Cardiology

Handbook for Clinicians

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SECTION 1
Cardiac Diseases

CHAPTER 1
Non-ST Elevation Acute Coronary Syndromes*

I. Types of ACS and definitions

A. Unstable Angina (UA) = crescendo chest pain: Chest pain that increases in intensity/duration/frequency, or chest pain that becomes resistant to nitroglycerin
- Or new-onset of severe chest pain occurring at ordinary activities performed at a normal pace in the last 2 mos
- Or rest chest pain
- Or chest pain within 2 wks after MI

B. Non-ST elevation myocardial infarction (NSTEMI) = (+) cardiac markers
- (+) Troponin I ± (+) CK-MB
- If troponin I (+) while CK-MB (–) → micro-infarction = minor myocardial damage†

C. ST elevation myocardial infarction (STEMI)

II. Mechanisms

A. UA/NSTEMIs are usually due to plaque rupture leading to platelet aggregation. This is followed by thrombus formation and microembolization of platelet aggregates. In UA/NSTEMI, the thrombus is most often nonocclusive, and is a platelet-rich thrombus as opposed to STEMI, which is due to an occlusive thrombus rich in platelets and fibrin. Also, NSTEMIs usually have greater collateral flow to the infarct zone than STEMIs.

Multiple plaque ruptures occur in ~30–80% of cases; this is due to the diffuse inflammation occurring in ACS. This shows the importance of medical therapy to "cool down" the diffuse process.

Occasionally, a ruptured plaque may lead to platelets and thrombi microembolization, impaired coronary flow, and ACS without leading to an angiographically significant lesion.

B. Always remember secondary ischemia/UA/NSTEMI, in which plaques are stable but there is $\uparrow O_2$ demand (demand/supply mismatch). In these cases, there is no acute coronary thrombosis. Examples: Severe HTN, acute HF, AS/HCM, GI bleed, hypoxia, tachyarrhythmias, hypotension, sepsis.‡

HF can lead to a positive troponin, but ACS with severe diffuse ischemia can also lead to HF. HF presentation associated with elevated troponin should be considered ACS until significant CAD is ruled out with a coronary angiogram.

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*For EKG findings, please refer to Chap. 24.

†Troponin I is more sensitive and specific than CK/CK-MB.

‡Note that, according to the ACC 2007, a rise in troponin per se is diagnostic of myocardial necrosis but is not sufficient to define MI. To diagnose MI, other evidence of ischemia is needed (angina, EKG ST/T/Q changes, or echocardiographic changes). Secondary myocardial necrosis and troponin increase without MI are very common in critically ill patients, and the tx is different (the main tx is tx of the underlying problem).

C. Coronary vasoconstriction: Most often occurs at the site of an atheroma, especially a ruptured plaque with platelet activation and release of vasoconstrictors, leading to a "mixed" origin of the ACS

Can occur without plaque rupture, with or without significant coronary stenosis (Prinzmetal's angina)

Can occur at the microvascular level (endothelial dysfunction with diffuse microvascular constriction)

III. Diagnosis of UA/NSTEMI (workup)

A. EKG

- ST depression >0.5 mm, especially if transient, dynamic, and occurring during the episode of CP
- Deep T wave inversion >3 mm (T inversion <3 mm is nonspecific)
- Transient ST elevations (lasting <20 mins)*
- Only 50% of non-ST elevation ACSs have an ischemic EKG. In particular, in the cases of NSTEMI and UA, 20% and 37%, respectively, have an absolutely normal EKG. This is most common in case of left circumflex ischemia.

Also, many will have LVH or bundle-branch blocks that make EKG changes less interpretable and less specific.

Of patients with normal EKGs, 1–5% will end up having NSTEMI, 4% will end up having UA.

Obtain serial EKGs to see dynamic changes, diagnostic of ACS; obtaining EKGs during each CP episode increases the sensitivity and the specificity of the EKG for ACS diagnosis. In case of persistent CP with a nondiagnostic initial EKG, serial EKGs should be obtained every 5–10 mins initially.

B. Troponin I, CK-MB, CK

These markers start to rise 3–12 hrs after CP onset, at about the same time. Note that the elevation can be delayed up to 12 hrs after the last episode of CP.

CK-MB is less specific than troponin. To be considered cardiac specific, an elevated CK-MB must be accompanied by a (+) troponin; also, CK-MB/CK ratio is usually >2.5% in the case of MI. CK-MB may increase earlier than troponin, but an elevated CK-MB with serially negative troponin is of muscular rather than myocardial origin. Any degree of troponin rise in the context of angina and in the absence of secondary ischemia causes, even if very mild, indicates a high risk. The higher the troponin level (meaning, >1 ng/ml, or worse, >5 ng/ml), the worse the prognosis. Also, an elevated troponin associated with elevated CK-MB signifies a worse short-term prognosis than an isolated rise in troponin.

Troponin I and CK-MB peak at ~24 hrs and 12–24 hrs, respectively. CK and CK-MB elevations last for 2–3 days. Troponin I elevation lasts for 7–10 days.

Repeat serial markers Q6–8 hrs (obtain at least two levels).

Notes

- Troponin rise and/or fall above the 99th percentile of the reference limit (i.e., 0.04–0.1 ng/ml depending on the assay) defines myocardial necrosis, and, in association with angina, EKG or echo changes, defines MI.
- In patients with recent infarction (within a few days), the diagnosis of reinfarction relies on:
  - CK or CK-MB elevation, as they normalize faster than troponin, or
  - change in the downward trend of troponin
- In the post-PCI context, MI is diagnosed by a troponin or a CK-MB rise above three times normal. In the post-CABG context, MI is diagnosed by a troponin or CK-MB

*This corresponds to a thrombus that occludes the lumen off and on, or to a ruptured unstable plaque associated with vasospasm, or, less commonly, to a stable plaque with vasospasm (Prinzmetal's angina).

elevation above five times normal, associated with new Q wave or LBBB, or new wall motion abnormality.
- Only ~50–60% of high-risk ACS cases have positive troponin. Other potential markers of high risk in ACS: BNP >80 pg/ml, ↑ hs-CRP, ↑ myeloperoxidase (these markers are less specific than troponin).

C. Echo
- The absence of wall motion abnormalities during active CP argues strongly against ischemia. For optimal sensitivity, the patient must be having active ischemia while performing the test. Wall motion abnormalities may persist after CP resolution in cases of stunning or of subendocardial necrosis involving >20% of the inner myocardial thickness.
- Wall motion abnormalities, when present, may be old. However, the patient is already in a high-risk category.
- Contrast echo assesses regional myocardial perfusion in addition to contractile function and improves the sensitivity of active ischemia detection.
- Acute resting nuclear scan, with the nuclear injection performed during active CP or within ~3 hrs of the last CP episode, has an even higher sensitivity than echo in detecting ischemia. An abnormal resting scan, however, is not specific, as this may be an old infarct.

IV. Classification of CP, likelihood of angina/ACS

A. Always assess for other serious causes of CP at least clinically, by CXR and by EKG (always think of PE, aortic dissection, pericarditis).

B. Assess the probability of angina/ACS:

1. High probability:
   - (+) Markers (NSTEMI) or (+) ischemic EKG
   - Or (+) typical angina or angina equivalent (general discomfort, malaise, or dyspnea):
     - Angina is typical through its relation to exertion: Typical angina is a progressively exertional angina. Angina may occur at rest without occuring on exertion in case of vasospasm; this, however, is not the usual case.
     - CP that is similar to a prior documented angina or MI.
     - Duration of CP: If a continuous CP lasts >20 mins, cardiac markers should be positive; otherwise, angina is unlikely. Remember that markers may be negative initially but should become positive 12 hrs after the last episode of CP, if at all. On the other hand, if CP lasts a few seconds only, angina is unlikely.
     - Diaphoresis and/or distress increases the likelihood of angina.
     - The relief of CP with sublingual NTG is not reliably predictive of ACS, nor does the relief of CP with GI cocktail predict its absence.
2. Intermediate probability: Previous CAD/vascular history, or lots of risk factors (age >70 yrs, DM)
3. Low probability: Atypical angina without CV history and without major risk factors

Note that only 25% of CP cases in the ED are true unstable angina/ACS. Remember to always rule out other serious causes of CP (e.g., PE, pericarditis, aortic dissection), at least by the clinical context/physical exam, EKG (pericarditis or PE signs), CXR (mediastinal enlargement and loss of aortic knob suggestive of aortic dissection).

V. Management of UA/NSTEMI

UA and NSTEMI have similar therapies, they are part of the same spectrum; the management of STEMI is different.

