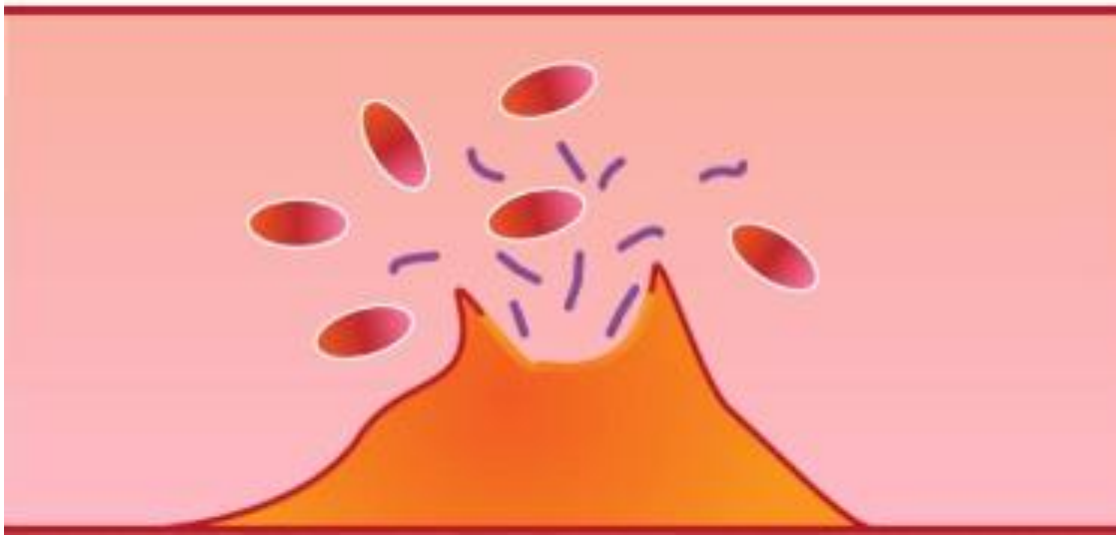
1. *Type 1: Spontaneous myocardial infarction* - Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one oor more of the coronary arteries leading to decrased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD. *is acute myocardial injury related to acute atherothrombotic coronary artery disease. It is usually precipitated by atherosclerotic plaque disruption that reduces blood supply to the myocardium. (Sandoval Y, et al.2017*.) Criteria for type 1 MI (Thygesen K, Eur Heart J. 2019.) Detection of a rise and/or fall in cardiac troponin(cTn) values with at least one value above the 99th percentile upper reference limit(URL) and with at least one of the following:

- 1*Symptoms of acute myocardial ischemia;*
- *New ischemic ECG changes;*
- *Development of pathological Q waves;*
- *Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology and*
- *Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy MI, myocardial infarction.(*a Post-mortem demonstration of an atherothromboses in the artery supplying the infarcted myocardium, or a macroscopically large circumscribed area of necrosis with or without intramyocardial hemorrhage, meets the type 1 MI criteria regardless of cTn values.*).* In the coronary artery with atherosclerosis plaque the core of the atherosclerotic plaque houses inflammatory cells and lipids which drive a chronic inflammation within the artery wall

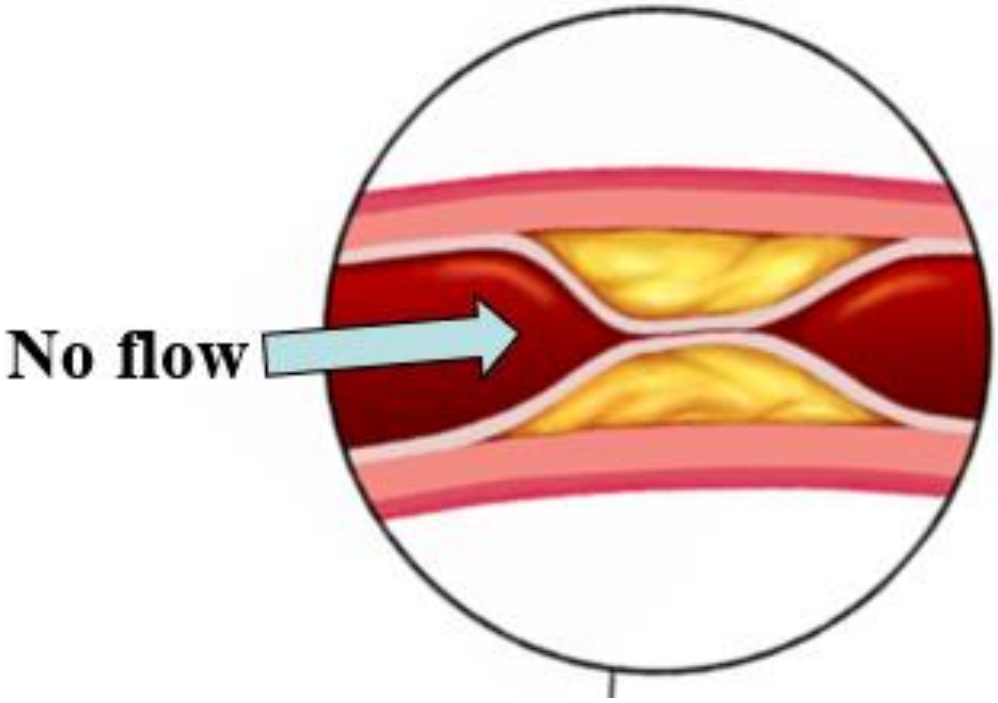


The atherosclerotic plaque is vulnerable(unstable). Rupture or erosion damage its cap, which exposes highly thrombogenic materials, Such materials activate platelets and

coagulation factors. Rupture is the disruption of a fibrous cap over a lipid core; erosion is the superficial disruption of a fibromuscular plaque without a core.

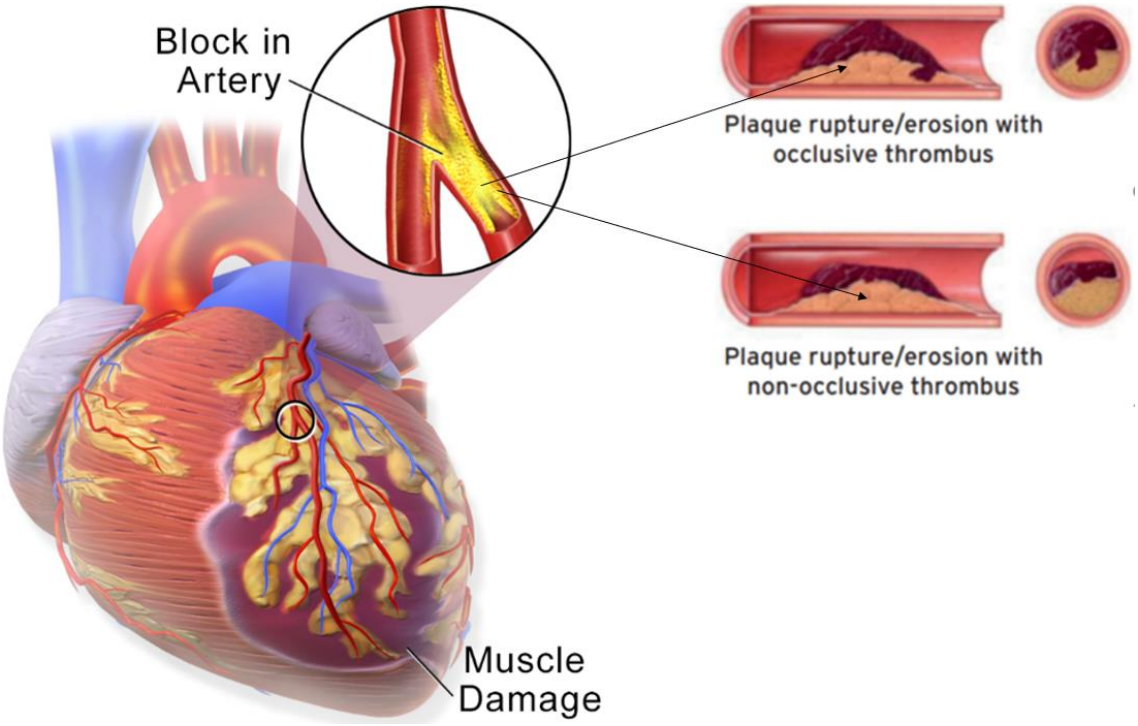


Activation of platelets and coagulation factors results in formation of a thrombus (atherothrombosis) Myocardium supplied by this artery becomes ischemic. Necrosis starts is flow is not restored within 30 minutes



