Pericarditis

DIAGNOSIS AND TREATMENT IN 2023

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Outline

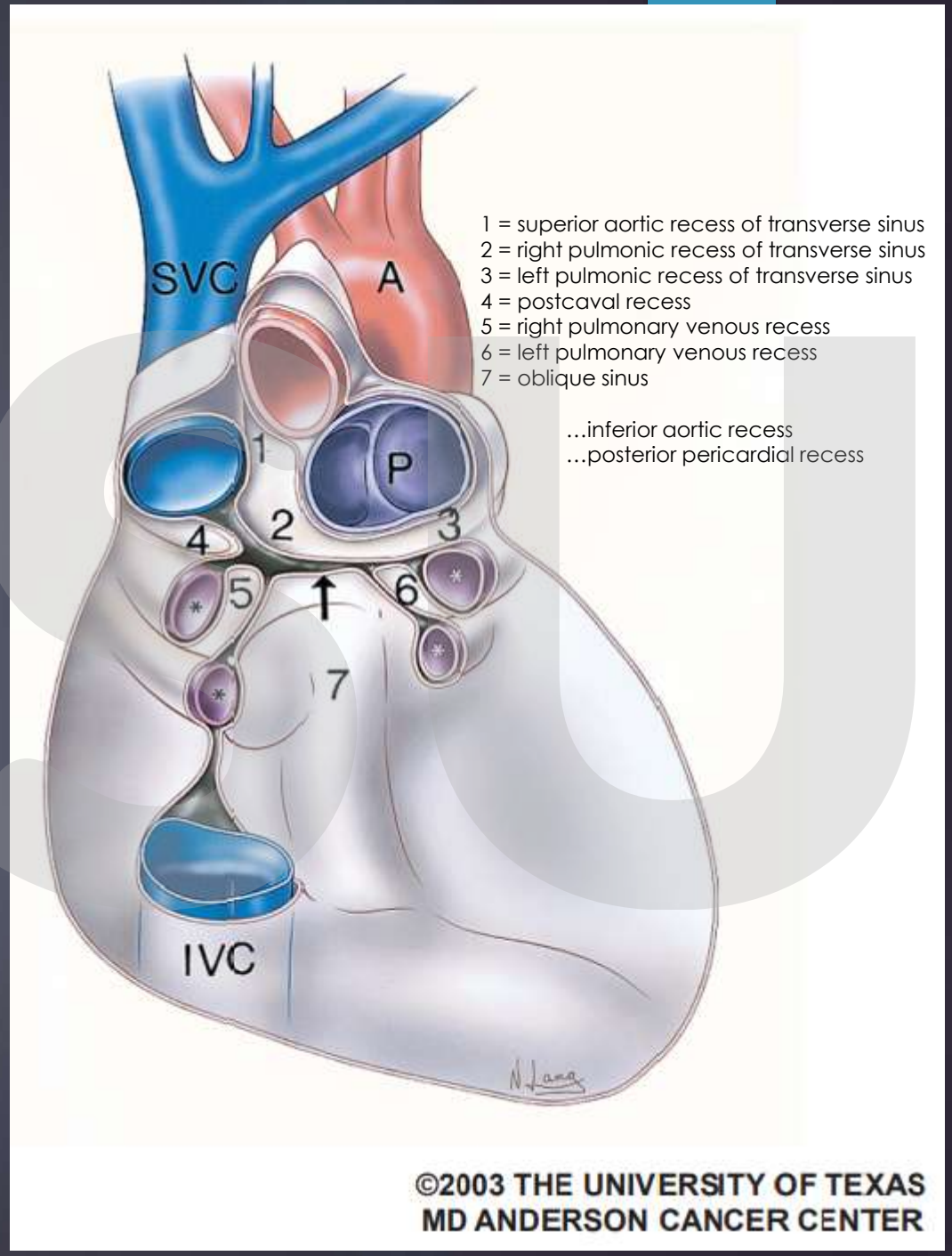
- Pericardial Anatomy
- Acute Pericarditis : Diagnosis & Treatment
- Complicated Pericarditis : Diagnosis & Treatment
- Advanced Imaging in Pericarditis
- Novel Anti-inflammatory Drugs for Pericarditis
- Pericardial Effusion
- Cardiac Tamponade
- Constrictive Pericarditis
- Pericardial Miscellany

Objectives

- Describe the currently used criteria for the diagnosis of acute pericarditis, as well as incessant, recurrent, and chronic pericarditis
- Describe the role of tests typically obtained in suspected pericarditis, including labs and imaging
- Review the first- and second-line treatment options for acute pericarditis
- Review the role of advanced cardiac imaging for recurrent and complicated pericarditis
- Describe novel anti-inflammatory agents for pericarditis and when their use might be appropriate