A. Types of therapies

1. Antiplatelets:
   a. ASA
   b. Thienopyridine antiplatelets: Clopidogrel (Plavix), prasugrel, or ticlopidine: irreversible antagonists of the platelet ADP receptor
   c. Platelet glycoprotein IIb/IIIa receptor antagonists: the strongest antiplatelet agents, IIb/IIIa being the final receptor for platelet aggregation. Thromboxane A2 and ADP, i.e., the respective targets of ASA and clopidogrel, ultimately act by activating the IIb/IIIa receptor.
2. Anticoagulants:
   - Heparin: inhibits thrombin action by activating antithrombin 3 (AT3); also inhibits factor Xa to a lesser extent
   - Or LMWH: primarily inhibits factor Xa and thus thrombin generation; also inhibits thrombin action to some extent
   - Or bivalirudin: direct thrombin inhibitor + has antiplatelet effects
   - Or fondaparinux: anti-Xa
3. No thrombolytics
   Thrombolytics are only useful for STEMI. In UA/NSTEMI, the thrombus is nonocclusive and seals a ruptured plaque; thrombolytics may reopen this sealed rupture. Also, giving thrombolytics will activate platelets and worsen NSTEMI.
4. Antianginal tx: β-Blockers, NTG, non-DHP CCB.
   Additional tx: ACE-I and blood pressure control.
5. Early coronary angiogram followed by PCI or CABG; PCI is usually not emergent (≠ STEMI)

B. Therapy per group

1. **High-risk ACS**—A definite or probable angina, with the following:
   - + Troponin (NSTEMI)
   - EKG changes (especially new ST depression ≥0.5 mm or transient ST elevation)
   - Hemodynamic instability or HF (S_3, pulmonary edema)
   - Ventricular arrhythmias
   - True typical angina at rest, true angina refractory to the initial antithrombotic and anti-ischemic therapies, or recurrent true angina at rest
   - EF <40%
   - Prior PCI <6–9 mos (time frame of restenosis), prior CABG, or prior CV events
   - TIMI risk score ≥3 (see Appendix 1-2)

   a. **Therapy** that will affect outcomes in high-risk patients:
      i. ASA 162–325 mg/day: High dose the first days; first dose should be chewed for rapid absorption
      ii. Clopidogrel 300–600 mg oral load, then 75 mg Q day
      iii. Heparin IV 60 U/kg bolus then 12 U/kg/hr (PTT goal of 1.5–2.5 × control at 6 hrs after heparin institution or change)
         - Or LMWH (Lovenox 1 mg/kg SQ BID; or QD if GFR <30 ml/min; may give an IV load of 30 mg)
         - Or fondaparinux 2.5 mg SQ QD
         - Or bivalirudin IV
         - Comparison of the overall efficacy and safety of these agents:
           - Fondaparinux > LMWH > heparin in case PCI is not planned.
           - Fondaparinux < LMWH = heparin ≤ bivalirudin if PCI is planned.
           - Anticoagulants should typically be stopped after the performance of PCI. If PCI is not performed, give anticoagulants for at least 48 hrs, and preferably longer, for the duration of hospitalization (up

to 8 days). Longer durations reduce rebound ischemia, which occurs mainly with heparin.

iv. IIb/IIIa receptor antagonists for the highest risk patients, mainly patients with elevated troponin I (see Appendix 1-1, IIB/IIA Antagonists)

v. β-Blockers: Such as oral metoprolol 25–50 mg Q6–8 hrs; may start with IV metoprolol 5 mg Q5–10 mins × 3 in case the patient has active CP. However, avoid them the 1st day and be extra cautious with IV β-blockers if there are any HF signs or an increased risk of cardiogenic shock: SBP <120 mm Hg, HR >110 bpm, or age >70 yrs.* Sinus tachycardia may be an ominous sign heralding cardiogenic shock.

vi. ACE-I, especially if HTN or HF/LV dysfunction; avoid ACE-I if SBP <100 mm Hg or <30 mm Hg below baseline or in case of acute renal failure.

Examples: Short acting captopril 6.25 mg TID, to be doubled with each subsequent dosage, up until 50 TID; or lisinopril 5 mg QD, to be increased to 20–40 QD.

vii. Statins: Start as soon as possible. Statins' benefit is not immediate, but may become evident within 1 mo. For patients on statin therapy, the harm from statin withdrawal is immediate.

Try to give the high doses used in secondary prevention trials, such as atorvastatin 80 mg QD.

b. **Adjunctive therapy includes:**

i. NTG sublingually as needed for CP (Q5 mins up to three times if tolerated). Avoid NTG if SBP <90 mm Hg or bradycardia <50 bpm. Acutely in ACS, one can give NTG at a lower BP level than one can give β-blockers. Later on, in case of borderline BP, the priority should be given to β-blocker administration.

NTG IV is indicated for frequently recurrent CP, for ischemia associated with HTN or HF, and for ongoing CP. CP that is not relieved by 400 mcg of SL NTG is often not relieved by the smaller infusion dose of IV NTG (10–200 mcg/min); the latter may however be tried, in conjunction with β-blockers and antithrombotic therapy. IV NTG is initiated at 10 mcg/min and increased by 10 mcg/min every 3–5 min until relief of symptoms or blood pressure response is noted. Avoid dropping SBP to <110. Oral or topical nitrates (patch, paste) are acceptable alternatives in the absence of ongoing CP. After stabilization, IV NTG should be converted within 24 hrs to an oral or topical nitrate, with a dosing that prevents tolerance and leaves a 10-hr nitrate-free interval (e.g., ISDN 10–40 mg or nitropaste 0.5–2 inches at 8 a.m., 2 p.m. and 8 p.m.).

ii. O_2 to keep O_2 saturation >95%.

iii. Telemetry/rhythm monitoring for 48 hrs at least.

Morphine may be given for CP refractory to the above after a decision is made as to whether emergent revascularization will be performed or not. Thus, morphine should not be used to mask "refractory CP," and resolution of a true angina only after morphine administration should not defer the emergent performance of a coronary angiogram ± PCI.

*Also, always avoid β-blockers acutely and chronically if 2nd- or 3rd-degree AV block, PR interval >240 ms, bradycardia <50–60 bpm, or active bronchospasm. Beyond the first day, SBP below 90–100, rather than 120, is the contraindication to β-blockers.

c. **Early invasive strategy** (improves outcomes/mortality in the intermediate- and high-risk groups):

Coronary angiogram + PCI (or CABG) are performed within hours to 48 hrs after presentation. Revascularization is not urgent except in cases of refractory true angina, hemodynamic instability or refractory VT; this differs from STEMI, in which PCI is emergent.*

After the coronary angiogram, a decision is made for CABG vs. PCI vs. continuing medical therapy alone, as dictated by the coronary anatomy:

- Triple-vessel disease, or double-vessel disease involving proximal LAD, especially in cases of DM or LV EF <50%: Perform CABG. CABG is also indicated for left main stenosis >50%. Try to hold clopidogrel for 5–7 days before CABG, if possible, and hold enoxaparin for 12–24 hrs and IIb/IIIa for 4 hrs.
- Single-vessel disease, or double-vessel disease with or without proximal LAD involvement: Perform PCI if technically feasible. In case of double-vessel disease with proximal LAD involvement, with or without DM or low EF, PCI is an alternative to CABG. In case of triple-vessel disease, especially with DM or low EF or complex lesions, CABG is preferred.
- Coronary angiogram may show:
  - Nonobstructive CAD with a plaque that ruptured and embolized distally but did not lead to an angiographically significant stenosis, or a plaque that stabilized with medical therapy.
  - Significant CAD not amenable to PCI or CABG, being in a small or very distal vessel or being too diffuse or technically challenging.

  Pure coronary spasm without plaque rupture is also a possibility, as it is the cause of ACS in 40–50% of patients who present with typical ACS and no culprit obstructive lesion on the coronary angiogram (4).

  Also look for other causes of CP and increased troponin: PE, myopericarditis, HTN crisis, acute HF, Takotsubo cardiomyopathy.

  In cases of CAD with stabilized ACS that does not require an intervention, medical therapy is continued:
  - ASA forever; clopidogrel for 1–12 mos (preferably, 12 mos)
  - Anticoagulation (enoxaparin, heparin, fondaparinux) for at least 48 hrs (and up to 8 days)

2. **Low-risk ACS and/or low probability of ACS**:

= markers negative at 12 hrs, no significant ST/T EKG abnormalities
and no typical CP at rest or at minimal exertion
and no prior cardiac hx + normal LV function

May have typical CP or lots of risk factors, but no typical CP at rest and no prior cardiac hx. A high probability ACS by angina features could be low-risk.

a. Stress test

- Stress test and LV function assessment by echo, or coronary CT angiogram should be performed for risk stratification at 12–24 hrs in low- or intermediate-risk patients as long as there has not been any ischemic CP or ischemic EKG or troponin rise within 12–24 hrs; stress test is performed after a short inpatient admission and monitoring.

*Note that performing the coronary angiogram at <6 hrs (immediate invasive strategy) is probably better than waiting 24–48 hrs, according to the ISAR-COOL trial (1) and to the SYNERGY timing substudy (2). On the other hand, and if necessary, PCI may be deferred a few days or weeks in hemodynamically stable ACS patients who do not experience recurrent severe angina even if they are high risk, according to the ICTUS trial. A pre-discharge stress test was performed in these high-risk ICTUS study patients after stabilization, but this is not the preferred approach in high-risk patients (3).