Type 1: Spontaneous myocardial infarction

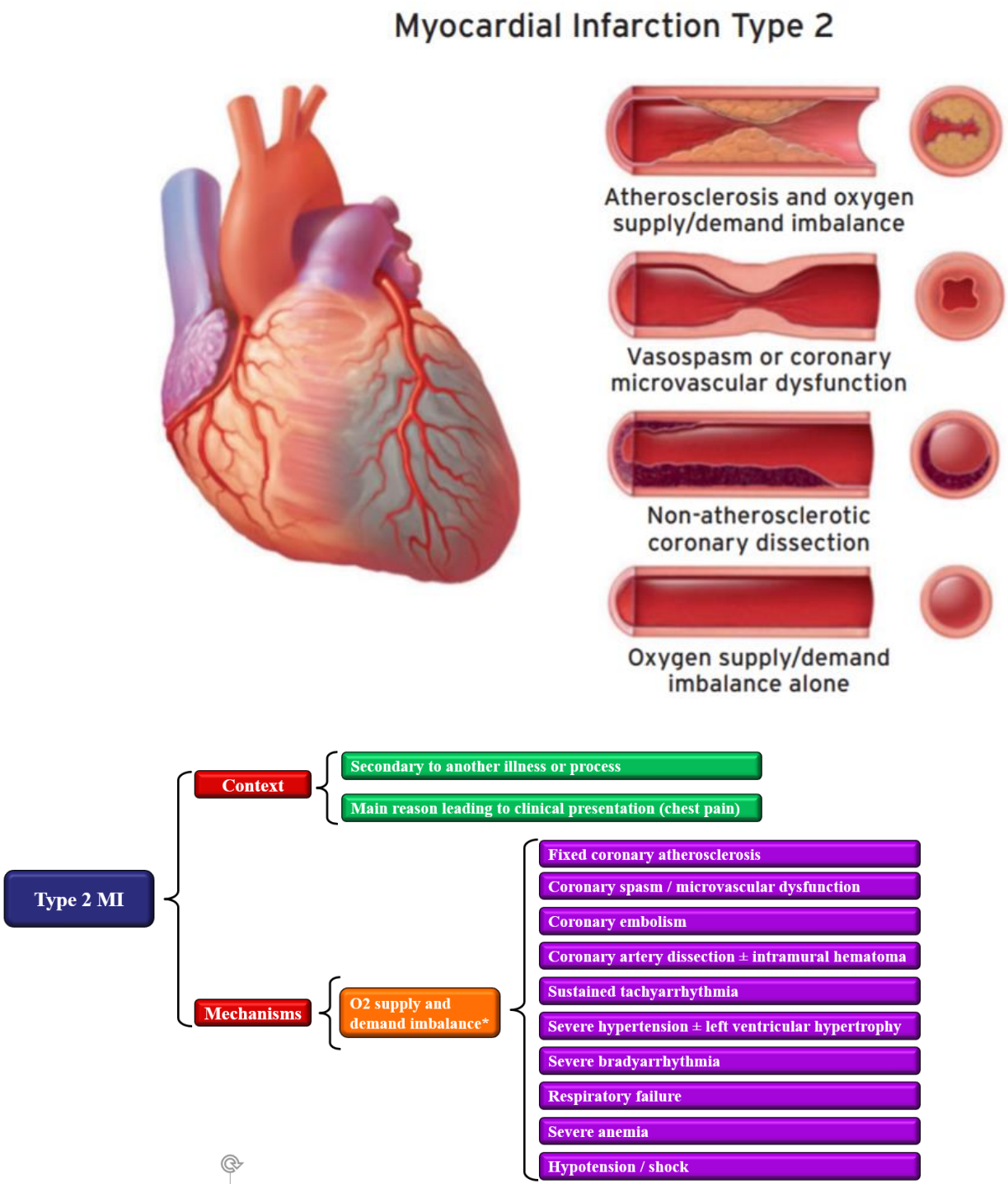
A type I myocardial infarction occurs when an atherosclerotic plaque slowly builds up in the inner lining of a coronary artery and then suddenly ruptures, causing catastrophic thrombus formation, totally occluding the artery and preventing blood flow downstream.



2. Type 2: Myocardial infarction (T2MI) secondary to an ischemic imbalance*:* In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythymias, anemia, respiratory failure, hypotension, and hypertension with o without LVH. Acute myocardial injury is related to an imbalance between myocardial oxygen supply and demand secondary to stressors unrelated to acute coronary atherothrombosis. (Myocardial infarction type 3 is related to patients who suffer cardiac death, with symptoms suggestive of acute myocardial ischaemia accompanied by new ischaemic ECG changes and die before biomarker values could be obtained) Myocardial infarction type 3 is related to patients who suffer cardiac death, with symptoms suggestive of acute myocardial ischemia accompanied by new ischemic ECG changes and die before biomarker values could be obtained*). Myocardial infarction type 2* (T2MI)*: is acute myocardial injury related to an imbalance between*

myocardial oxygen supply and demand secondary to stressors unrelated to acute coronary atherothrombosis. The development and implementation of sensitive and high-sensitivity cardiac troponin assays has not only expedited the early ruling in and ruling out of acute myocardial infarction, but has also contributed to the identification of patients at risk for myocardial injury with necrosis, as confirmed by the presence of cardiac troponin concentrations above the 99th percentile. Myocardial injury with necrosis may occur either in the presence of overt ischemia from MI, or in the absence of overt ischemia from myocardial injury accompanying other conditions. T2MI has been a focus of attention; conceptually T2MI occurs in a clinical Elevated troponin level findings among patients presenting with suspected ACS or another intercurrent illness undeniably identifies patients at increased risk of mortality. Whilst enhancing our capacity to discriminate risk, the use of high-sensitivity troponin assays frequently identifies patients with myocardial injury (i.e. troponin rise without acute signs of myocardial ischemia) or type 2 myocardial infarction (T2MI; O2 supply-demand imbalance). This leads to the clinically challenging task of distinguishing type 1 MI (T1MI); coronary plaque rupture). from myocardial injury and T2MI in the context of concurrent acute illness. Diagnostic discernment in this context is crucial because MI classification has implications for further investigation and care. Early invasive management is of well-established benefit among patients with T1MI. However, the appropriateness of this investigation in the heterogeneous context of T2MI, where there is high competing mortality Although coronary angiography in T2MI is advocated by some, there is insufficient evidence in existing literature to support this opinion as highlighted by current national guidelines. This prospective, pragmatic, multicenter, randomized trial among patients with suspected supply demand ischemia leading to troponin elevation (n=1,800; T2MI [1,500], chronic myocardial injury [300]) compares the impact of invasive angiography (or computed tomography angiography as per local preference) within 5 days of randomization versus conservative management (with or without functional testing at clinician discretion) on all-cause mortality by 2 years. Randomized treatment allocation setting with overt myocardial ischemia where a condition other than an acute atherothrombotic event is the major contributor to a significant imbalance between myocardial O2 supply and/or