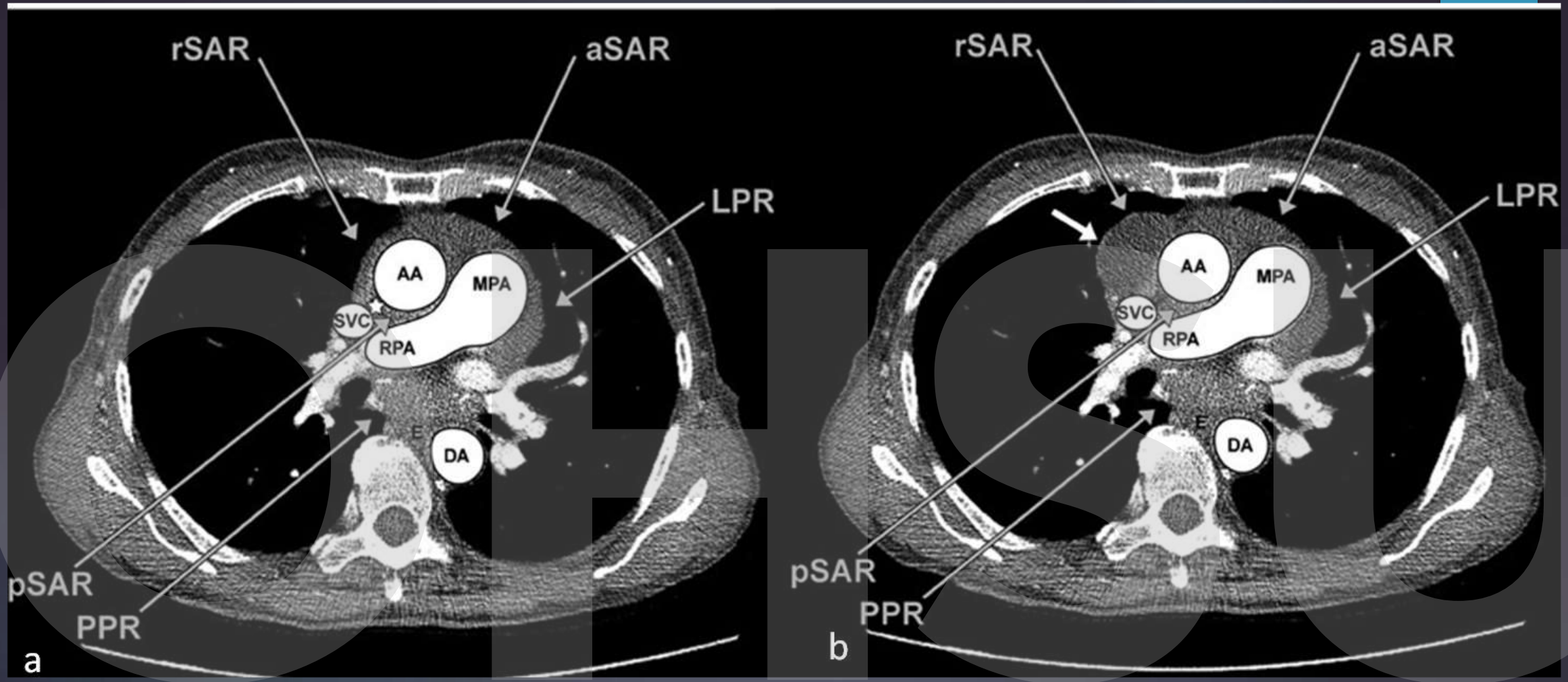
Pericardial Anatomy

- The pericardium is a sac which encloses the heart:
  - The visceral layer -- surrounds and is affixed to the heart (epicardium) and great vessels.
  - The parietal layer
- Normal pericardial thickness is <2 mm; >4 mm is considered definitely abnormal



Pericardial Anatomy

- Normal pericardium contains up to 50 ml of serous fluid, diffusely distributed over the surface of the heart and in pericardial recesses:
  - Transverse sinus
  - Oblique sinus
  - Superior & inferior aortic recesses
  - Left & right pulmonic recess
  - Left & right pulmonic vein recess
  - Posterior recess
  - Postcaval recess



- rSAR = right lateral portion of the **superior aortic recess**
- aSAR = anterior portion of the **superior aortic recess**
- pSAR = posterior portion of the **superior aortic recess**
- LPR = left pulmonic recess
- PPR = posterior pericardial recess

Pericarditis

- Inflammation of the visceral and/or parietal pericardium.
- Often results in typical "pericarditic" pain – pain that is pleuritic, sharp, and positional (typically worse supine, improved by leaning forward)
- Associated with typical ECG findings (diffuse ST elevation and PR depression)
- Often associated with pericardial effusion.
- Rarely can result in cardiac tamponade – impaired cardiac filling due to increased intrapericardial pressure

Diagnosis & Classification of Pericarditis

- **Acute Pericarditis -- 2 of 4:**
  - *Chest pain -- >85-90% of cases*
    - *typically **sharp, pleuritic, & positional***
  - *A rub is often absent (present in <33%)*
  - *Typical ECG changes – 60% of cases*
    - *Diffuse STE and PRD*
  - *Pericardial effusion -- 60% of cases*
- **Incessant Pericarditis**
- **Recurrent Pericarditis**
  - *Recurrences develop in 20-30% of acute pericarditis patients by 18 months*
  - *Up to 50% of patients with recurrent pericarditis experience multiple recurrences!*
- **Chronic Pericarditis**

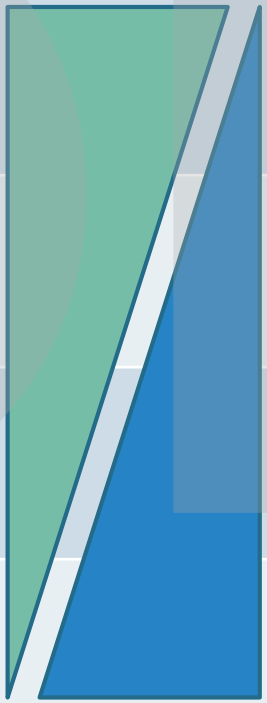
2015 ESC Guidelines for the diagnosis and management of pericardial diseases

European Heart Journal (2015) **36**, 2921–2964
doi:10.1093/eurheartj/ehv318

Pericarditis	Definition and diagnostic criteria
Acute	Inflammatory pericardial syndrome to be diagnosed with at least 2 of the 4 following criteria: (1) pericarditic chest pain (2) pericardial rubs (3) new widespread ST-elevation or PR depression on ECG (4) pericardial effusion (new or worsening) Additional supporting findings: - Elevation of markers of inflammation (i.e. C-reactive protein, erythrocyte sedimentation rate, and white blood cell count); - Evidence of pericardial inflammation by an imaging technique (CT, CMR).
Incessant	Pericarditis lasting for >4–6 weeks but <3 months without remission.
Recurrent	Recurrence of pericarditis after a documented first episode of acute pericarditis and a symptom-free interval of 4–6 weeks or longer[a].
Chronic	Pericarditis lasting for >3 months.