- Alternatively, may observe in a chest pain unit, get two sets of troponin over 6–12 hrs, and perform an earlier stress test or a coronary CT angiogram at 6–12 hrs. The patient may also be discharged after ruling out MI and an outpatient stress test performed within 72 hrs after discharge; ASA, β-blockers and SL NTG are prescribed while awaiting stress test results.
- May perform exercise treadmill EKG testing
  - Or treadmill imaging modality (echo, nuclear) if the patient has baseline EKG abnormalities that would make the EKG changes during exercise less specific, or if the exercise testing will be low level.
  - Or pharmacologic imaging modality if the patient is unable to walk.
- The stress imaging modalities are more sensitive and provide slight additional prognostic information.
- If the stress test shows high-risk features (large, reversible perfusion defect on stress imaging; large, fixed perfusion defect with LV dilatation; LV dysfunction <35%; or early, diffuse, or deep ST depression on EKG stress test), then perform coronary angiogram ± PCI or CABG.

b. Therapy for low-risk ACS:
- ASA, β-blockers
- Clopidogrel is useful for probable or definite ACS even if the patient is classified as low risk by the above criteria.
- ± LMWH (one dose can be given until MI is ruled out with the 2nd set of enzymes and until it is certain the patient is low risk)

3. **Always remember secondary ischemia/myocardial necrosis:**
Treat the underlying cause (HF, HTN, sepsis, hypotension, anemia, hypoxia)
Administer ASA if possible without any of the other ACS therapies. In the case of acute HF associated with a positive troponin and when CAD has not been ruled out previously, full ACS tx may be warranted.

VI. Discharge

A. After high-risk ACS (in which a coronary angiogram ± PCI done), discharge patients home on:

1. ASA 81 mg/day. Low dose chronically is probably as effective as higher doses, with lower risk of GI bleed. However, if PCI is performed, use 162–325 mg/day for 1 mo after BMS and 3–6 mos after DES, followed by 81 mg/day afterward.
2. Clopidogrel 75 mg/day
   - At least 1 mo, and preferably 12 mos, even if no PCI is done. This includes patients who underwent CABG in the context of ACS (start clopidogrel few days after CABG)
   - If PCI is done, give clopidogrel for at least 1 mo if BMS is used, and at least 12 mos if DES is used
   - In the absence of stenting, clopidogrel may be stopped if needed (bleeding, surgical procedure). However, if a stent is placed, the discontinuation of clopidogrel before the above timelines should be absolutely avoided except in case of massive bleeding, as discontinuation may lead to subacute stent thrombosis and massive MI.
3. β-Blocker titrated to the maximal tolerated dose before discharge (e.g., try to reach 200 mg of metoprolol daily); only high doses have been shown to improve long-term outcomes after MI and in HF. Titrate β-blocker slower in case clinical HF occurred at any time.
4. ACE-I to all CAD patients, especially in case of HTN or LV dysfunction. Control BP to <130/80.
5. Statin, regardless of LDL. The LDL goal is <100 mg/dl, but a better goal after ACS is <70 mg/dl. Statins can be titrated up for this goal or other agents can be combined (e.g., bile acid-binding resins, niacin). (See first part of Chap. 15.)

6. Aldosterone antagonist in case of EF <40% associated with any degree of clinical HF or with DM; creatinine must be <2 mg/dl.
7. NTG SL PRN
8. Warfarin when indicated (Afib, LV thrombus) in the absence of a high bleeding risk. In that case, use the triple combo ASA/clopidogrel/warfarin for the shortest time, by reducing the duration of clopidogrel to 4 wks after BMS and ± totally avoiding clopidogrel if no stent is placed. Warfarin may need to be withheld during these 4 wks if high bleeding risk.
9. Patients on dual antiplatelet therapy (or on antiplatelet/warfarin combination), patients with a hx of GI bleed, and older patients (>60 yrs) with dyspepsia should be placed on PPI.* Patients with a hx of peptic ulcer should be tested for *H. pylori*.
10. Return to regular activities including sexual activities in 1–2 wks.

B. After a low-risk ACS: If the stress test is normal or low-risk, discharge the patient home, continue ASA and preventive measures. Clopidogrel may be continued for 1–12 mos if the patient had a probable unstable angina, even if it was a low-risk unstable angina.

APPENDIX 1-1
Notes on Antiplatelet and Anticoagulant Agents

IIB/IIIA ANTAGONISTS

In patients already treated with ASA and clopidogrel, IIb/IIIa antagonists are mainly beneficial when they are used in conjunction with PCI in the highest-risk group—mainly in patients with (+) troponin or ± with other high-risk features, such as ST changes and/or refractory/recurrent ischemia. Note that the antiplatelet IIb/IIIa antagonists are not a "better" alternative to anticoagulants and do not obviate anticoagulant use (5).

In that context, IIb/IIIa antagonists can be started during PCI or, better yet, upstream of PCI. Upstream administration is especially beneficial with longer delays to PCI (delays longer than a few hours). With delays longer than 24 hrs, abciximab is not the IIb/IIIa antagonist of choice.

The use of IIb/IIIa antagonists in patients who do not undergo revascularization (PCI or CABG) within 30 days is of questionable benefit, if any.

IIb/IIIa antagonists are also indicated during any PCI, whether the patient is low- or high-risk, in the absence of adequate clopidogrel preload just as they are indicated for elective PCI performed without adequate clopidogrel or aspirin preload.

IIb/IIIa antagonists are also indicated during any PCI when there is a complication (dissection, visible thrombus, slow flow/no reflow).

Because of the bleeding risk, IIB/IIIa antagonists' contraindications are ~ similar to thrombolytic contraindications (see Chap. 2).

Examples of IIb/IIIa Antagonists

- Abciximab (ReoPro)—Used only in conjunction with PCI, during PCI, or up to 24 hrs upstream of PCI, followed by 12 hrs infusion post PCI. It has not shown a benefit when used for ACS patients not undergoing PCI. It inhibits platelets irreversibly, thus, its effects last 48 hrs. In end-stage renal disease, abciximab is the only IIb/IIIa antagonist that can be used, as it is not renally cleared.

*PPI, especially omeprazole, may inhibit the activation of clopidogrel. The clinical impact of this interaction, however, is unknown and should not preclude the use of PPI.

- Eptifibatide (Integrilin), tirofiban—Used with or without PCI. Given as a 48- to 96-hr infusion in case medical therapy is used and no PCI is performed. If PCI is performed, continue the infusion for 18–24 hrs post PCI; a 2-hr infusion of eptifibatide post PCI has recently been shown to be as effective as the 18-hr infusion in elective PCI. Eptifibatide and tirofiban are reversible platelet inhibitors; their effect lasts 4–8 hrs but, unlike abciximab's effect, it is not reversed with platelet transfusions. Reduce the infusion rate by 50% in case of renal failure, and totally avoid them in case of ESRD.

CLOPIDOGREL AND OTHER THIENOPYRIDINES

- **Clopidogrel** (Plavix)—Clopidogrel is indicated for all cases of definite ACS, high or low risk. Clopidogrel 75 mg QD achieves its full antiplatelet effect in 5–7 days. A clopidogrel oral load of 300 mg achieves its full antiplatelet effect in 6 hrs. The benefit of clopidogrel on mortality and MI reduction starts early, after just 2 hrs of therapy, becomes significant within 24 hrs, then maximal within a few days (6,7). Clopidogrel leads to an absolute reduction of mortality and MI of ~2–3%, with ~1% reduction at 24 hrs (as in the CURE trial [6]). This maximal benefit is sustained for the duration of therapy. However, when used in conjunction with PCI, the early clinical benefit of a 300-mg load is seen only when given more than 15 hrs before PCI (CREDO trial [8]).

A clopidogrel oral load of 600 mg achieves a faster and more complete antiplatelet effect (peak effect, 2 hrs) without a significant increase in bleeding risks and is the best option when PCI is to be performed within the next 24 hrs. It is also the best option for ad hoc, unplanned PCI.

If the patient requires CABG, clopidogrel should be held 5 days before CABG (because it increases perioperative bleeding). Some institutions prefer to withhold clopidogrel until the coronary angiogram is done to prevent this waiting time in the event that coronary anatomy dictates CABG. However, this may not always be the best approach, especially when there is a delay in performing coronary angiography or CABG, because there is a benefit in the very early administration of clopidogrel in ACS, in pretreatment of patients who undergo PCI, and in the prevention of ischemic events during the waiting time pre-CABG.

In case clopidogrel is held for CABG considerations, the use of IIb/IIIa antagonists in the high-risk subgroup (in whom an invasive strategy is planned) becomes an even higher priority. The use of IIb/IIIa antagonists during any PCI (including elective PCI) is mandatory if the patient is not adequately preloaded with clopidogrel.

Grossly, clopidogrel and the IIb/IIIa antagonists increase the absolute major bleeding risk by ~1%. They do not increase the risk of intracranial bleed.

IIb/IIIa antagonists increase the immediate bleeding risk. Clopidogrel increases the major bleeding risk by ~1% over the course of 1 yr, with a small increase in the immediate bleeding risk (<0.5%). Clopidogrel does not increase the risk of life-threatening bleeding.

- **Clopidogrel resistance** is defined by the post-treatment, in vitro platelet reactivity of a blood sample. Using various in vitro tests, such as the inhibition of ADP-induced platelet aggregation after clopidogrel tx, 20–40% of patients are clopidogrel nonresponders or poor responders, especially in the context of ACS. This is related to impaired clopidogrel absorption or conversion to the active metabolite. 15% of the clopidogrel administered is converted to the active metabolite by CYP 2C19. ~30% of patients have CYP 2C19 gene variant with reduced function. These patients have higher event rates and higher risk of stent thrombosis. The benefit of using IIb/IIIa antagonists peri-PCI in this high-risk population and in ACS can be seen.