demand. Much debate has surrounded T2MI and its interrelationship with myocardial injury. T2MI and myocardial injury are frequently encountered in clinical practice and are associated with poor outcomes in both the short term and long term. Diagnostic strategies to facilitate the clinical distinction between ischemic myocardial injury with or without an acute atheroma-thrombotic event vs non-ischemic-mediated myocardial injury conditions are urgently needed, as well as evidence based therapies tailored toward improving outcomes for patients with T2MI. .(Sandoval Y, et al. 2017). will be stratified by baseline estimated risk of mortality using the Acute Physiology, Age, and Chronic Health Evaluation APACHE: (Acute Physiology, Age, Chronic Health Evaluation) III risk score.(Knaus WA1, et al. 1991.) Cost-effectiveness will be evaluated by follow-up on clinical events, quality of life, and resource utilization over 24 months. Ascertaining the most appropriate first-line investigative strategy for these commonly encountered high-risk T2MI patients in a randomized comparative study will be pivotal in informing evidence-based guidelines that lead torisk, remains polemic. better patient andhealth care outcomes.(Lambrakis K 2019), Type 2 MI: Settings with oxygen demand and supply imbalance unrelated to acute coronary athero-thrombosis; new next two figures Figures 4 and 5. • Type 2 MI: Relevance of presence or absence of CAD to prognosis and therapy. • Differentiation of myocardial injury from type 2 myocardial infarction; third Figure.



*Ischemic thresholds vary substantially in relation to the magnitude of the stressor and the extent of underlying cardiac disease. Framework for type 2 myocardial infarction considering the clinical context and pathophysiological mechanisms attributable to acute myocardial ischemia. The illustration above is modified from Januzzi and Sandoval.(Januzzi JL,et al. 2017..)

3. *Type 3 Myocardial infarction resulting in death when biomarker values are unavailable*- Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be ob*tained, before cardiac biomarker could rise, oor in rare cases cardiac biomarkers were not collected. is related to patients who suffer cardiac death, with symptoms suggestive of acute myocardial ischemia accompanied by new ischemic ECG changes and die before biomarker values could be obtained.* Type 3 myocardial infarction: Clarify why type 3 myocardial infarction is a useful category to differentiate from sudden cardiac death. Criteria for type 3 MI Patients who suffer cardiac death, with symptoms suggestive of myocardial ischemia accompanied by presumed new ischemic ECG changes or ventricular fibrillation, but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination.
4. *Type 4a Myocardial infarction related to PCI0* MI associated with wit PCI is arbitrary defined by elevation of cTn values .5x99th percentile URL in patients with normal baseline values($\leq 99^{th}$ percentile URL) or a rise of cTc values >20% if the baseline values are elevated and are stable or falling. In addition, either symptoms suggestive of myocardial ischemia, or new ischemic ECG changes or new LBBB or angiographic loss of patency of a major coronary artery or a side branch or persistent slow-or no- flow or embolization, or imaging demonstration of new loss of viable myocardium o renew regional wall motion abnormality are required. *Type 4a denotes PCI-related increases of cTn values >5 times the 99th percentile URL from a normal or if elevated, stable pre-procedural baseline. New myocardial ischaemia evidenced by ECG or imaging, or complications leading to reduced coronary blood flow are required*. Yang et al. studied the Type 4a MI in a cohort of patients undergoing PCI for stable coronary disease or non ST-elevation ACS with stable or falling cardiac troponin levels. The authors studied prospectively in routine practice. The study included 516 patients undergoing eligible PCI at a single institution. Data were extracted from the National Cardiovascular Data Registry, review of electronic medical records, andtelephone interviews. Clinical outcomes assessed at one year included all-cause mortality, recurrent MI, or any repeat coronary revascularization. Based on the Third Universal Definition of MI, 53 (10.3%)

patients met criteria for Type 4a MI and 116 (22.5%) had myocardial injury. The Type 4a MI and myocardial injury groups each had significantly higher numbers of stents, longer stent lengths, and more use of rotational atherectomy than the control group. Type 4a MI was not associated with one-year mortality. The composite endpoint of death or recurrent MI at one year was similar between the Type 4a MI and myocardial injury groups, which were both higher compared with the control group. Type 4a MI and myocardial injury were frequent, and associated with more complicated index PCI and more frequent death or recurrent MI at one year as compared with the control group .(Yang X, et al. 2017.)

Type 4b Myocardial infarction related to stent thrombosis - Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL. It is acute myocardial ischemic injury related to stent thrombosis and MI type 4c is acute myocardial ischemic injury associated with restenosis. Myocardial infarction type 4b is acute myocardial ischemic injury related to stent thrombosis and MI type 4c is acute myocardial ischemic injury associated with restenosis.(Thygesen K, et al 2018 Nov.)

Myocardial infarction type 4c MI restenosis that both meet type 1 MI criteria Occasionally MI occurs and—at angiography, in-stent restenosis, or restenosis following balloon angioplasty in the infarct territory—is the only angiographic explanation since no other culprit lesion or thrombus can be identified. This PCI-related MI type is designated as type 4c MI, defined as focal or diffuse restenosis, or a complex lesion associated with a rise and/or fall of cTn values above the 99th percentile URL applying, the same criteria utilized for type 1 MI. (Thygesen K 2018 Nov). The level of inhibition of platelet aggregation immediately before PCI) is known to be related to early periprocedural outcomes. Ticagrelor is a reversible P2Y12 inhibitor that provides faster and more effective platelet inhibition compared toclopidogrel. Yang IH et al. compare the antiplatelet effect on residual thrombus between early vs. delayed administration of ticagrelor following PCI in patients presenting with (NSTE-

ACS). Early initiation of ticagrelor at the time of presentation in patients with NSTE-ACS appears to be safe with a greater level of platelet inhibition. However, post-PCI residual thrombus burden did not differ between early and delayed administration of ticagrelor.(Yang IH1, et al. 2019.)

5. *Type 5 MI related to CABG It is arbitrarily defined by elevation of cardiac biomarker values (cTn values >10 times 99th percentile URL) in patients with normal baseline cTn values(≤ 99th percentile URL). In addition, either new pathological Q waves or new LBBB or angiographic documented new graft or new native coronary artery occlusion or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.* Numerous factors can lead to procedural myocardial injury during a CABG. Many of them are related to the details of the cardiac preservation, the extent of the direct traumatic injury to the myocardium, as well as any potential ischemic injury. For that reason, increases in cTn values should be expected after all CABG,(Pegg TJ, et al.2011) (Jørgensen PH, et al. 2014..) which need to be taken into account when comparing the extent of procedural myocardial injury after cardiac surgery with that associated with less invasive approaches. Depending on whether it is off-pump or on-pump surgery, procedural myocardial injury is observed among 32% to 44% of CABG patients when quantified by LGE-CMR.(Selvanayagam JB, et al. 2004.) (Rahimi K, et al. 2009.). The area under the curve (AUC) and routine cTn sampling has demonstrated an excellent linear relationship with the mass of the new injury as defined by LGE-CMR. AUC for CK-MB is also good, although clearly inferior to cTnI. However, these relationships vary depending on the nature of the procedure, the nature of the cardioplegia, and the specific assay used to measure cTn. Very high cTn values are most often associated with coronary artery–related events. .(Selvanayagam JB, et al. 2004.), (Rahimi K, et al. 2009.). (Pegg TJ, et al.2011) Thus, although that cTn appear robust for the detection of procedural myocardial injury and also, in the presence of new myocardial ischemia, for the detection of type 5 MI, a specific cut-off value for all procedures and all cTn assays is difficult to define. However, in order to ensure consistency with the analogous standards of the preceding definition of type 5 MI and because of the lack of new scientific evidence that identifies superior criteria for defining this MI subtype, it is suggested that a cTn value

>10 times the 99th percentile URL is applied as the cut-off point during the first 48 hours following CABG, occurring. Types 4–5 MI: Emphasis on distinction between procedure-related myocardial injury and procedure-related MI

5.