Myocardial involvement

Syndrome	Description	Clinical Findings
Pericarditis	Isolated pericardial inflammation	Pericarditic chest pain, ECG changes, pericardial effusion
Myopericarditis	Predominant pericardial inflammation	Pericarditis with abnormal Tn and/or CK
Perimyocarditis	Predominant myocardial inflammation	Myocarditis with pericarditic chest pain, ECG changes, pericardial effusion
Myocarditis	Isolated myocardial inflammation	Segmental or global ventricular dysfunction, signs/symptoms of heart failure



Etiology

May occur in isolation, or may be a manifestation of a systemic disorder (e.g. autoimmune disease); infectious vs. non-infectious

- "Idiopathic"
- Infectious
  - Viral (enteroviruses, parvovirus, etc.)
  - Fungal (histoplasmosis, coccidioidomycosis, candidiasis, etc.)
  - Bacetrial & mycobacterial (TB, etc.)
- Post-cardiac injury syndromes
  - Post-traumatic
  - Post-pericardiotomy syndrome
  - Peri-infarction pericarditis (pericarditis epistenocardica)
  - Subacute/delay post-infarction pericarditis (Dressler syndrome)
- Rheumatologic disease
  - SLE
  - RA
  - Systemic sclerosis
  - MCTD
  - Behcet's
  - Sarcoidosis
- Auto-inflammatory diseases (FMF, TRAPS, CAPS, Still's disease)
- ESRD (uremic & dialysis-associated) – usually effusive-constrictive
- Cardiac amyloidosis
- Aortic dissection (type A)
- Drugs -
  - Lupus-like: procainamide, hydralazine, methyldopa, isoniazid, phenytoin
  - Antineoplastic drugs: anthracyclines, cyclophosphamide, 5-FU
  - Anti-TNF drugs
  - Minoxidil
- Radiation heart disease
- Malignancy
- Graft-versus-host disease (GVHD)
- Pulmonary arterial hypertension (PAH)
- Chronic heart failure
- Myxedema
- Chylopericerdium
- Asbestosis
- Yellow nail syndrome
- IgG4-related diease
- Erdheim-Chester disease

Etiology

- "Idiopathic" (**80-90%** in the US & Western Europe, assumed to be post-viral)
- Tuberculosis (most common cause in developing countries)
- Post-cardiac injury syndromes
  - Post-infarction, post-pericardiotomy, post-PCI & EP procedures, trauma
- Autoimmune diseases
- Chest irradiation
- Malignancy

Extensive laboratory testing (including an ANA!) is not routinely recommended.

Testing for rheumatologic conditions should be considered if there is evidence of other organ involvement.

Initial Evaluation of Acute Pericarditis

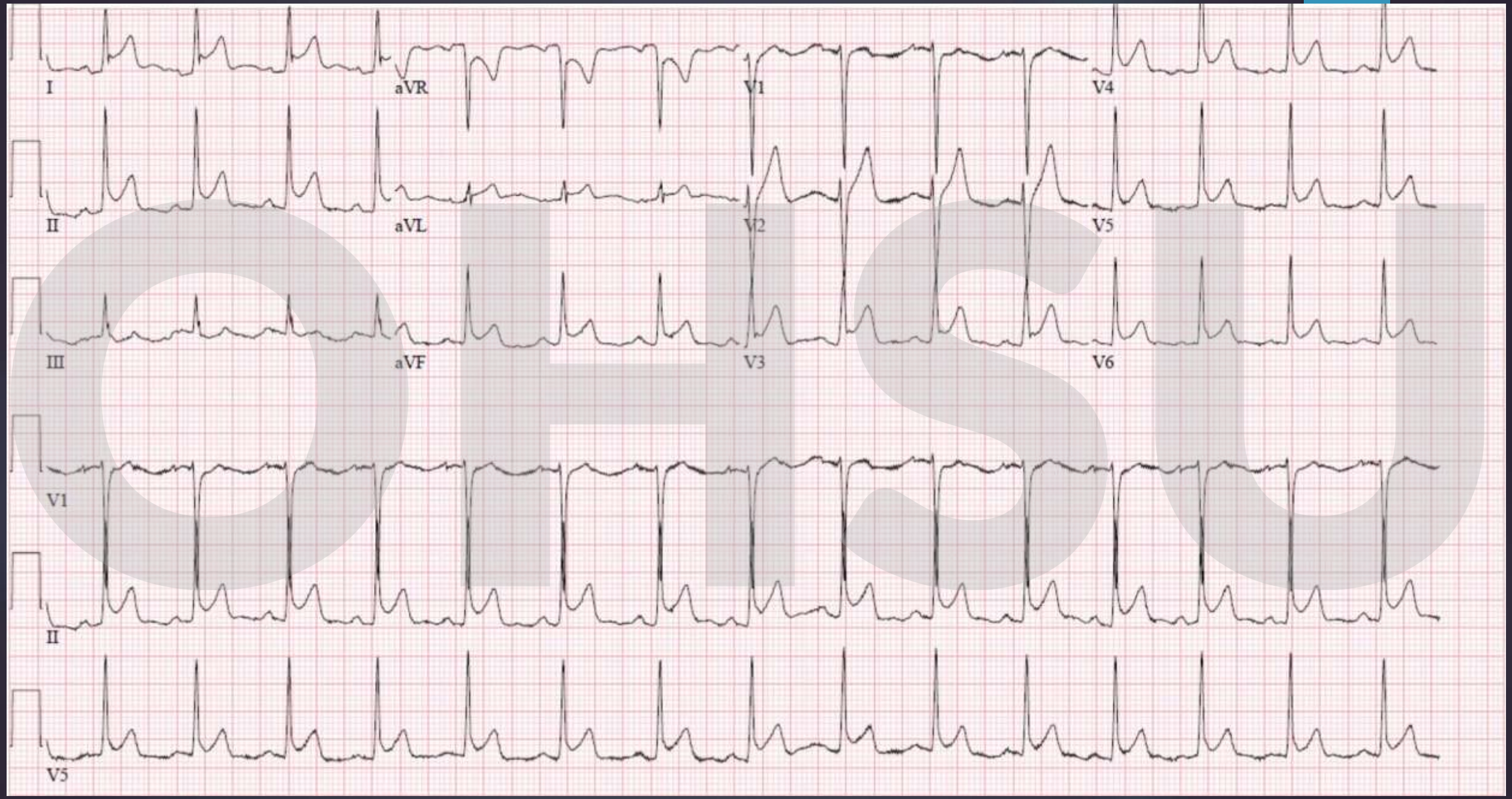
- H&P
- ECG
- CXR
- TTE (may show effusion, but normal in 40%)
- CRP and ESR (elevated in 80%)
- CBC (WBC sometimes elevated)
- CMP
- TSH
- Troponin