  The large-scale use of platelet reactivity tests is not yet recommended, as their clinical value is not yet clear. Repeating clopidogrel loading (600 mg at 24 hrs and 2

hrs before PCI), loading guided by aggregation tests, or using a higher maintenance dose (150 mg/day) are potential solutions to clopidogrel resistance, but are not yet approved. Using prasugrel is another potential solution.

Also, ACS patients who are on chronic clopidogrel tx may benefit from clopidogrel reload before PCI. Clopidogrel reload is not useful for elective PCI (9).

Note that ASA resistance (defined by various in vitro tests, including the ADP or arachidonic acid aggregation testing) also occurs in 5–20% of patients.

- **Prasugrel** (Effient; not yet FDA approved) is a new ADP receptor irreversible antagonist, achieves a more complete and faster antiplatelet effect than clopidogrel within 30 mins of administration. For ACS managed with PCI, prasugrel decreases ischemic events by an additional ~2% in comparison to clopidogrel, but may increase bleeding in the subgroup of patients having the highest bleeding risk (patients with a hx of any cerebrovascular accident, older patients [>75 yrs old], smaller patients [<60 kg]).
- Ticlopidine is the older-generation ADP antagonist. It is not used anymore except in cases of clopidogrel allergy (ticlopidine has a 2.4% risk of agranulocytosis).

HEPARIN VS. LMWH VS. OTHER ANTICOAGULANTS (TABLE 1-1)

Enoxaparin SQ is preferred to heparin IV when medical therapy is selected and no PCI is planned (which is suboptimal care in high-risk ACS). In that context, enoxaparin further reduces ischemic events compared to heparin. Heparin or LMWH should be given for the duration of the hospital stay (up to 8 days for LMWH).

If an invasive strategy is planned, it has been found that heparin IV drip and enoxaparin 1 mg/kg SQ given within 8 hrs of PCI have an equivalent effect on ischemic and bleeding risks, provided that at least two doses of enoxaparin SQ have been given already (10); also, when PCI is performed between 8 to 12 hrs after an SQ enoxaparin dose, supplement with 0.3 mg/kg IV dose of enoxaparin.

Heparin is seen by many as a better standardized agent for anticoagulation during PCI, and thus may be preferred in many institutions.

Either way, avoid switching from LMWH to heparin within 24 hrs before PCI; this strategy seems to worsen outcomes (it is preferred to pick up one agent and stick with it [10]). Post PCI, the anticoagulant is generally stopped; antiplatelets are continued.

IV heparin half-life increases with the dose used and is usually ~1.0–1.5 hrs. SQ enoxaparin effect peaks at ~3–5 hrs and is accelerated by the IV administration of enoxaparin 30 mg one time dose; its half-life is 4.5–7.0 hrs and is longer in case of renal failure. The short half-life of heparin may contribute to "the heparin rebound" phenomenon, wherein the abrupt cessation of heparin leads to a rebound increase in ischemia in the following 48 hrs. Enoxaparin's antithrombotic effect wanes much more slowly as compared to IV UFH. In addition, enoxaparin not only inhibits thrombin action but thrombin generation as well. This leads to an attenuation of the heparin rebound effect and may explain enoxaparin's added benefit if no PCI is performed (11).

OTHER ALTERNATIVE ANTICOAGULANTS

- **Bivalirudin** (Angiomax) IV bolus then drip. Bilvalirudin is an antithrombin agent; PTT monitoring is not necessary—Can be used as an alternative to heparin or LMWH before and during PCI, with or without ACS (12). Do not use it if PCI is not planned.

  In patients adequately preloaded with clopidogrel, the use of bivalirudin may make the use of IIb/IIIa antagonists unnecessary, even in the highest-risk subgroups, bivalirudin being almost equivalent to the combination of heparin and IIb/IIIa antagonists in decreasing ischemic events, with a significantly lower major bleeding risk: 5.7% vs. 3%, respectively, according to the ACUITY trial (12). Heparin ± LMWH have platelet activating effect; bivalirudin, on the other hand, may have some antiplatelet activity.

Table 1-1
Comparison of different anticoagulants

	Heparin	LMWH	Bivalirudin	Fondaparinux
Action	Binds to AT3: inhibits II > Xa	Is a small heparin derivative Binds to AT3 in a way that inhibits Xa > II Inhibits II generation	Direct thrombin (II) inhibitor	Is a smaller heparin derivative Binds to AT3: inhibits Xa only
Effect on platelets	Potential activation	± Neutral	Inhibits platelets	Neutral
Time to peak effect	Immediate after IV bolus; few hours if infusion without bolus	3–5 hrs after SQ dose	Immediate	2–3 hrs after SQ dose
Half-life	1–1.5 hrs	4–7 hrs. Longer in renal failure	25 min. Longer in renal failure (1 hr if GFR <30 ml/min, 3.5 hrs if GFR <10 ml/min)	17–21 hrs; longer in renal failure
Dose	ACS: 60 U/kg bolus then 12 U/kg/hr IV drip	ACS and PE: 1 mg/kg SQ BID	During PCI: 0.75 mg/kg IV bolus then 1.75 mg/kg/hr	ACS: 2.5 mg SQ QD
	DVT/PE: 80 U/kg bolus then 15–18 U/kg/hr In both cases, PTT goal at 6 hrs: 1.5–2	May start with 30 mg IV bolus	If started before PCI: 0.25 mg/kg/hr	DVT/PE: 5–10 mg SQ QD (depending on weight)
Effect of renal failure on dosage	None	Change to QD if GFR <30 ml/min Avoid in dialysis patients/end-stage renal disease	Avoid if GFR <30 ml/min	Avoid if GFR <30 ml/min
Reversing of effect	Protamine IV: 1 mg for every 100 units of heparin	Protamine IV: 1 mg for every 1 mg of enoxaparin; neutralizes $^2/_3$ of the effect	—	—

Bivalirudin can be given as an IV infusion of several hrs (up to 72 hrs) in patients with ACS in whom PCI is planned. It is stopped after PCI (immediately or up to 4 hrs after the end of the procedure); its half-life is 25 mins and its antithrombotic effects last 2 hrs. No renal adjustments are necessary, but it should be avoided if GFR <30 ml/min.

Also, switching from heparin or LMWH to bivalirudin appears to be safe and to have a beneficial effect on bleeding endpoints.

- **Fondaparinux** (Arixtra) 2.5 mg SQ QD (half-life ~20 hrs)—Can be used as an alternative anticoagulant for ACS treated medically with no PCI planned. It has the same beneficial effect on ischemic outcomes and less bleeding risk than enoxaparin,

and, thus, may improve the overall outcomes and mortality in comparison to enoxaparin (13). It is particularly safer in patients with renal failure, as it has a lower bleeding risk. It appears to be the preferred anticoagulant in patients at higher risk of bleeding managed with a noninvasive strategy.

However, it should be avoided if creatinine is >3 mg/dl, and it should not be used as the sole anticoagulant in patients undergoing PCI. When used alone, fondaparinux is associated with a risk of catheter thrombosis. If an invasive strategy is performed in patients receiving fondaparinux SQ, the use of adjunctive heparin 50 units/kg IV bolus during PCI ~ abolishes the risk of catheter thrombosis (13), without affecting fondaparinux's benefit on bleeding risk.

Note that the fondaparinux effective dose in ACS is lower than that effective for PE/DVT therapy and is equal to the dose used for DVT prophylaxis!

PATIENTS ON CHRONIC WARFARIN THERAPY WHO PRESENT WITH ACS

Warfarin (Coumadin) per se is protective against coronary events.

There are no data on the management of patients appropriately anticoagulated who present with ACS. If a conservative strategy is selected, it may be reasonable to continue warfarin along with other therapies and withhold from adding any other anticoagulant. There is no reason to believe that combining two anticoagulants helps (because overlapping two anticoagulants worsened the bleeding risk in the SYNERGY trial [10]).

If an invasive strategy is selected, warfarin should be held before the coronary angiogram and a short-acting anticoagulant used instead before and during the procedure. This way, the anticoagulant can be stopped after the procedure, reducing the bleeding complications and allowing for the removal of the arterial sheath. Heparin or LMWH should be started as soon as the INR starts to trend down (especially below 2). The angiogram may be performed when the INR is <1.6. Restart warfarin several hrs to 24 hrs after the procedure, and make sure heparin or LMWH is started along with warfarin until the INR is >2, because an early procoagulant effect occurs on warfarin reinitiation and would not be tolerated post ACS.

GI BLEED IN PATIENTS RECEIVING ASA AND CLOPIDOGREL AFTER A RECENT STENT PLACEMENT

In case of chronic blood loss and increased cardiovascular risk, such as a recently placed stent, dual antiplatelet therapy should probably be continued as mandated, and, if indicated, endoscopic intervention performed while the patient is on dual antiplatelet therapy. Also, give PPI and test for *H. pylori* (14).

In case of a major GI bleed, the cessation of one antiplatelet agent may be judged necessary. Following successful endoscopic therapy of upper GI bleed combined with continuous PPI infusion, it may be reasonable to reintroduce antiplatelet therapy in 3–7 days in those who remain free of rebleeding. In case of lower GI bleed, one may have to delay antiplatelet therapy for 7–10 days, based upon lesion size and adequacy of endoscopic treatment.