Prizmental

Synonyms: Prinzmetal's syndrome; Prinzmetal's variant angina; Prinzmetal’s variant of angina pectoris; Prinzmetal-Massumi syndrome (The three original papers are: Prinzmetal M, MassumiRA:*The anterior chest wall syndrome-chest pain resembling pain or cardiac origin. Journal of the American Medical Association, Chicago, 1955, 159: 177-184*.)(Prinzmetal M, Kennamer R,. Merliss, T. Wada, N. Bor: *Angina pectoris. 1. A variant form of angina pectoris. (Preliminary report).* American Journal of Medicine, New York, 1959, 27: 375-388). (M. R. Prinzmetal, A. Ekmek, R. Keimamer, et al: *Variant form of angina pectoris.* Journal of the American Medical Association, Chicago, 1960, 174: 1794-1800.), Angina inversa, anterior chest wall syndrome, anterior thoracic wall syndrome, coronary syndrome, acute coronary insufficiency, mild myocardial infarction, spasm angina pectoris, variant angina.

Definition: "A clinical syndrome characterized by the development of CHEST PAIN at rest with concomitant transient ST segment elevation in the electrocardiogram, but with preserved exercise capacity."

Coronary Artery Vasospasm: "Spasm of the large- or medium-sized coronary arteries."

Description:

An unusual and uncommon form of angina, often with long-lasting attacks, in which pain is experienced at rest and sometimes while in bed rather than during activity. It is caused by total occlusion of proximal coronary arteries due to spasm. Most commonly seen during the night and accompanied by severe disturbances of the heart rhythm. The electrocardiogram taken during an attack will indicate S-T segment elevation rather than depression. The condition occurs without preceding changes in heart rate and blood pressure. Most patients have underlying coronary artery disease, but some have normal arteries. A prolonged attack may lead to ventricular arrhythmia, myocardial infarction, heart block, and sudden death (SCD).

Background: Angina pectoris is the result of myocardial ischemia caused by an imbalance between myocardial blood supply and oxygen demand. Angina is a common presenting symptom (typically, chest pain) among patients with coronary artery disease. A comprehensive approach to diagnosis and to medical management of angina pectoris is an integral part of the daily responsibilities of physicians.

Pathophysiology: Myocardial ischemia develops when coronary blood flow becomes inadequate to meet myocardial oxygen demand. This causes myocardial cells to switch from aerobic to anaerobic metabolism, with a progressive impairment of metabolic, mechanical, and electrical functions. Angina pectoris is the most common clinical manifestation of myocardial ischemia. It is caused by chemical and mechanical stimulation of sensory afferent nerve endings in the coronary vessels and myocardium. These nerve fibers extend from the first to fourth thoracic spinal nerves, ascending via the spinal cord to the thalamus, and from there to the cerebral cortex.

Recent studies have shown that adenosine may be the main chemical mediator of anginal pain. During ischemia, ATP is degraded to adenosine, which, after diffusion to the extracellular space, causes arteriolar dilation and anginal pain. Adenosine induces angina mainly by stimulating the A1 receptors in cardiac afferent nerve endings.

Heart rate, myocardial inotropic state, and myocardial wall tension are the major determinants of myocardial metabolic activity and myocardial oxygen demand. Increases in the heart rate and myocardial contractile state result in increased myocardial oxygen demand. Increases in both afterload (ie, aortic pressure) and preload

(ie, ventricular end-diastolic volume) result in a proportional elevation of myocardial wall tension and, therefore, increased myocardial oxygen demand. Oxygen supply to any organ system is determined by blood flow and oxygen extraction. Because the resting coronary venous oxygen saturation is already at a relatively low level (approximately 30%), the myocardium has a limited ability to increase its oxygen extraction during episodes of increased demand. Thus, an increase in myocardial oxygen demand (eg, during exercise) must be met by a proportional increase in coronary blood flow.

The ability of the coronary arteries to increase blood flow in response to increased cardiac metabolic demand is referred to as coronary flow reserve (CFR). In healthy people, the maximal coronary blood flow after full dilation of the coronary arteries is roughly 4-6 times the resting coronary blood flow. CFR depends on at least 3 factors: large and small coronary artery resistance, extravascular (ie, myocardial and interstitial) resistance, and blood composition.

Myocardial ischemia can result from:

(1) A reduction of coronary blood flow caused by fixed and/or dynamic epicardial coronary artery (ie, conductive vessel) stenosis;

(2) Abnormal constriction or deficient relaxation of coronary microcirculation (ie, resistance vessels) OR;

(3) Reduced oxygen-carrying capacity of the blood.

Atherosclerosis is the most common cause of epicardial coronary artery stenosis and, hence, angina pectoris. Patients with a fixed coronary atherosclerotic lesion of at least 50% show myocardial ischemia during increased myocardial metabolic demand as the result of a significant reduction in CFR. These patients are not able to increase their coronary blood flow during stress to match the increased myocardial metabolic demand, thus they experience angina. Fixed atherosclerotic lesions of at least 90% almost completely abolish the flow reserve; patients with these lesions may experience angina at rest.

Coronary spasm can also reduce CFR significantly by causing dynamic stenosis of coronary arteries. Prinzmetal angina is defined as resting angina associated with ST-segment elevation caused by focal coronary artery spasm. Although most patients with Prinzmetal angina have underlying fixed coronary lesions, some have angiographically normal coronary arteries. Several mechanisms have been proposed for Prinzmetal angina: focal deficiency of nitric oxide production, hyperinsulinemia, low intracellular magnesium levels, smoking cigarettes, and using cocaine.

Approximately 30% of patients with chest pain referred for cardiac catheterization have normal or minimal atherosclerosis of coronary arteries. A subset of these patients demonstrates reduced CFR that is believed to be caused by functional and structural alterations of small coronary arteries and arterioles (ie, resistance vessels). Under normal conditions, resistance vessels are responsible for as much as 95% of coronary artery resistance, with the remaining 5% being from epicardial coronary arteries (ie, conductive vessels). The former is not visualized during regular coronary catheterization. Angina due to dysfunction of small coronary arteries and arterioles is called microvascular angina. Several diseases, such as diabetes mellitus, hypertension, and systemic collagen vascular diseases (eg, systemic lupus erythematosus, polyarteritis nodosa), are believed to cause microvascular abnormalities with subsequent reduction in CFR.

The syndrome that includes angina pectoris, ischemialike ST-segment changes and/or myocardial perfusion defects during stress testing, and angiographically normal coronary arteries is referred to as syndrome X. Most patients with this syndrome are postmenopausal women, and they usually have an excellent prognosis. Syndrome X is believed to be caused by microvascular angina. Multiple mechanisms may be responsible for this syndrome, including (1) impaired endothelial dysfunction, (2) increased release of local vasoconstrictors, (3) fibrosis and medial hypertrophy of the microcirculation, (4) abnormal cardiac adrenergic nerve function, and/or (5) estrogen deficiency.

A number of extravascular forces produced by contraction of adjacent myocardium and intraventricular pressures can influence coronary microcirculation resistance and thus reduce CFR. Extravascular compressive forces are highest in the subendocardium and decrease toward the subepicardium. Left ventricular (LV) hypertrophy together with a

higher myocardial oxygen demand (eg, during tachycardia) cause greater susceptibility to ischemia in subendocardial layers.

Myocardial ischemia can also be the result of factors affecting blood composition, such as reduced oxygen-carrying capacity of blood, as is observed with severe anemia (hemoglobin, <8 g/dL), or elevated levels of carboxyhemoglobin. The latter may be the result of inhalation of carbon monoxide in a closed area or of long-term smoking.