Recommendations	Class[a]	Level[b]	Ref.[c]
ECG is recommended in all patients with suspected acute pericarditis	I	C	
Transthoracic echocardiography is recommended in all patients with suspected acute pericarditis	I	C	
Chest X-ray is recommended in all patients with suspected acute pericarditis	I	C	
Assessment of markers of inflammation (i.e. CRP) and myocardial injury (i.e. CK, troponin) is recommended in patients with suspected acute pericarditis	I	C	

ECG

- ECG changes imply inflammation involving the epicardium. The parietal pericardium is electrically inert.
- DDx includes acute coronary syndrome (ACS) and early repolarization (ER)

- Stage 1: Diffuse PR depression & ST elevation
  - **STE** present in 60-90% of cases
  - **PRD** present in ~80% of cases, often present when ST changes are absent; PRE in aVR in ~100%!
- Stage 2 (1-5 days): ST segments normalize, T waves flatten
- Stage 3: T waves are inverted
- Stage 4: Normalization of the ECG


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1
II
V5

Chest X-ray

- Usually normal with acute pericarditis.
- Can be helpful in narrowing DDx:
  - Concomitant pleural disease – suggestive of certain disease processes which affect multiple serosal surfaces
  - Pericardial calcification suggest chronic constrictive pericarditis
  - The cardiothoracic ratio generally only increases once a pericardial effusion is > 300 ml.

Echocardiography

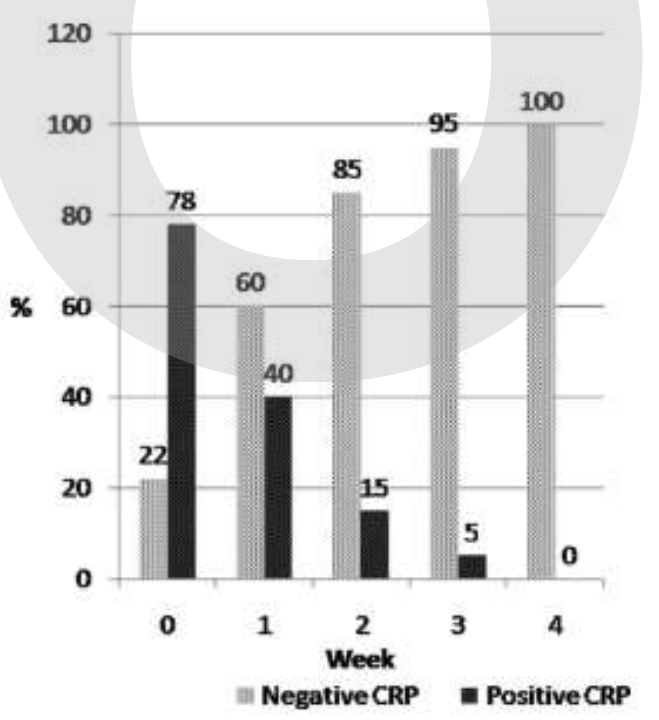
- Aides in differential diagnosis & risk stratification
- May identify a pericardial effusion
  - **Small** : < 10 mm (in diastole)
  - **Moderate** : 10-20 mm
  - **Large** : ≥ 20 mm
- May identify pericardial tamponade
- May identify features of constrictive pericarditis
- May identify wall motion abnormalities signifying myocardial infarction (MI) or concomitant myocardial involvement (perimyocarditis)