APPENDIX 1-2
Other Notes: CCBs, TIMI Risk Score, Management According to Coronary Angiographic Findings

CALCIUM CHANNEL BLOCKERS IN ACS

Short-acting DHP CCBs should be avoided in ACS because they lead to reflex tachycardia. Long-acting DHPs may, however, be used in combination with β-blockers. Also, non-DHP CCBs may be given for ongoing ischemia or Afib if β-blockers are contraindicated and in the absence of LV systolic dysfunction or hypotension.

DHP CCBs act on the vessels = vasodilators (nifedipine, amlodipine).

Non-DHPs act on the heart and vessels and decrease inotropism and chronotropism (verapamil, diltiazem).

TIMI RISK SCORE

The TIMI risk score for UA/NSTEMI can be used once the diagnosis of ACS is established or is highly likely. *The score is not useful for the diagnosis of ACS; it is used purely for prognostic assessment:*

1. Age ≥65 yrs
2. ≥ Three risk factors
3. History of coronary stenosis ≥50%
4. ≥ Two episodes of CP in the last 24 hrs
5. Use of ASA in the prior 7 days (this means the patient is ASA resistant)
6. (+) Troponin
7. ST deviation >0.5 mm

Score: 3 or 4 is intermediate risk; 5–7 is high risk. Early invasive strategy improves outcomes in patients with TIMI risk score ≥3, and thus, a score of 3–7 qualifies for an early invasive strategy and full ACS therapy. Risk of mortality/MI/urgent revascularization at 14 days: 13% if score = 3; 20% if score = 4; 26% if score = 5; 40% if score = 6/7.

Also, chronic kidney disease is a marker of bad prognosis, included in the GRACE risk score.

ON AVERAGE, THE CORONARY ANGIOGRAM IN ACS PATIENTS SHOWS:

- Normal coronaries or mild disease in 10–20% of patients. Even when troponin is elevated, ~10% of ACS patients have insignificant CAD. These tend to be younger females and have very good outcomes, but not as good as patients with normal coronaries and negative troponin. The cause may be ruptured plaque(s) that stabilized with medical therapy or coronary spasm. Rule out other causes of CP and increased troponin: HTN crisis, acute HF, PE, myocarditis, Takotsubo cardiomyopathy.
- Single-vessel disease in 25–30% of patients.
- Double-vessel disease in 25–30% of patients.
- Triple-vessel disease in 25–30% of patients (→ perform CABG in cases of LV dysfunction or DM; perform CABG or PCI in the absence of DM or LV dysfunction).
- Left main disease in 5–10% of patients (→ CABG).

In modern clinical trials, ~60–70% of patients undergo PCI after coronary angio-

gram, 10–20% undergo CABG, and ~30% undergo medical therapy only (as in ACUITY and SYNERGY trials [10,12]).

On the coronary angiogram, the culprit lesion is characterized by hazy contours with irregular borders and by the persistence of contrast at the lesion site even after it clears from the rest of the vessel ("staining," this signifies thrombus). The coronary flow may be impaired even in the absence of coronary occlusion because of distal microthrombi embolization. It is common in ACS to have multiple complex plaques and multiple plaque ruptures (they are found in >40% of ACS patients) (15). This is related to the diffuse inflammation and platelet aggregability that destabilizes plaques throughout the coronary vasculature; hence, the importance of medical therapy in conjunction with PCI.

MULTIVESSEL PCI

Multivessel PCI is possible in stable coronary disease and in non-ST elevation ACS (16) but should be avoided in STEMI, in which only the culprit vessel is treated with PCI. Multivessel PCI is better performed in a staged fashion, especially in the case of complex lesions. In multivessel disease with numerous lesions, including tandem lesions in series, only the most severe lesions are stented (spot stenting); stenting the intermediate ones should be avoided. PCI is only beneficial for lesions producing ischemia. PCI guided by flow reserve measurements across a coronary stenosis (FFR) or by IVUS provides the best results. According to clinical trials, multivessel PCI (including proximal LAD PCI) compares favorably with CABG if the stenoses morphology and location are technically amenable to PCI and if full functional revascularization can be achieved with PCI (17). The presence of a chronic total occlusion, of one or more technically difficult lesions or long lesions, or of diabetes, should favor CABG, especially in that CABG provides a more complete revascularization.

CORONARY ANGIOGRAM SHOWING NORMAL CORONARIES, OR MODERATE DISEASE

If the coronary angiogram shows normal coronaries or minimal disease, there is a "warranty period" of 5 yrs during which the patient is at very low risk of ischemic events and in which the coronary angiogram does not need to be repeated unless there is strong evidence of MI.

The coronary angiogram may show single- or multivessel moderate disease (30–70%), or severe disease (>70%) in a small branch for which PCI was not technically possible or beneficial. If these patients return with recurrent or persistent CP a few months or 1–2 yrs later, they do not need a repeat coronary angiogram unless there is a dramatic change in the severity of a typical exertional angina or they present with ischemic ST changes or a positive troponin. It may also be worthwhile assessing the true functional significance of intermediate stenoses (50–70%) using imaging stress testing or coronary flow measurements (pressure wire).

Note that moderate stenoses occurring in the context of ACS may progress rapidly over the course of the next few weeks to months when not appropriately treated with ASA, clopidogrel, and a statin (18).

SHORT-TERM MORTALITY AFTER ACS

In-hospital mortality is higher for STEMI and Q-wave MI than for NSTEMI. However, short-term mortality (30 days) for high-risk, non-ST elevation ACS is similar to STEMI mortality (5%). Long-term mortality of NSTEMI is also similar to STEMI mortality

or may be slightly worse in the absence of revascularization (7–10% at 6–12 mos).

Short-term mortality of UA without positive markers or ST changes is lower (1.7%).

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CHAPTER 9
Pericardial Diseases

ACUTE PERICARDITIS

I. Causes

A. **Viral or idiopathic** → the most common form (80–90% of acute pericarditis).
B. **Metastatic cancer** → usually presents with moderate to large effusions.
C. **Uremia:** There is often an effusion (in >50% of patients).
D. **Connective tissue disease** → SLE, rheumatoid arthritis.
E. **Infections** → fungal, tuberculosis, bacterial, Lyme disease, HIV.
F. **Radiation.** Acute pericarditis, with or without effusion, may develop soon after radiation.
G. **Post-MI** → pericarditis can occur early post-MI or late (Dressler's syndrome).
H. **Post-cardiac surgery:** Pericarditis may occur early (in the first few days) or late (between 2 wks to 2 mos, similar to Dressler syndrome and called *post-pericardiotomy syndrome*).
I. **Trauma (blunt or penetrating).**

II. Hx and physical findings

A. **Chest pain**
- Sharp pleuritic; not constricting.
- Radiates to the trapezius ridge (a typical radiation of pericarditis) and/or the left arm.
- It is positional: Pain is relieved by leaning forward and worsens when swallowing and when moving.

B. **Friction rub**
- Heard during systole and diastole (three components). Heard best at the LLSB with the patient leaning forward.
- It is dynamic (it comes and goes), and all three components may not be evident all the time.

In addition to symptoms (such as CP), the diagnosis of pericarditis typically requires one of the following two: rub on exam, or pericarditis EKG changes.

III. EKG findings

A. **Diffuse concave ST elevation in all leads except aVR and V_1** (most commonly in the inferior and lateral leads; aVR typically has ST depression).
- Present in >90% of patients.
- ST normalizes in 1–5 days, often within 7 days; this is why the EKG of pericarditis can look normal within a few days.
- The return of ST segment to baseline is followed, sometimes, by T-wave inversion that may last weeks or months. Note that, unlike STEMI, T wave does not usually invert if ST has not returned to baseline.

B. **PR depression**
- Present in 82% of patients.
- May be the earliest change.
- Occurs in all leads except in aVR, where it is always elevated.
- It can be an isolated change in ~25% of patients.

C. **These EKG changes are seen mainly in idiopathic pericarditis,** post-cardiac surgery pericarditis, and in hemorrhagic pericarditis. They are rarely seen in uremic, malignant, tuberculous, or autoimmune pericarditis.

D. If an effusion is present → low voltage on EKG and sometimes QRS electrical alternans (which means an alternation of two different QRS morphologies every other beat). There may also be P and T alternans, in which P and T morphologies alternate: This increases the likelihood of pericardial effusion. Sinus tachycardia + low voltage or QRS alternans should suggest tamponade.

Differential diagnosis of the EKG findings

1. STEMI
   a. In pericarditis:
      i. ST elevation is more diffuse (occurs in some discordant leads [e.g., in the inferior and anterior leads]).*
      ii. ST elevation >5 mm is uncommon.
      iii. ST elevation and T-wave inversion are not concomitant, unless T inversion pre-existed before the pericarditis; vs. ST elevation and T inversion may be concomitant in MI, or hyperacute ample T may coexist.
      iv. There are no reciprocal ST changes except for a frequent ST depression in leads aVR ± V_1.
      v. ST elevation is concave in pericarditis vs. convex in MI.
      vi. PR depression.
      vii. No Q waves.
2. Normal variant ST elevation, also known as *early repolarization*.
   a. There is no PR depression and, if present, is minimal (<1 mm).
   b. There is less diffuse ST elevation (ST elevation occurs most often in the precordial leads), typically 1–2 mm high.
   c. There is a notched and sharp J point.
   d. Tall T wave in lead V_6 with ST/T ratio <0.25.

IV. Cardiac enzymes

A. If positive, this means there is myopericarditis.
   1. Clinical myocarditis is myocarditis associated with LV dysfunction and HF; it portends a bad prognosis, as only ~$^1/_3$ of patients recover LV function.