Recently, ambulatory ECG monitoring has shown that silent ischemia is a common phenomenon among patients with established coronary artery disease. In one study, as many as 75% of episodes of ischemia (defined as transient ST depression of >1 mm persisting for at least 1 min) occurring in patients with stable angina were clinically silent. Silent ischemia occurs most frequently in early morning hours and may result in transient myocardial contractile dysfunction (ie, stunning). The exact mechanism(s) for silent ischemia is not known. However, autonomic dysfunction (especially in patients with diabetes), a higher pain threshold in some individuals, and the production of excessive quantities of endorphins are among the more popular hypotheses.

Frequency:

In the US: Approximately 6.3 million Americans are estimated to experience angina. An estimated 350,000 new cases of angina occur every year. Each year, 1.1 million new and recurrent cases of an acute coronary event occur in this country, of which more than 40% are fatal. Roughly, more than 12 million Americans had a history of myocardial infarction (MI) and/or angina pectoris in the year 2000.

Mortality/Morbidity: Coronary artery disease is the single most common cause of death in the United States, accounting for almost one death per minute. More than half of those who die suddenly from coronary artery disease have no previous symptoms.

Race: The rate of angina pectoris in women older than 20 years ranges from 3.9% in non-Hispanic white women to 6.2% in non-Hispanic black women and 5.5% in Mexican American women. The rates of angina pectoris for men in the same ethnic groups are 2.6%, 3.1%, and 4.1%, respectively. Among American Indians aged 65-74 years, the rates (per 1000 persons) of new and recurrent heart attacks are 25.1% for men and 9.1% for women.

Sex: Angina pectoris is more often the presenting symptom of coronary artery disease in women than in men, with a female-to-male ratio of 1.7:1. It has a prevalence of 3.9 million in women and 2.3 million in men. The frequency of atypical presentations is also more common among women compared with men. Women have a slightly higher rate of mortality from coronary artery disease compared with men, in part because of an older age at presentation and a frequent lack of classic anginal symptoms. The estimated age-adjusted prevalence of angina is greater in women than in men.

Age: The prevalence of angina pectoris increases with age. Age is a strong independent risk factor for mortality.

History: Most patients with angina pectoris report of retrosternal chest discomfort rather than frank pain. The former is usually described as a pressure, heaviness, squeezing, burning, or choking sensation. Anginal pain may be localized primarily in the epigastrium, back, neck, jaw, or shoulders. Typical locations for radiation of pain are arms, shoulders, and neck. Typically, angina is precipitated by exertion, eating, exposure to cold, or emotional stress. It lasts for approximately 1-5 minutes and is relieved by rest or nitroglycerin. Chest pain lasting only a few seconds is not usually angina pectoris. The intensity of angina does not change with respiration, cough, or change in position. Pain above the mandible and below the epigastrium is rarely anginal in nature.

1) Ask patients about the frequency of angina, severity of pain, and number of nitroglycerin pills used during angina episodes;
2) Angina decubitus is a variant of angina pectoris that occurs at night while the patient is recumbent. Some have suggested that it is induced by an increase in myocardial oxygen demand caused by expansion of the blood volume with increased venous return during recumbency.
3) The Canadian Cardiovascular Society grading scale is used for classification of angina severity, as follows:

    - Class I - Angina only during strenuous or prolonged physical activity

    - Class II - Slight limitation, with angina only during vigorous physical activity

- Class III - Symptoms with everyday living activities, ie, moderate limitation

- Class IV - Inability to perform any activity without angina or angina at rest, ie, severe limitation

The New York Heart Association classification is also used to quantify the functional limitation imposed by patients' symptoms, as follows:

- Class I - No limitation of physical activity (Ordinary physical activity does not cause symptoms.)

- Class II - Slight limitation of physical activity (Ordinary physical activity does cause symptoms.)

- Class III - Moderate limitation of activity (Patient is comfortable at rest, but less than ordinary activities cause symptoms.)

- Class IV - Unable to perform any physical activity without discomfort, therefore severe limitation (Patient may be symptomatic even at rest.)

Unstable angina is defined as new-onset angina (ie, within 2 mo of initial presentation) of at least class III severity, significant recent increase in frequency and severity of angina, or angina at rest.

Physical:

For most patients with stable angina, physical examination findings are normal. Diagnosing secondary causes of angina, such as aortic stenosis, is important. A positive Levine sign (characterized by the patient's fist clenched over the sternum when describing the discomfort) is suggestive of angina pectoris.Look for physical signs of abnormal lipid metabolism (eg, xanthelasma, xanthoma) or of diffuse atherosclerosis (eg, absence or diminished peripheral pulses, increased light reflexes or arteriovenous nicking upon ophthalmic examination, carotid bruit).Examination of patients during the angina attack may be more helpful. Useful physical findings include third and/or fourth heart sounds due to LV systolic and/or diastolic dysfunction and mitral regurgitation

secondary to papillary muscle dysfunction.Pain produced by chest wall pressure is usually of chest wall origin.

Causes:

Decrease in myocardial blood supply due to increased coronary resistance in large and small coronary arteries

- Significant coronary atherosclerotic lesion in the large epicardial coronary arteries (ie, conductive vessels) with at least a 50% reduction in arterial diameter
- Coronary spasm (ie, Prinzmetal angina)
- Abnormal constriction or deficient endothelial-dependent relaxation of resistant vessels associated with diffuse vascular disease (ie, microvascular angina)
- Syndrome X
- Systemic inflammatory or collagen vascular disease, such as scleroderma, systemic lupus erythematous, Kawasaki disease, polyarteritis nodosa, and Takayasu arteritis

Increased extravascular forces, such as severe LV hypertrophy caused by hypertension, aortic stenosis, or hypertrophic cardiomyopathy, or increased LV diastolic pressures

Reduction in the oxygen-carrying capacity of blood, such as elevated carboxyhemoglobin or severe anemia (hemoglobin, <8 g/dL)

Congenital anomalies of the origin and/or course of the major epicardial coronary arteries

Structural abnormalities of the coronary arteries

- Congenital coronary artery aneurysm or fistula
- Coronary artery ectasia
- Coronary artery fibrosis after chest radiation

- Coronary intimal fibrosis following cardiac transplantation

Risk factors

- Major risk factors for atherosclerosis: These include a family history of premature coronary artery disease, cigarette smoking, diabetes mellitus, hypercholesterolemia, or systemic hypertension.

- Other risk factors: These include LV hypertrophy, obesity, and elevated serum levels of homocysteine, lipoprotein (a), plasminogen activator inhibitor, fibrinogen, serum triglycerides, or low high-density lipoprotein (HDL).
- Metabolic syndrome: This has recently been characterized by the presence of hyperinsulinemia (fasting glucose level, >110 mg/dL), abdominal obesity (waist circumference, >40 in for men or >35 in for women), decreased HDL cholesterol levels (<40 mg/dL for men or <50 mg/dL for women), hypertriglyceridemia (>150 mg/dL), and hypertension (>130/85 mm Hg). Based on data from the 2000 US census, an estimated 47 million Americans have the metabolic syndrome. Patients with the metabolic syndrome have a 3-fold increased risk for coronary atherosclerosis and stroke compared with those without this syndrome.

Precipitating factors: These include factors such as severe anemia, fever, tachyarrhythmias, catecholamines, emotional stress, and hyperthyroidism, which increase myocardial oxygen demand.

Preventive factors: Factors associated with reduced risk of atherosclerosis are a high serum HDL cholesterol level, physical activity, estrogen, and moderate alcohol intake (1-2 drinks/d).