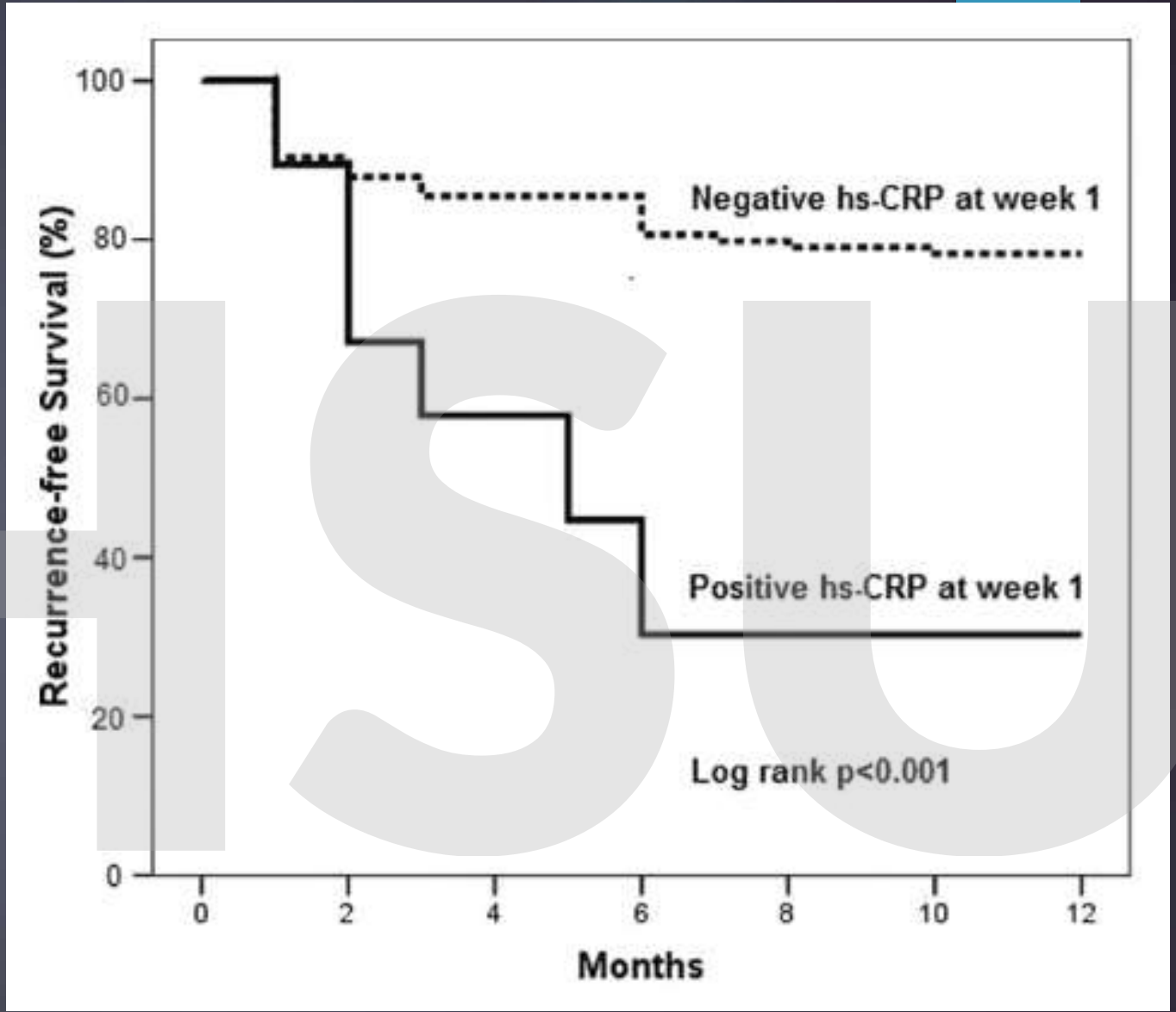
Inflammatory Markers & Cardiac Enzymes

- Erythrocyte sedimentation rate (ESR)
- C-reactive protein (CRP)
- White blood cell count
- Creatine kinase (CK) & troponin (in myopericarditis)

CRP

- Elevated > 3 mg/L in **80%**, but in **97%** pts not on any anti-inflammatory drugs
- May also be normal if tested within the first 6-12 hours of symptom onset (**97%** abnormal after that)
- Typically normalizes by 2-4 weeks in acute pericarditis
- Degree of elevation predicts complications
- Persistent elevation predicts recurrence