V. Echocardiography

A. Usually normal.

B. Most often, no effusion is appreciated; a small effusion can be seen in 40% of pericarditis cases.

C. Moderate or large effusions are uncommon, and are present in 5% of acute pericarditis cases. They make idiopathic pericarditis a less likely dx, although it remains the most likely dx even in this context: 25–50% of cases of moderate to large pericardial effusions are idiopathic, whereas pericarditis with no or with small effusion is idiopathic in 80–90% of the cases.

D. Looks for an associated severe myocarditis with LV dysfunction.

Initial Testing

- EKG
- Echo
- Cardiac enzymes
- CXR
- ESR
  - If it is very high, it may be a clue to an autoimmune cause or to a tuberculous pericarditis.

*However, mid-LAD occlusion between the first septal and the first diagonal may lead to diffuse ST elevation.

- CBC
- ANA (→ in young women)

Treatment

I. Pericarditis is a self-limiting disease. Treatment should consist of

A. NSAIDs for 1–2 wks.

1. One dose usually has dramatic symptomatic effects.
2. If no response to NSAIDs: Use narcotics, colchicine, or steroids as alternatives or in combination.
3. There is no need for hospitalization unless
   a. No response to NSAIDs
   b. Moderate effusion
   c. Suspicion of a specific etiology (e.g., infectious, SLE/rheumatoid arthritis, neoplastic)

B. Fifteen to 30% of patients with pericarditis (idiopathic, Dressler's, autoimmune, postoperative, traumatic pericarditis) will develop recurrent pericarditis within weeks to years after the initial episode. Recurrent idiopathic pericarditis is not associated with constriction. In such cases, repeat the course of NSAIDs with slow tapering over 3 mos and/or give a course of colchicine (0.5–1 mg BID the first day, then 0.5 mg QD or BID for 6 mos); after a second recurrence, start chronic colchicine prophylactic therapy (1 mg daily). Avoid glucocorticoids except for refractory pericarditis, as glucocorticoids may increase the risk of recurrence.

C. If an effusion is present, perform follow-ups with serial echocardiographic exams.

D. The development of constrictive pericarditis after an acute pericarditis is rare (10% of patients may have transient constrictive physiology that resolves in a few months).

CONSTRICTIVE PERICARDITIS

Constrictive pericarditis is due to pericardial scarring that takes years to develop. In some instances, it only takes a few months. Scarring impairs the LV and, mainly, the RV filling, leading to a right heart failure picture with or without left heart failure.

Note that there can be a transient constrictive physiology without pericardial scarring after any pericardial inflammation (such as after 10% of acute pericarditis cases).

I. Causes

A. Any of the causes of acute pericarditis

B. Causes listed in order, from the most common to the least common: Idiopathic, radiation therapy, post-cardiac surgery, infections, uremia, autoimmune disease, neoplasia

Constrictive pericarditis occurring after cardiac surgery may appear as early as 2 wks or as late as several years after surgery, the majority appearing 3–12 mos postoperatively; it may be related to the post-pericardiotomy syndrome. Constrictive pericarditis occurring within 2 mos postoperatively warrants medical therapy with steroids, because of the high likelihood of a more inflammatory component with less fibrosis.

Constrictive pericarditis typically develops years after radiation therapy.

II. Hx and physical and EKG findings

A. Signs of left heart failure:

Dyspnea, orthopnea, PND

B. Signs of right heart failure; sometimes isolated right heart failure. Constrictive pericarditis should always be considered in the Ddx of isolated right heart failure.
1. JVD with the following particularities
   a. Kussmaul's sign (i.e., increased JVD with inspiration)
   b. Deep x and y descents on JVP pulsations exam (Figs. 9-1 and 9-2)
2. Edema
3. Ascites, hepatic congestion with jaundice (differentiate from cirrhosis by the presence of JVD and hepatomegaly).

C. Low-output signs (fatigue); pulsus paradoxus in $^1/_3$ of the cases.

D. Pericardial knock in diastole (sounds like a high-pitched S_3).

E. The EKG is almost always abnormal; low QRS voltage (very commonly), and nonspecific T-wave abnormalities (flat, inverted).

Diagnosis

I. Constrictive pericarditis is characterized by heart failure clinically, with the following echo findings

A. Normal EF and normal LV-RV sizes

B. Restrictive LV filling

C. Moderate bi-atrial enlargement

D. ~Similar to severe diastolic failure

Thus, the main Ddx of constrictive pericarditis is restrictive cardiomyopathy, in which the LV and RV are stiff and restricted with severe diastolic dysfunction.

II. Differentiating constrictive pericarditis from RCM

A. Echocardiography
1. In both RCM and constrictive pericarditis
   a. Signs of high right- and left-sided pressure
      i. High pulmonary artery pressure
      ii. Dilated IVC
      iii. Bi-atrial dilatation with normal RV and LV sizes
   b. Restrictive mitral inflow (↑ E/A velocity ratio) and restrictive pulmonary venous flow
2. Differences between RCM and constrictive pericarditis
   a. There is >25% inspiratory decrease in mitral and pulmonary venous flow in constrictive pericarditis vs. no respiratory changes in RCM
   b. In constrictive pericarditis: Opposite changes in LV and RV sizes with inspiration → bigger RV, smaller LV with inspiration
   c. In constrictive pericarditis: Septal bounce related to respiratory and systolic-diastolic RV size changes. On M-mode, the posterior wall is flat and motionless throughout diastole (restricted motion).
   d. The E' mitral annular diastolic velocity (tissue Doppler) is reduced in restrictive cardiomyopathy (<10 cm/s) reflecting severe diastolic dysfunction, vs. normal in constrictive pericarditis.
   e. Velocity of propagation of the diastolic mitral flow on color M-mode is reduced in RCM (vs. normal in constrictive pericarditis).
   f. Moderate MR and TR are more frequently seen in RCM, and the atria are more severely enlarged in RCM.
   g. Hepatic veins diastolic flow reversal: *R*estriction → reversal during *I*nspiration; Constriction → reversal during *E*xpiration, the flow increases during inspiration (mnemonic: RICE)
   h. Pericardial thickening and brightness in constrictive pericarditis

B. RHC and LHC
1. In RCM and in constrictive pericarditis (see Figs. 9-1 and 9-2)

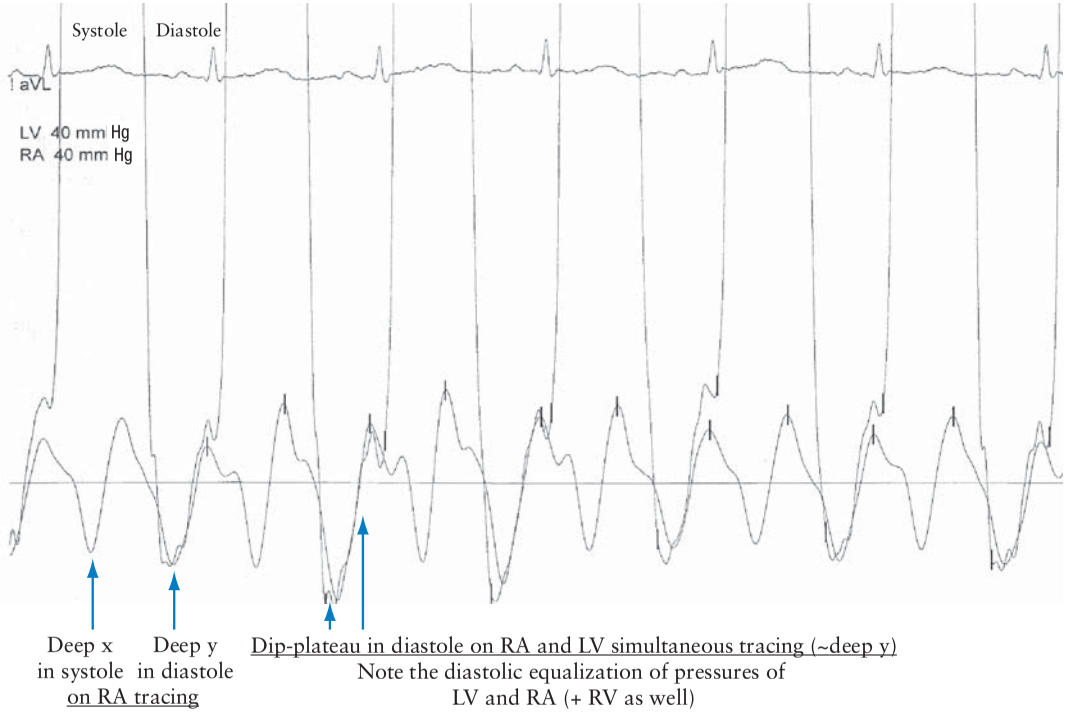

Figure 9-1. LV and RA simultaneous tracing.