Differential diagnosis possibilities;

1) Anemia;

2) Anxiety Disorders;
3) Aortic dissection;
4) Biliary colic;
5) Hypertrophic Cardiomyopathy;
6) Cholecystitis;
7) Coronary Artery Abnomalies;
8) Coronary artery atherosclerosis;
9) Coronary artery vasospasm;
10) Diabetes Mellitus type 1;
11) Diabetes Mellitus type 2;
12) Gastric Ulcer;
13) Acute Gastritis;
14) Gastroespphageal Reflux Disease;
15) Hiatal Hernia;
16) Familial Hypercholeserolemia;
17) Polugenic Hypercholesterolemia;
18) Hypertension;
19) Hyperthyroidism;
20) Kawasaky Disease;
21) Mitral Regurgitation;
22) Mitral Valve Prolapse;
23) Panic Disorder;
24) Pericarditis Acute;
25) Pleurodynia;
26) Polyarteritis Nodosa;
27) Pott Disease ;
28) Pulmonary Embolism;
29) Primary Pulmonary Hypertension;
30) Pulmonary Hypertension, Secondary
31) Scleroderma;
32) Systemic Lupus Erythematousous;
33) Takayasy Arteritis;
34) Cocaine Toxicity;
35) Varicella-Zoster Virus;

36) Brugada syndrome

Other Problems to be considered:

Esophageal spasm;

Esophageal rupture

Costochondritis;

Herpes zoster;

Pneumonia with pleural involvement

DIFFERENTIAL CHARACTERISTICS BETWEEN BRUGADA SYNDROME AND VASOSPASTIC ANGINA

	BRUGADA SYNDROME	VASOSPASTIC ANGINA
Precordial pain:	No.	Yes.
Tendency to VT/VF:	High.	High.
Structural heart disease:	Absent.	Could exist.
Response to nitrates and nitroglycerine:	Null.	Improves or suppresses clinical/electrocardiographic manifestations.
Permanence of ST segment elevation:	Persistent (or fluctuating) and without pain.	Brief, transitory and accompanied by pain.
Cause:	Genetic alteration of Na^+ channel.	Possible alteration in production nitrous oxide in vascular wall.

Presence of image in mirror or reciprocal in ECG:	Could be present.	Present.
Topography of ST elevation:	Right precordial leads of V1 to V3; it could rarely be observed in inferior wall and triggered or increased by antiarrhythmic agents of the IC^1 and IA classes.	Variable. It could alternate between precordial leads and inferior ones. It could be triggered by hyperventilation.
Dromotropic disorders:	AV block of the first degree by extension of H-V in 50% of casesand in carriers of the mutation.	It could happen in a transitory way until a high degree of AV block during the episode; it is associated with a higher risk of arrhythmia and SCD.
Persistent T wave inversion:	Negative T wave in precordial leads from V_1 to V_3, characteristic of type 1.	Inverted and deep T waves from V_1 to V_4 associated to anterior hypokinesia, suggesting myocardial "stunning" that indicates critical lesion of the anterior descending artery: "LAD-T wave pattern".
Presence of transitory Q wave:	No.	It could happen.
Effort test:	It could normalized the variation during effort.	Variable response.
Myocardial scintigraphy with thallium 201:	Normal.	Transitory transmural hypo-uptake.

Response to test of maleate of ergonovine in doses of 0.05 to 0.40 mg (stimulant of alpha adrenergic and seratoninergic receptor)	There could be a mild diffuse reduction of caliber without spasm when doses are equal to or less than 0.40 mg are used.	Intense coronary spasm accompanied by pain and ST elevation. Possible cardiac block, asystole and VT.
Response to hyperventilation:	It does not modify.	Severe spasm and reproduction of clinical electrocardiographic manifestations.
Response to intracoronary acetylcholine, each dose given in a time above one minute, in doses of10, 25, 50 and 100μg doses separated by five minute intervals:	It could worse the ST elevation with paradoxical dilation of coronary vessels.	Severe spasm and reproduction of clinical electrocardiographic manifestations.
Response to magnesium sulfate:	Not mentioned.	Suppresses attacks induced by hyperventilation and exercise.
Treatment:	Automatic implantable cardioverter defibrillator in association with amiodarone, a drug that contributes to diminish the number of shocks. Isoproterenol indicated in elctric storm associated	Calcium antagonists, such as nifedipine, diltiazem, verapamil, and felodipine associated to nitrates. Benefit with prazosin is mentioned.

	with general anesthesia and cardiopulmonary “bypass” or Amiodarone?	

1) Nakamura W, Segawa K, Ito H, et al. Class IC antiarrhytmic drugs: flecainide and pilsicainide, produce ST segment elevation simulating inferior myocardial ischemia. J Cardiovasc Electrophysiol 1998; 9: 855-85.

Imaging Studies:

Chest radiograph findings are usually normal in patients with angina pectoris. However, they may show cardiomegaly in patients with previous MI, ischemic cardiomyopathy, pericardial effusion, or acute pulmonary edema. Calcification of coronary arteries frequently correlates with major coronary artery disease.

Graded exercise stress testing is the most widely used test for the evaluation of patients presenting with chest pain. In patients with established stable angina pectoris, it also can provide prognostic information about the extent of disease.

Exercise stress testing can be performed alone and in conjunction with echocardiography or myocardial perfusion scintigraphy tests. Stress echocardiography has an overall sensitivity of 78% and specificity of 86%; myocardial perfusion scintigraphy has an overall sensitivity of 83% and specificity of 77%. Exercise stress testing alone generally has somewhat lower sensitivity and specificity, but it is cheaper and therefore is a reasonable choice in those with a low probability of disease.

These test results must be interpreted in the context of the likelihood of the presence of coronary artery disease determined from the patient's history and physical examination findings. In a population with low prevalence, the predictive abilities of these tests are low; however, in patients with a high likelihood of coronary artery disease, the predictive value is much higher.

Stress echocardiography can be used to evaluate segmental wall motion during exercise. It detects changes in regional wall motion that occur during myocardial ischemia. Normal myocardium becomes hyperdynamic during exercise; ischemic segments become hypokinetic or akinetic.

Stress echocardiography has the advantage of simultaneous evaluation of LV function, cardiac dimensions, and valvular disease. It is especially useful in patients with baseline ECG abnormalities and those with systolic murmurs suggestive of aortic stenosis or hypertrophic cardiomyopathy.

It is also helpful for localizing ischemia and evaluating its severity.

Signs of severe coronary artery disease during exercise stress echocardiography include LV dilation, a decrease in global systolic function, and new or worsening mitral regurgitation. However, with dobutamine stress echocardiography, even in patients with severe coronary artery disease, the LV cavity may not dilate and global systolic function may improve.

A major problem with stress echocardiography is the technical difficulty with obtaining adequate images in some patients.

Thallium Tl 201 and technetium Tc 99m sestamibi are the most frequently used myocardial perfusion scintigraphy tests. These tests are especially useful in patients with baseline ECG abnormalities, to localize the region of ischemia, and as prognostic indicators. The presence of increased lung uptake upon thallium imaging is associated with a poor prognosis. Increased lung uptake, together with poststress dilation of the LV and multiple perfusion defects, is suggestive of either left main coronary artery disease or severe 3-vessel disease. The number of affected myocardial segments is predictive of long-term survival. Smaller perfusion defects are usually associated with peripheral coronary artery lesions, which are associated with a better prognosis. The absence of perfusion defects even in the presence of symptoms indicates an excellent prognosis.

The frequency of infarction or death is 1 case per 10,000 stress tests. Absolute contraindications include symptomatic cardiac arrhythmias, severe aortic stenosis, acute MI within the previous 2 days, acute myocarditis, or pericarditis. Discontinue the exercise stress test in the presence of chest pain, a drop in systolic blood pressure of

more than 10 mm Hg, severe shortness of breath, fatigue, dizziness or near syncope, ST depression of more than 2 mm, ST elevation of at least 1 mm without diagnostic Q waves, or development of ventricular tachyarrhythmia.

Other Tests:

ECG is useful for evaluating persons with angina pectoris; however, findings are variable among patients.

Approximately 50% of patients with angina pectoris have normal findings after a resting ECG. However, abnormalities such as evidence for prior MI, intraventricular conduction delay, various degrees of atrioventricular block, arrhythmias, or ST-T–wave changes may be seen.