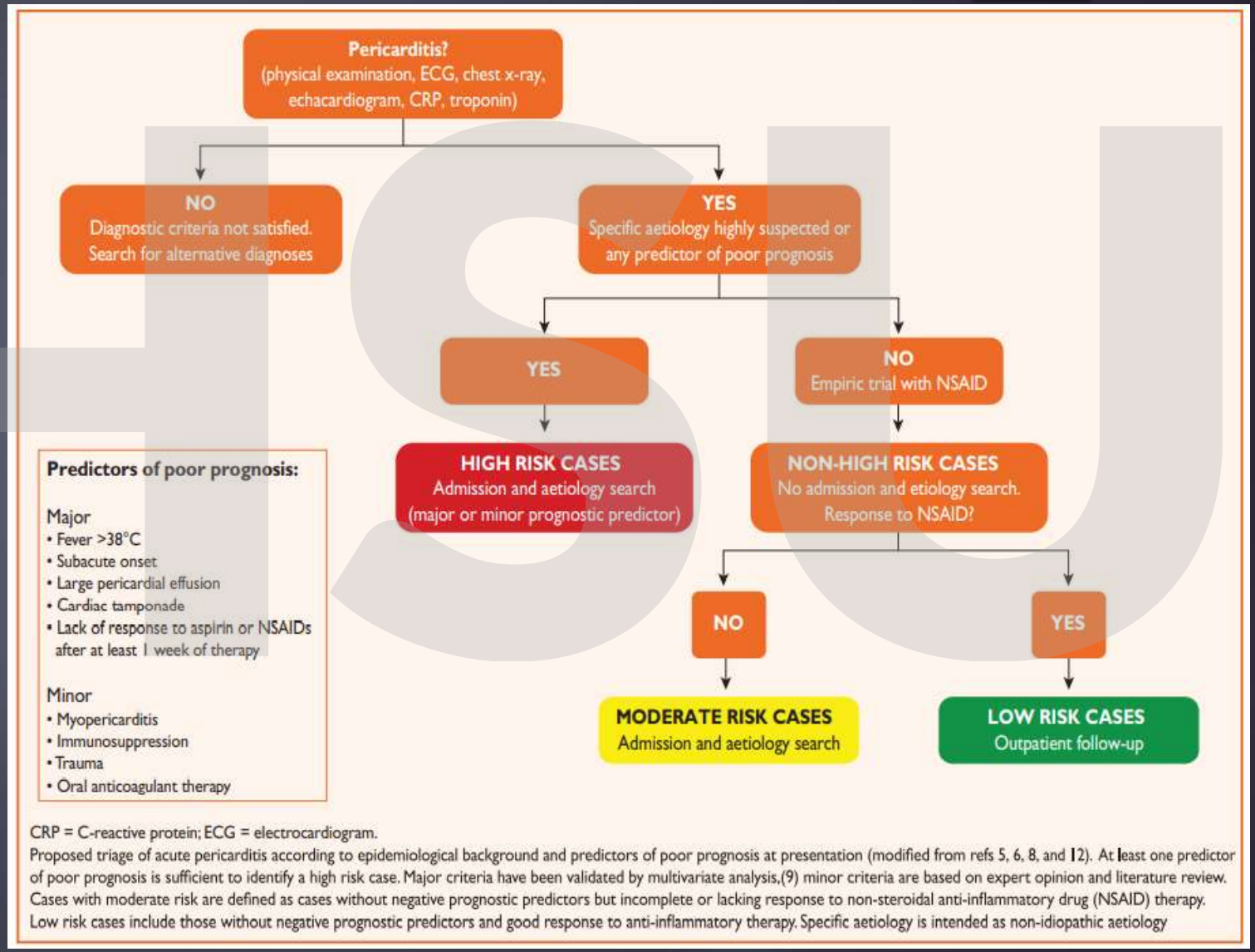


Imazio et al C-Reactive Protein for Acute Pericarditis *Circulation* March 15, 2011

IMAJ • VOL 21 • NOVEMBER 2019

Further Work Up of Acute Pericarditis

- Most cases of acute pericarditis are idiopathic and an extensive etiologic investigation will be unfruitful, unless the H&P are suggestive of a specific etiology
- Cases with elevated troponin may require **ICA** or **CCTA** to rule out ACS
- **CMR** may be helpful if there is uncertainty regarding the Dx or in cases where there is concern for more extensive myocardial involvement / myocarditis



CRP = C-reactive protein; ECG = electrocardiogram.
Proposed triage of acute pericarditis according to epidemiological background and predictors of poor prognosis at presentation (modified from refs 5, 6, 8, and 12). At least one predictor of poor prognosis is sufficient to identify a high risk case. Major criteria have been validated by multivariate analysis,(9) minor criteria are based on expert opinion and literature review. Cases with moderate risk are defined as cases without negative prognostic predictors but incomplete or lacking response to non-steroidal anti-inflammatory drug (NSAID) therapy. Low risk cases include those without negative prognostic predictors and good response to anti-inflammatory therapy. Specific aetiology is intended as non-idiopathic aetiology

Further Work Up

- **Autoimmune**: ANA/ENA, ANCA, ACE, 24-hr urine calcium, ferritin, FDG-PET (for vasculitis or sarcoidosis)
- **TB:** IGRA, chest CT, pericardial AFB stain/Cx, TB PCR, ADA, IFN-gamma, sputum AFB/Cx, pericardial biopsy
- **Malignancy**: chest/abdomen CT +/- PET, pericardial fluid cytology, tumor markers, pericardial biopsy
- **Viral infections**: consider HIV, HCV serology, viral PCR
- **Bacterial infections**: consider BCx, Coxiella serology (Q fever), Borrelia serology (Lyme disease), chest CT, pericardial fluid GS/Cx, pericardial fluid glucose, +/- pericardial biopsy
- **Auto-inflammatory disease**: NGS panel (esp. FMF, TRAPS, CAPS genes) – esp. if familial, poor response to colchicine, periodic fever

Physical Activity Restriction

- Physical activity restriction
  - No more than limited walking (e.g. day-to-day sedentary activities) until resolution of symptoms and normalization of CRP
  - Athletes are advised restriction of at least 3 months and until normalization of CRP, ECG, and TTE

ASA and NSAIDs

Drug	Usual Dose	Minimal Duration*	Tapering
Aspirin	650 – 1000 mg q8h	1 – 2 weeks	Decrease by 250-500 mg every 1-2 weeks
Ibuprofen	600 - 800 mg q8h	1 – 2 weeks	Decrease by 200-400 mg every 1-2 weeks
Indomethacin	25 – 50 mg q8h	1 – 2 weeks	Decrease by 25 mg every 1-2 weeks

- ASA is preferred in cases of post-infarction pericarditis / concomitant ASCVD
- Indomethacin is more often used for recurrent pericarditis ***
- Ketorolac IV may be an option for patients unable to take PO medications
- Duration should be guided by symptoms and CRP, may be extended
- In low-risk cases, tapering may begin once the patient is symptom-free for at least 24 hours
- In most cases, tapering should begin only after the CRP is normalized

Colchicine

Drug	Usual Dose	Minimal Duration*	Tapering
Colchicine	0.5-0.6 mg QD (<70 kg) 0.5-0.6 mg BID (>70 kg)	3 months	Not mandatory. May consider reducing to QD dosing, then QOD in the last few weeks of treatment.

- Colchicine should be added in all patients with acute idiopathic or viral pericarditis or post-cardiac injury syndromes without contra-indications.
- GI intolerance develops in 5-10%. Improved by not loading, and by reducing the dose.
- **COPE:** open-label trial of 120 patients with acute pericarditis. Recurrence was 11% with colchicine + ASA vs. 32% with ASA alone.
- **ICAP:** randomized, double-blind study of colchicine vs. placebo added to standard NSAID/ASA therapy. 240 patients. Recurrence was 17% vs. 38%. RRR = 0.56 (95% CI 0.30-0.72)

Colchicine halves the recurrence rate!