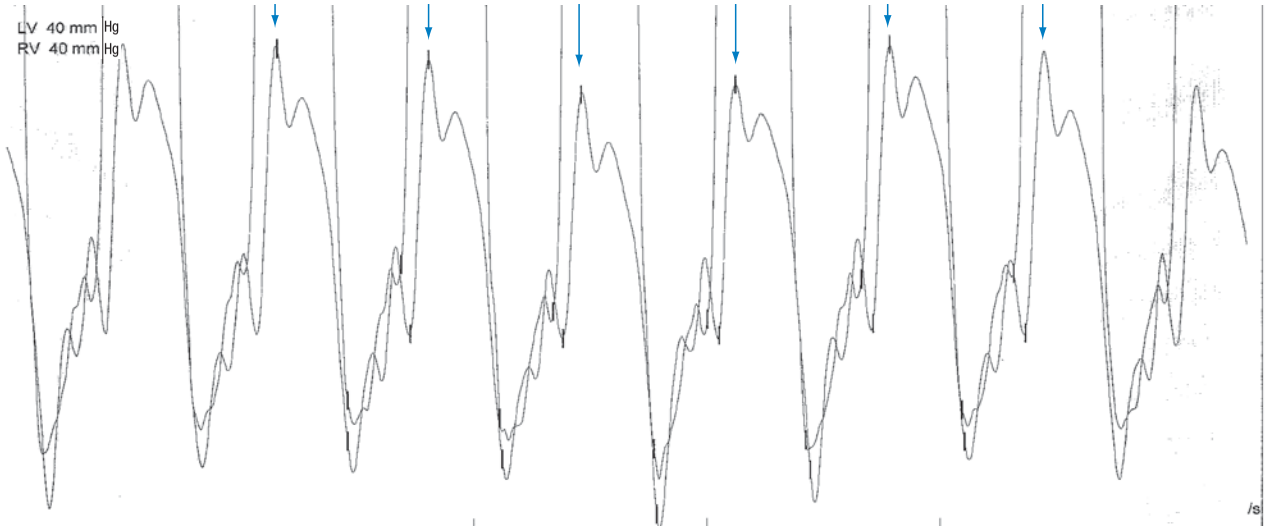

Figure 9-2. RV and LV simultaneous tracings: RV and LV have equalization of diastolic pressures, with dip-plateau in diastole (same as RA). Note how the peak systolic pressure of RV (*arrows*) ↑ with inspiration, while the peak systolic LV pressure ↓ with inspiration (the LV peak is not seen here). This is typical of constrictive pericarditis rather than RCM.

a. RA/RV and LA/LV diastolic pressures have dip-plateau shape (dip-plateau = early diastolic filling followed by an abrupt cessation of flow due to a very poor LV and RV compliance)
b. Deep x and y descent on RA pressure tracing

2. Differences between constrictive pericarditis and RCM
   a. In constrictive pericarditis, there is equalization of diastolic pressures (LV diastolic pressure = RV diastolic pressure = RA pressure = CVP). These pressures are equal to the constricting pressure of the pericardium. This is also seen in pericardial tamponade.
      In RCM, LV pressure >RV pressure + 5 mm Hg.
   b. Respiratory changes in constrictive pericarditis: RV systolic pressure increases with inspiration, and LV systolic pressure decreases with inspiration in constrictive pericarditis.
      No respiratory changes with RCM.
   c. In constrictive pericarditis, the systolic PAP is <55 mm Hg.
      In RCM, systolic PAP can be >55 mm Hg.

- Dip-plateau pattern and deep x and y may also be seen with acute RV infarct, tricuspid regurgitation, and sometimes with any decompensated HF where ventricular filling is very restricted.
- These hemodynamics may be masked by hypovolemia. Rapid volume challenge may reveal the hemodynamic features of constrictive pericarditis. Respiratory changes and pulsus paradoxus, on the other hand, may be accentuated by hypovolemia and masked by hypervolemia.

C. Other helpful tools:
- In RCM, BNP is ~ always >200 pg/ml, whereas in idiopathic constrictive pericarditis, it is <200 pg/ml. BNP may be >200 pg/ml in other forms of constrictive pericarditis. CT imaging may also help by showing pericardial thickening >3–5 mm in 72% of constrictive pericarditis cases, ± pericardial calcifications. Endomyocardial biopsy may be helpful when the hemodynamic and imaging studies fail to establish a diagnosis. Biopsy may establish a specific diagnosis of restrictive cardiomyopathy (such as amyloidosis).

Treatment

I. Pericardiectomy

A. Carries a mortality risk of approximately 10%.
B. Patients with NYHA functional class III–IV and patients with ascites and cachexia have the worst outcomes and improve the least.
C. Clinical improvement occurs in 70–80% of patients.
D. Echocardiographic improvement occurs in approximately 60% of patients. It may take months to see the improvement.
E. Causes of absence of improvement after pericardiectomy:
1. LV myocardial atrophy from long-standing underfilling of the LV
2. Extensive pericardial scarring, with incomplete resection
3. Visceral pericardium scarring and extension of the pathologic process to the LV myocardium

PERICARDIAL EFFUSION AND TAMPONADE

Tamponade

Tamponade is an effusion that compresses the RV during diastole, preventing it from filling, which leads to an "obstructive shock." The hemodynamic effect of an effusion is related to the volume of the effusion and to its acuity.

I. Tamponade is a clinical dx: Tamponade is an effusion (seen on echocardiography) that leads to a hemodynamic compromise as evidenced clinically by any one of the following

A. Increased JVP

B. Pulsus paradoxus = a decrease in SBP of >10 mm Hg with inspiration (pathophysiology: Inspiration increases the venous return and the RV volume, which compresses the LV and decreases the LV volume and the BP)

Later on, the patient will develop frank hypotension and peripheral hypoperfusion.

C. Dyspnea, tachypnea, orthopnea

D. Tachycardia

II. Echocardiographic findings supporting the hemodynamic compromise of tamponade

A. RV collapse in diastole (sometimes just an early RV diastolic indentation seen on M-mode).

B. RA collapse in ventricular systole (RA collapse lasting $>^1/_3$ of systole → specific for tamponade). RA collapse is generally more sensitive and less specific than RV collapse for tamponade.

C. Inspiratory decrease of left-sided trans-mitral flow by >25% (this is equivalent to the pulsus paradoxus) and inspiratory increase of right-sided transtricuspid flow.

D. IVC dilation: sensitivity 97%, specificity 40%. May be absent in low-pressure tamponade.

E. A rapid change in the effusion size is suggestive of a threatened tamponade.

III. Equalization of diastolic pressures in the RV, LV, and PA is seen if the patient has a PA catheter. These pressures are equal to the pericardial sac pressure.

CVP becomes equal to pulmonary arterial diastolic pressure = PCWP = LV diastolic pressure

Treatment

I. IV hydration

II. Avoid preload reduction (avoid diuretics, nitrates)

III. Emergent closed pericardiocentesis

Afterward, leave the catheter in place for approximately 24 hrs, then remove it if it drains <25 ml per 24 hrs and if no reaccumulation of fluid is evidenced on echocardiography.

IV. Open pericardiocentesis with pericardiotomy

A. Also known as *pericardial window* (= cut the pericardium and leave it open to prevent recurrences).

B. Used in cases of

1. Recurrent tamponade
2. Need for a tissue sample to establish a dx
3. Loculated effusion (as in post-cardiac surgery)

C. Send the pericardial fluid and the pericardial tissue for lab analysis.

Pulsus paradoxus may not be seen in tamponade when there is severe underlying right or left HF with severely elevated right- or left-ventricular pressure precluding compression by the pericardial pressure, or if there is a left-to-right shunt.

Outside tamponade, pulsus paradoxus may be seen in cases of severe asthma/COPD. It is also exaggerated by hypovolemia.

Hypovolemia promotes the occurrence of hypotension and pulsus paradoxus at lower levels of filling pressure and JVD (i.e., low pressure tamponade) in the setting of a pre-existing effusion that would not otherwise be significant.

PERICARDIAL EFFUSION WITHOUT TAMPONADE

By definition, pericardial effusion without tamponade is asymptomatic, except for a possible dull ache. A large asymptomatic effusion is usually chronic (that is why it is well tolerated).

I. **Causes of effusions with or without tamponade (same causes as acute pericarditis, except for H and I)**
   - A. **Viral → viral pericarditis rarely leads to tamponade, but it is still one of the most common causes of tamponade and effusions** (20–50% of pericardial effusion cases are viral/idiopathic). HIV pericarditis has a high rate of progression to tamponade.
   - B. **Cancer (lung, breast, Hodgkin's):** 20–30% of pericardial effusion cases
   - C. **Uremia**
   - D. **Connective tissue disorder**
   - E. **Infections/TB**
   - F. **Post-CABG,** early effusion or late post-pericardiotomy syndrome (the effusion usually resolves within weeks); **post-MI,** early effusion (resolves slowly over months) or late effusion (along with Dressler syndrome)
   - G. **Radiation therapy,** early or late effusion
   - H. **Hypothyroidism**
   - I. **HF or volume overload states**
   - J. **Drugs**
   - K. **Hemorrhagic pericardial effusion**

II. **Diagnosed with echocardiography**
   - A. **Small effusions** (0.2–0.5 cm) tend to localize to the posterior side.
   - B. **Large effusions** (>1.5–2.0 cm) are diffuse.
   - C. **Look for tamponade signs (see Tamponade).** Tamponade may occur with smaller or localized effusions that compress the pulmonary veins or the IVC or RA and impede cardiac output (as in post-cardiac surgery); look for a localized impaired flow or compressed chamber.