During an attack of angina pectoris, 50% of patients with normal findings after resting ECG show abnormalities. A 1-mm or greater depression of the ST segment below the baseline, measured 80 milliseconds from the J point, is the most characteristic change. Reversible ST-segment elevation occurs with Prinzmetal angina. Some patients with coronary artery disease may show pseudonormalization of the resting ECG ST-T–wave abnormalities during episodes of chest pain.

Exercise with ECG monitoring alone is the initial procedure of choice in patients without baseline ST-segment abnormalities or in whom anatomic localization of ischemia is not a consideration.

Horizontal or down-sloping ST-segment depression of at least 1 mm, measured 80 milliseconds from the J point, is considered the characteristic ischemic response.

ST-segment depression of more than 2 mm at a low workload or that persists for more than 5 minutes after termination of exercise and a failure of blood pressure to rise or an actual drop in blood pressure are signs of severe ischemic heart disease and a poor prognosis.

Withhold beta-blockers for approximately 48 hours before the stress test, whenever possible. Patients on digoxin and those with LV hypertrophy with repolarization

abnormalities more often show positive results. Exercise stress tests have lower sensitivity and specificity in women and in patients with left bundle-branch block.

Pharmacologic agents (eg, dobutamine, dipyridamole, adenosine) can be used in patients who are unable to exercise.

Ambulatory ECG monitoring can be used for diagnostic purposes in patients with chest pain suggestive of Prinzmetal angina but is primarily used to evaluate the frequency of silent ischemia. Silent ischemia has been shown to be an independent predictor of mortality in patients with angina pectoris.

Several studies have shown that calcium in the coronary arteries as detected by electron-beam computed tomography is an important indicator of coronary artery stenosis. In these studies, the sensitivity of a positive electron-beam computed tomography scan ranged from 85-100% and the specificity varied from 41-76%, while the positive predictive value varied from 55-84% and the negative predictive value varied from 84-100%. However, several studies have shown inconsistent reproducibility in repeated measures of coronary calcium with electron-beam computed tomography. Thus, its proper role at this time remains controversial.

Procedures:

Selective coronary angiography is the definitive diagnostic test for evaluating the anatomic extent and severity of coronary artery disease.

Consider coronary angiography in symptomatic patients with inconclusive noninvasive study results, in survivors of sudden cardiac death, in those who are considered to have a poor prognosis based on the results of noninvasive studies, in those with occupational requirements for a definite diagnosis (eg, pilots), or in patients with coronary artery disease who are severely symptomatic despite maximal medical therapy.

In patients in whom Prinzmetal angina is suggested, provocative testing with ergonovine maleate during coronary angiography may be useful.

Intra-aortic balloon counterpulsation can be used in patients who continue to have unstable angina pectoris despite maximal medical treatment. This procedure should be followed promptly by coronary angiography with possible coronary revascularization.

In patients whose angina is refractory to medical therapy who are not suitable candidates for either percutaneous or surgical revascularization, enhanced external counterpulsation is a safe and noninvasive alternative therapy. It increases coronary perfusion and reduces myocardial oxygen demand by diastolic augmentation of the central aortic pressure. Several studies have shown that patients treated with enhanced external counterpulsation have a significantly reduced number of anginal episodes, improved exercise tolerance, and decreased daily use of nitroglycerin tablets. Its therapeutic effects on quality of life are noted to remain at 1-year follow-up.

TREATMENT

Medical Care: The main goals of treatment in angina pectoris are to relieve the symptoms, slow the progression of disease, and reduce the possibility of future events, especially MI and premature death.

General measures

Smoking cessation results in a significant reduction of acute adverse effects on the heart and may reverse, or at least slow, atherosclerosis. Strongly encourage patients to quit smoking, and take an active role in helping them to achieve this goal.

Treat risk factors, including hypertension, diabetes mellitus, obesity, and hyperlipidemia.

Several clinical trials have shown that in patients with established coronary artery disease, reduction of low-density lipoprotein (LDL) level with a beta-hydroxy-beta-methylglutaryl coenzyme A reductase inhibitor (ie, statin) is associated with significant reductions in both mortality rate and major cardiac events.

These benefits are present even in patients with mild-to-moderate elevations of LDL cholesterol level.

Recent trials with cholesterol-lowering agents have confirmed the benefits of the therapeutic LDL lowering in older persons.

Angiographic studies demonstrate that a reduction of the LDL level in patients with coronary artery disease could cause slowing of progression, stabilization, or even regression of coronary artery lesions.

A recent study demonstrates a significant reduction of symptomatic myocardial ischemia in patients with unstable angina or non–Q-wave infarction with the administration of a statin during the early acute phase.

In a more recent study of 10,001 patients with stable coronary artery disease, an aggressive cholesterol-lowering approach with atorvastatin 80 mg daily (mean cholesterol level of 77 mg/dL) compared to a less-aggressive approach with atorvastatin 10 mg daily (mean cholesterol level of 101 mg/dL) resulted in a 2.2% absolute reduction and a 22% relative reduction in the occurrence of a first major cardiovascular event (defined as death from coronary heart disease; nonfatal, non–procedure-related myocardial infarction; resuscitation from cardiac arrest; or fatal or nonfatal stroke).This occurred with a greater incidence of elevated aminotransferase levels with the aggressive cholesterol-lowering approach (1.2% vs 0.2%, $p<0.001$).

On the basis of several recent studies that have demonstrated the benefits of more aggressive LDL-lowering therapies in high-risk patients with coronary artery disease, the Committee of the National Cholesterol Education Program recently made the following modifications to the Adult Treatment Panel III (ATP III) guidelines.

In high-risk patients, a serum LDL cholesterol level of less than 100 mg/dL is the goal.

In very high-risk patients, an LDL cholesterol level goal of less than 70 mg/dL is a therapeutic option. Patients in the category of very high risk are those with established coronary artery disease with one of the following: multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (especially continued cigarette smoking), multiple risk factors of the metabolic syndrome (especially high triglyceride levels [$\geq$200 mg/dL] plus non-HDL cholesterol level [$\geq$130 mg/dL] with low HDL cholesterol level [<40 mg/dL]), and patients with acute coronary syndromes.

For moderately high-risk persons (2+ risk factors), the recommended LDL cholesterol level is less than130 mg/dL, but an LDL cholesterol level of 100 mg/dL is a therapeutic option.

Some triglyceride-rich lipoproteins, including partially degraded very LDL levels, are believed to be independent risk factors for coronary artery disease. In daily practice, non-HDL cholesterol level (ie, LDL + very LDL cholesterol [total cholesterol - HDL cholesterol]) is the most readily available measure of the total pool of these atherogenic lipoproteins. Thus, the ATP III has identified non-HDL cholesterol level as a secondary target of therapy in persons with high triglyceride levels (>200 mg/dL). The goal for non-HDL cholesterol level (for persons with serum triglyceride levels >200 mg/dL) is 30 mg/dL higher than the identified LDL cholesterol level goal.

Patients with established coronary disease and low HDL cholesterol levels are at high risk for recurrent events and should be targeted for aggressive nonpharmacological (ie, dietary modification, weight loss, physical exercise) and pharmacological treatment.

A recent study demonstrated that in patients with established coronary artery disease who have low HDL and low-risk LDL levels, drug therapy with medications that raise HDL cholesterol levels and lower triglyceride levels but have no effect on LDL cholesterol levels (eg, gemfibrozil) could significantly reduce the risk of major cardiac events.

Currently, the accepted approach to the management of patients with coronary artery disease and low HDL levels is as follows:

In all persons with low HDL cholesterol levels, the primary target of therapy is to achieve the ATP III guideline LDL cholesterol level goals with diet, exercise, and drug therapy as needed.