Corticosteroids

- Second-line option when NSAIDs or ASA have either failure or are contra-indicated; or used to treat pericarditis related to a specific etiology (e.g. autoimmune condition)
- **Use of corticosteroids increases the likelihood of recurrence and disease chronicity**
- Low initial doses are recommended (e.g. prednisone 0.2-0.5 mg/kg/day), maintained without tapering until symptom resolution and CRP normalization
- Once the CRP is normalized, the steroid is tapered VERY slowly

Gastrointestinal Protection

- ASA/NSAIDs should not be prescribed longer than is necessary
- Addition of a PPI (e.g. omeprazole, etc.) is recommended for:
  - History of peptic ulcer disease
  - Age > 60
  - Concurrent antiplatelet drugs (ASA, clopidogrel), corticosteroids, or anticoagulation
  - Dyspepsia or GERD
- Patients with peptic ulcer disease should be tested & treated for *H. pylori* if not already done

Bhatt *et al.*
ACCF/ACG/AHA Expert Consensus Document: Antiplatelets, NSAIDs, and GI Risk

JACC Vol. 52, No. 18, 2008
October 28, 2008:1502–17

Follow Up

- All patients should have close follow up to ensure resolution of symptoms and normalization of CRP
- Failure to respond to NSAID/ASA therapy can suggest an underlying autoimmune disorder or other specific etiology
- Approximately 15-30% of patients with acute idiopathic pericarditis develop recurrent or incessant disease, especially if not treated with colchicine
- Constrictive pericarditis occurs in <1% of patients with acute idiopathic pericarditis, and is also very low in recurrent idiopathic pericarditis, but 2-5% of patients with autoimmune etiologies, and 20-30% for bacterial/TB/purulent pericarditis

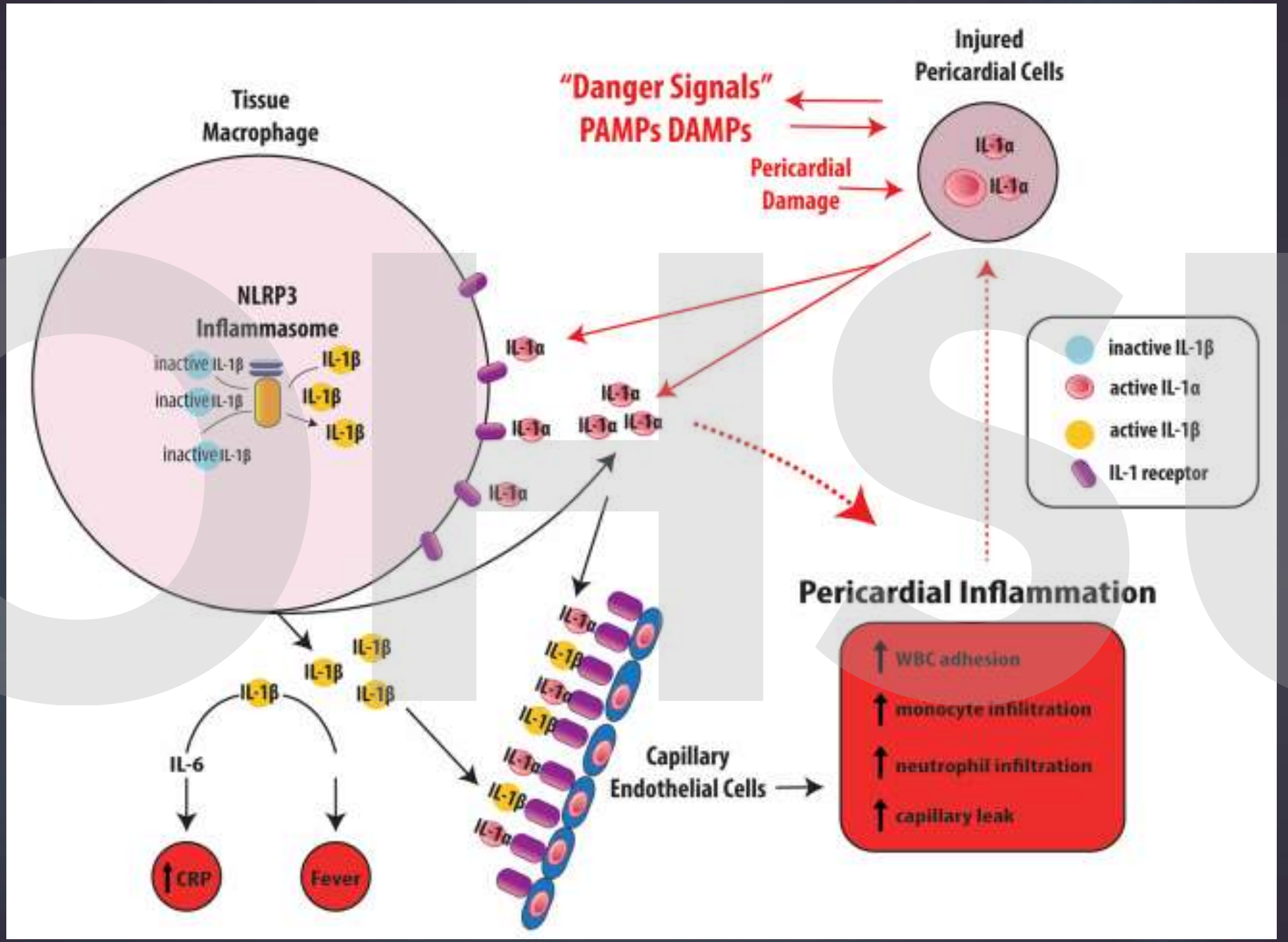
Recurrence – Etiology & Risk Factors

- Etiology
  - Inadequate / incomplete initial treatment
  - Deranged local immune response
  - Underlying autoimmune or autoinflammatory disease
- Risk Factors
  - Inconsistent use or early discontinuation of NSAID/ASA
  - Incomplete response to NSAID/ASA
  - Persistent CRP elevation
  - Corticosteroid use
  - Colchicine non-use