Management

I. **Identify the cause.**
   - A. **The cause of a pericardial effusion is more often identifiable than the cause of acute pericarditis, though 20–50% of the cases are viral/idiopathic.**
   - B. **Use the clinical context** (clinical suspicion of cancer, tuberculosis, uremia).
   - C. **Screen for common cancers** (CT chest, mammogram), autoimmune diseases (ANA, rheumatoid factor, ESR), tuberculosis (PPD), HIV, hypothyroidism (TSH).

II. **Pericardiocentesis is indicated in case a malignant, purulent, tuberculous, or hemorrhagic effusion is suspected, based on the context/initial workup.**
   - Purulent, tuberculous, or hemorrhagic effusions progress rapidly and need to be drained, even if asymptomatic (→ considered "threatened tamponade").
   - A moderate to large effusion that is increasing in size needs to be drained.
   - A suspected neoplastic effusion needs to be drained for staging or for diagnostic purposes.

III. **If a large, chronic, asymptomatic effusion is present without a specific cause suggested:**
   - A. **Follow-up closely clinically and echocardiographically.**
   - B. **± Give NSAID, colchicine, or corticosteroid course (may help with idiopathic or autoimmune cases).**

C. **Patients are usually stable, and specific causes usually do not emerge with time.** There is a low risk of progression to tamponade.
D. **Pericardiocentesis is usually not indicated for diagnostic purposes and has a low diagnostic yield (<30%) in this context.** However, it can be done to attempt making a dx and to prevent the low risk of tamponade. It has a higher yield in cases of malignant, tuberculous, or purulent pericarditis. It is certainly indicated if the size of the effusion increases upon follow-up.
E. **In the context of a chronic effusion,** if drainage is considered, an open drainage with biopsy may be a better option than pericardiocentesis because it has a higher diagnostic yield.

Effusive constrictive pericarditis
In this case, the patient typically has hemodynamic compromise along with a moderate pericardial effusion. After pericardiocentesis, JVD and the hemodynamic compromise persist, unveiling the constrictive component.

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CHAPTER 21
Acute Dyspnea

I. Causes

A. Cardiac

1. Acute pulmonary edema due to decompensated HF, acute MI, acute HTN, acute valvular problem, arrhythmias
   Dx: Hx (orthopnea, paroxysmal nocturnal dyspnea, and past cardiac hx), exam (↑ JVP, $S_3 \pm S_4$, crackles, peripheral edema), chest x-ray
2. Tamponade (↑ JVP, pulsus paradoxus)
3. Always remember that dyspnea could be an angina equivalent

Two other forms of nocturnal dyspnea must be distinguished from HF:

- Patients with COPD may have mucus hypersecretion; after a few hours of sleep, secretions can accumulate and produce dyspnea and wheezing, which are relieved by cough and sputum expectoration.
- Patients with asthma may have their most severe obstruction between 2 a.m. and 4 a.m. and wake up with severe dyspnea and wheezing. Inhaled bronchodilators usually improve symptoms quickly.

In HF, PND usually develops 2–4 hrs after sleep and improves after 15–30 mins of sitting upright or walking. Dyspnea is often accompanied by cough (dry or productive of frothy sputum), wheezing, and sweating. Nocturnal or exertional cough may be the primary complaint of patients with HF.

Orthopnea is mainly seen in HF but may also be seen with pericardial diseases, advanced asthma/COPD with diaphragmatic flattening and weakness, and bilateral diaphragmatic paralysis.

B. PE: Diagnosed by the context (DVT risk factors and/or DVT signs) and by the absence of other causes of dyspnea (no gross abnormalities on CXR).
→ Immediately start heparin or LMWH if the suspicion is high, then perform CT PE protocol or V/Q scan.

C. Pulmonary

1. Pneumonia.
2. Asthma attack-COPD exacerbation: Asthma may occasionally lead to cough and/or dyspnea in the absence of wheezes on examination (variant or atypical asthma).
   Wheezing may be uncovered with maximal forced expiration.
   Also, severe asthma exacerbation may not have wheezes (airways are so narrow that there is total interruption of airflow and decreased breath sounds).
3. Pneumothorax.
4. ARDS in the context of pneumonia, aspiration, septic shock, trauma.

D. Laryngeal causes (laryngospasm, laryngeal edema [anaphylaxis]): Lead to an inspiratory stridor and difficulty inhaling; may be associated with urticaria.

E. Metabolic causes: Metabolic acidosis (such as DKA), hypocalcemia, dyskalemia, severe acute anemia, hyperthyroid storm.
+ Shock of any cause will lead to hyperventilation and tachypnea.

II. Notes

A. Shock + respiratory distress

1. Ddx
   - Cardiogenic shock with pulmonary edema

- Septic shock due to pneumonia or septic shock with ARDS
- Tamponade
- Massive PE
- Anaphylactic shock with bronchospasm, laryngeal edema

+ Any shock leads to tachypnea (the patient hyperventilates in order to ↑ O_2 supply)

B. Wheezing: May signify COPD/asthma but may also be pulmonary edema ("cardiac asthma"), PE, pneumonia. In cardiac asthma, cyanosis and diaphoresis occur more often than in bronchial asthma, and adventitious breath sounds are more common (crackles, rhonchi). CXR will show pulmonary congestion in the case of cardiac asthma.

C. Most of the disorders (Section I. Causes, A–C) will lead to a pulmonary shunt effect in which blood is not oxygenated because of obstruction of the airways or to a true shunt of the pulmonary circulation in case the alveoli are filled.

This leads initially to hypocapnia, hypoxemia or normoxemia (pO_2 may be normal early on), and elevated A-a gradient.* A-a gradient increases in most pulmonary pathologies, as a result of V/Q mismatch, and thus is not specific for PE. It signifies there is a problem but does not identify it (could be PE, pulmonary edema, COPD exacerbation, pneumonia, ARDS). The more severe the process, the higher the A-a gradient.

As the illness progresses, the patient gets tired and starts hypoventilating → this leads to a worsening of the hypoxia and development of hypercapnia.

Hypercapnia occurs sooner in COPD (COPD may have chronic hypercapnia that worsens during exacerbations) and in pulmonary edema. It occurs later in asthma and in other disorders, and is rare in the case of PE.

D. Cyanosis: Corresponds to having a deoxygenated Hb concentration of >5 g/dl. The cause can be respiratory, in relation to severe hypoxemia (= central cyanosis), or peripheral, in relation to a shock state with normal arterial O_2 saturation but peripheral tissue hypoxia. There is tongue cyanosis in the former, not in the latter.

Cyanosis manifests less easily in anemic patients.

Respiratory distress without gross abnormalities on CXR.

- PE
- Bronchospasm, COPD exacerbation
- Severe sepsis, shock states, or metabolic acidosis
- Dyspnea that is angina equivalent
- Also, myocardial ischemia or severe HTN on exertion can increase the pulmonary capillary filling pressures and lead to dyspnea on exertion without leading to pulmonary edema.

III. Management

Get EKG (check for ischemia, arrhythmias), ABG, CXR stat.

Keep O_2 saturation >88–90%. May use high FiO_2 >40–50%; this can only be delivered with a regular or a nonrebreather face mask.

Assess quickly the hemodynamics and the volume status. BNP helps differentiate dyspnea of cardiac versus pulmonary origin in the acute setting (BNP <100 → no HF; BNP >400 → dyspnea due to HF).

*A-a gradient: = PA O_2 – PaO_2
= FiO_2 × (P atmospheric – 47) – $PaCO_2$/0.8 – PaO_2
= ~150 (on ambient air, sea level) – $PaCO_2$/0.8 – PaO_2
Normal <10–15 mm Hg on ambient air, <50–75 mm Hg on high-flow O_2 (A-a gradient normally increases by 5–7 mm Hg with each 10% increase in FiO_2)

A. Institute quick, specific therapies.

1. In the case of suspicion of pulmonary edema
   → Try furosemide (Lasix) (40–80 mg IV) and/or vasodilators (e.g., NTG SL then IV). May wait for CXR before giving furosemide if not sure of the diagnosis and the patient is stable.
   → Perform echo.
   → Look for ischemia and treat it.
2. Wheezes → albuterol nebulizer delivered continuously for 1 hr or more.
3. Any suspicion of pneumonia → broad spectrum antibiotics + blood/sputum cultures.
4. High suspicion of PE → give heparin bolus followed by a drip and perform a CT PE protocol when the patient is stable.

B. Consider intubation in the following cases:

1. Respiratory distress with a respiratory rate >35/min, not improving quickly with furosemide/O_2/nebulizer therapy regardless of O_2 saturation (the patient is getting more tired, breathing is getting more shallow, with accessory muscle use and paradoxical respiration).
2. Hypoxia not responding to maximal O_2 (O_2 saturation <88% despite the administration of 100% O_2 via a face mask).
3. Acute hypercapnia or worsening of chronic hypercapnia with pH <7.25.
4. Any shock associated with respiratory distress.
5. Alteration in mental status.

In COPD and in acute pulmonary edema, while waiting for the initial measures to take effect, may try to support the ventilation with noninvasive ventilation (CPAP, BiPAP).

Noninvasive ventilation is particularly helpful for:

- HF (the positive pressure in the thorax reduces the preload and the afterload)
- Decompensated COPD with ventilatory failure and hypercapnia

If there is no improvement within the first 30–60 mins of noninvasive ventilation and initial therapeutic measures institution, or if there are mental status changes, or severe acidosis (pH 7.1), or hemodynamic compromise: Proceed with immediate intubation.

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