After reaching the targeted LDL level goal, emphasis shifts to other issues. That is, in patients with low HDL cholesterol levels who have associated high triglyceride levels (>200 mg/dL), the secondary priority is to achieve the non-HDL cholesterol level goal of 30 mg/dL higher than the identified LDL cholesterol level goal. In patients with isolated low HDL cholesterol levels (triglycerides <200 mg/dL), drugs to raise the HDL cholesterol level (eg, gemfibrozil, nicotinic acid) can be considered.

Exercise training results in improvement of symptoms, increase in the threshold of ischemia, and improvement of patients' sense of well-being. However, before enrolling a patient in an exercise-training program, perform an exercise tolerance test to establish the safety of such a program.

Consider enteric-coated aspirin at a dose of 80-325 mg/d for all patients with stable angina who have no contraindications to its use. In patients in whom aspirin cannot be used because of allergy or gastrointestinal complications, consider clopidogrel.

Although early observational studies suggested a cardiovascular protective effect with the use of hormone replacement therapy, recent large randomized trials failed to demonstrate any benefit with hormone replacement therapy in the primary or secondary prevention of cardiovascular disease.

In fact, these studies even demonstrated an increased risk of coronary artery disease and stroke in patients on hormone replacement therapy.

The Women's Health Initiative study demonstrated that the use of hormone replacement therapy for 1 year in 10,000 healthy postmenopausal women is associated with 7 more instances of coronary artery disease, 8 more strokes, 8 more pulmonary emboli, 8 more invasive breast cancers, 5 fewer hip fractures, and 6 fewer colorectal cancers.

Based on these data, the risks and benefits of hormone replacement therapy must be assessed on an individual basis for each patient.

Sublingual nitroglycerin has been the mainstay of treatment for angina pectoris. Sublingual nitroglycerin can be used for acute relief of angina and prophylactically before activities that may precipitate angina. No evidence indicates that long-acting nitrates improve survival in patients with coronary artery disease.

Beta-blockers are also used for symptomatic relief of angina and prevention of ischemic events. They work by reducing myocardial oxygen demand and by decreasing the heart

rate and myocardial contractility. Beta-blockers have been shown to reduce the rates of mortality and morbidity following acute MI.

Long-acting heart rate–slowing calcium channel blockers can be used to control anginal symptoms in patients with a contraindication to beta-blockers and in those in whom symptomatic relief of angina cannot be achieved with the use of beta-blockers, nitrates, or both. Avoid short-acting dihydropyridine calcium channel blockers because they have been shown to increase the risk of adverse cardiac events.

Anginal symptoms in patients with Prinzmetal angina can be treated with calcium channel blockers with or without nitrates. In one study, supplemental vitamin E added to a calcium channel blocker significantly reduced anginal symptoms among such patients.

In patients with syndrome X and hypertension, ACE inhibitors may normalize thallium perfusion defects and increase exercise capacity.

Surgical Care:

Revascularization therapy (ie, coronary revascularization) can be considered in patients with left main artery stenosis greater than 50%, 2- or 3-vessel disease and LV dysfunction (ejection fraction, <45%), poor prognostic signs during noninvasive studies, or severe symptoms despite maximum medical therapy. The 2 main coronary revascularization procedures are percutaneous transluminal coronary angioplasty, with or without coronary stenting, and coronary artery bypass grafting.

Patients with 1- or 2-vessel disease and normal LV function who have anatomically suitable lesions are candidates for percutaneous transluminal coronary angioplasty and coronary stenting. Restenosis is the major complication, with symptomatic restenosis occurring in 20-25% of patients. Restenosis mostly occurs during the first 6 months after the procedure and can be managed by repeat angioplasty. Several recent trials have demonstrated that the use of drug-eluting stents (eg, sirolimus-eluting stents, paclitaxel-coated stents) can remarkably reduce the rate of in-stent restenosis. Recently, with the introduction of these drug-coated stents, patients with multivessel coronary artery disease are more frequently treated with percutaneous revascularization as opposed to the surgical revascularization.

Patients with single-vessel disease and normal ventricular function treated with percutaneous transluminal coronary angioplasty show improved exercise tolerance and fewer episodes of angina compared with those who receive medical treatment. However, no difference in the frequency of MI or death has been shown between these two groups.

Patients with significant left main coronary artery disease, 2- or 3-vessel disease and LV dysfunction, diabetes mellitus, or lesions anatomically unsuitable for percutaneous transluminal coronary angioplasty have better results with coronary artery bypass grafting. The overall operative mortality rate for coronary artery bypass grafting is approximately 1.3%. The rate of graft patency 10 years after surgery is less than 50% for vein grafting, although more than 90% of grafts using internal mammary arteries are patent at 10 years. In recent years, interest has increased regarding surgery without cardiopulmonary bypass (ie, off-pump) in an attempt to avoid the morbidity associated with cardiopulmonary bypass. A recent randomized study demonstrated that off-pump coronary surgery was as safe as on-pump surgery and caused less myocardial damage. However, the graft-patency rate was lower at 3 months in the off-pump group than in the on-pump group.

Recently, laser transmyocardial revascularization has been used as an experimental therapy for the treatment of severe, chronic, stable angina refractory to medical or other therapies. This technique has been performed with either an epicardial surgical technique or by a percutaneous approach. In both approaches, a series of transmural endomyocardial channels are created to improve myocardial perfusion. The surgical transmyocardial revascularization technique has been associated with symptomatic relief for end-stage chronic angina in the short term. However, no published data address the long-term efficacy of surgical transmyocardial revascularization. Nonetheless, this technique appears to provide at least symptomatic relief for end-stage chronic angina in the short term.

Diet: A diet low in saturated fat and dietary cholesterol is the mainstay of the Step I and Step II

Activity: The level of activity that aggravates anginal symptoms is different for each patient. However, most patients with stable angina can avoid symptoms during daily

activities simply by reducing the speed of activity.

Deterrence/Prevention:

Coronary atherosclerosis is the main preventable cause of mortality in the United States. A rigorous effort to address correctable risk factors is the mainstay of preventive cardiovascular medicine.

Smoking cessation is the single most effective preventive intervention to reduce coronary atherosclerosis prevalence. It has been associated with a coronary artery disease reduction of 7-47% in primary prevention settings.

Aggressive treatment of diabetes mellitus, hypertension, LV hypertrophy, hyperlipidemia, and obesity has an important role in the prevention of coronary artery disease.

The most important recent development in coronary atherosclerosis risk modification is the introduction of inhibitors of beta-hydroxy-beta-methylglutaryl coenzyme A reductase. Reductions of total and LDL cholesterol levels by 25% and 35%, respectively, can achieve a similar reduction in rates of total and coronary mortality, MI, and need for coronary revascularization.

Complications:

Complications of angina pectoris include unstable angina, MI, and death.

Prognosis:

Important prognostic indicators in patients with angina pectoris include LV function, severity and location of atherosclerotic lesions, and response of symptoms to medical treatment.

LV function is the strongest predictor of long-term survival. Elevated LV end-diastolic pressure and volume along with reduced LV ejection fraction (<40%) are poor prognostic signs.

Critical lesions of left main and proximal left anterior descending coronary arteries are associated with a greater risk. Mortality rates are also directly associated with the number of epicardial arteries involved.

Unstable angina, recent MI, or both is a sign of atherosclerotic plaque instability, which is a strong predictor of increased risk of short-term coronary events.

A number of signs during noninvasive testing are predictive of a higher risk of coronary events, including ST-segment depression of more than 2 mm at a low workload, ST-segment depression that persists for more than 5 minutes after termination of exercise, and failure of blood pressure to rise or an actual drop in blood pressure.

Patients who continue to smoke after an MI have a 22-47% increased risk of reinfarction and death.

In general, Prinzmetal angina and syndrome X are associated with excellent long-term prognoses.

Patient Education:

Educating patients about the benefits of smoking cessation, a low-cholesterol diet, physical activity, and periodic screening for diabetes mellitus and hypertension is the prime component of a long-term management plan.

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