The Innate Immune Response & Inflammasome

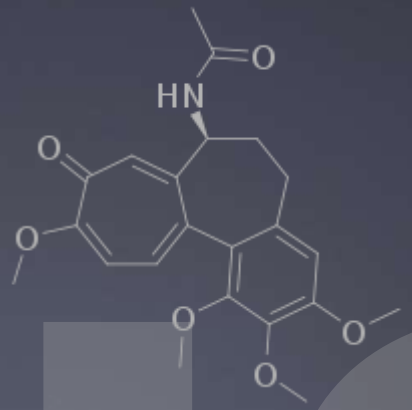
- Innate immune response plays a pivotal role in idiopathic & recurrent pericarditis
- Inflammasomes are an integral part of the innate immune system
- Respond to molecular patterns from tissue injury and pathogens (DAMPs and PAMPs) via Toll-like receptors (TLRs)
- The **NLRP3 inflammasome** is the best understood; once activated, this leads to release of IL-1, which recruits myeloid cells to the site of injury/infection

- Shared mechanisms with autoinflammatory / periodic fever disorders -- and some patients with recurrent pericarditis may have mild forms of autoinflammatory disorders
  - Gain-of-function mutation in NLRP3 → **CAPS** (cryopyrin-associated periodic syndromes), autosomal dominant autoinflammatory disorder
  - Missense mutations in the TNFα receptor → **TRAPS**
  - Pyrin (*MEFV)* mutation → **FMF** (familial Mediterranean fever) – **8%** of idiopathic recurrent pericarditis patients are heterozygous for pathogenic or likely pathogenic *MEFV* variants (European population)



Current Cardiology Reports (2022) 24:23–30

Colchicine is an Inflammasome Inhibitor



- Colchicine is an alkaloid extracted from the roots of the autumn crocus (*Colchicum autumnale*), a common garden flower native to Europe
- In use since antiquity for treatment of gout
- Also used for familial Mediterranean fever (FMF) & other autoinflammatory diseases, Behcet's disease, pericarditis, and coronary artery disease
- Binds **tubulin** monomers → blocks microtubule assembly → interferes with cell migration (**chemotaxis**) and mitosis (esp. affecting leukocyte function)
- **Interferes with inflammasome assembly**, thus acting to reduce IL-1β release

Y.Y. Leung et al. / Seminars in Arthritis and Rheumatism 45 (2015) 341–350

Colchicine Trials in Pericarditis

Trial	Date	*N*	Setting	Intervention	Outcome
COPE	2005	120	Acute pericarditis	ASA + colchicine vs. ASA [open label]	Recurrence rate: 11% vs. 32% (at 18 mo)
ICAP	2013	120	Acute pericarditis	Colchicine vs. placebo [randomized, double-blind, added to std tx]	Recurrent/incessant rate: 17% vs. 38% (at 18 mo)
CORE	2005	84	Recurrent pericarditis	ASA + colchicine vs. ASA [open label]	Recurrence rate: 24% vs. 51% (at 18 mo)
CORP	2011	120	Recurrent pericarditis	Colchicine vs. placebo [randomized, double-blind, added to std tx]	Recurrence rate: 24% vs. 55% (at 18 mo)
CORP-2	2014	240	Multiply Recurrent pericarditis	Colchicine vs. placebo [randomized, double-blind, added to std tx]	Recurrence rate: 22% vs. 43% (at 20 mo)
COPPS	2010	360	Post-pericardiotomy	Colchicine vs. placebo [randomized, double-blind, added to std tx]	PPS occurrence at 12 mo: 9% vs. 21%.
COPPS-2	2014	360	Post-pericardiotomy	Colchicine vs. placebo [randomized, double-blind, added to std tx]	PPS occurrence at 3 mo: 19% vs. 29%. Increased GI side fx.

Complicated Pericarditis

- **Recurrent Pericarditis** : Diagnosed with acute pericarditis recurs after a symptom-free interval of >4 weeks
- **Incessant Pericarditis** : Acute pericarditis which persists without clear-cut remission for >4-6 weeks
- **Chronic Pericarditis** : Pericarditis which persists for > 3 months.

- Diagnosis of recurrence or persistence follows the same criteria as for acute pericarditis, but may be aided in atypical or difficult cases via CT or CMR.

Clinical Stages of Pericarditis With Imaging and Treatment Considerations

Stage of pericarditis	Acute	First recurrence	Multiple recurrences	Colchicine-resistant or steroid dependent	Constrictive
Imaging 	• Echocardiogram for pericardial effusion, myocardial involvement, constriction	• Echocardiogram for constriction • CMR in select cases for pericardial inflammation or constriction	Same as for "first recurrence"	Same as for "first recurrence"	Same as for "first recurrence" Plus possible CT for extent of calcification and preoperative planning
Treatment 	• NSAIDS (weeks) • Colchicine (3 mos.)	• NSAIDS (wks–mos.) • Colchicine (≥6 mos.)	• NSAIDS + Colchicine + Prednisone (>6 mos., taper steroid as tolerated) • Consider steroid-sparing agent (warrants further study)	• NSAIDS + Colchicine + Prednisone + Steroid-sparing agent (>6–12 mos., taper steroid as tolerated) • Consider pericardiectomy (warrants further study)	• Intensify medical therapy if inflamed • Pericardiectomy if "burnt out"

Cremer, P.C. et al. J Am Coll Cardiol. 2016;68(21):2311-28.

Recurrent Pericarditic Pain without Objective Evidence of Disease

- May develop in up to 10% of patients following acute pericarditis
  - Risk factors : female sex, corticosteroid use, hx of recurrent pericarditis
  - May represent subclinical recurrence OR may be related to central pain sensitization / supratentorial
- Patients present with typical pericarditic pain but absence of a pericardial rub, ECG changes, inflammatory markers, pericardial effusion, and (if done) absence of pericardial inflammation by CT or MRI
- Recurrent pain may be a harbinger of recurrence of objective disease
- These patients should be monitored for recurrence . Consider repeat ECGs, ESR, and CRP for recurrent pain episodes.
- Typically treated with NSAIDs/ASA and other analgesics (e.g. APAP)
- Steroids and immunosuppressive medications should be avoided

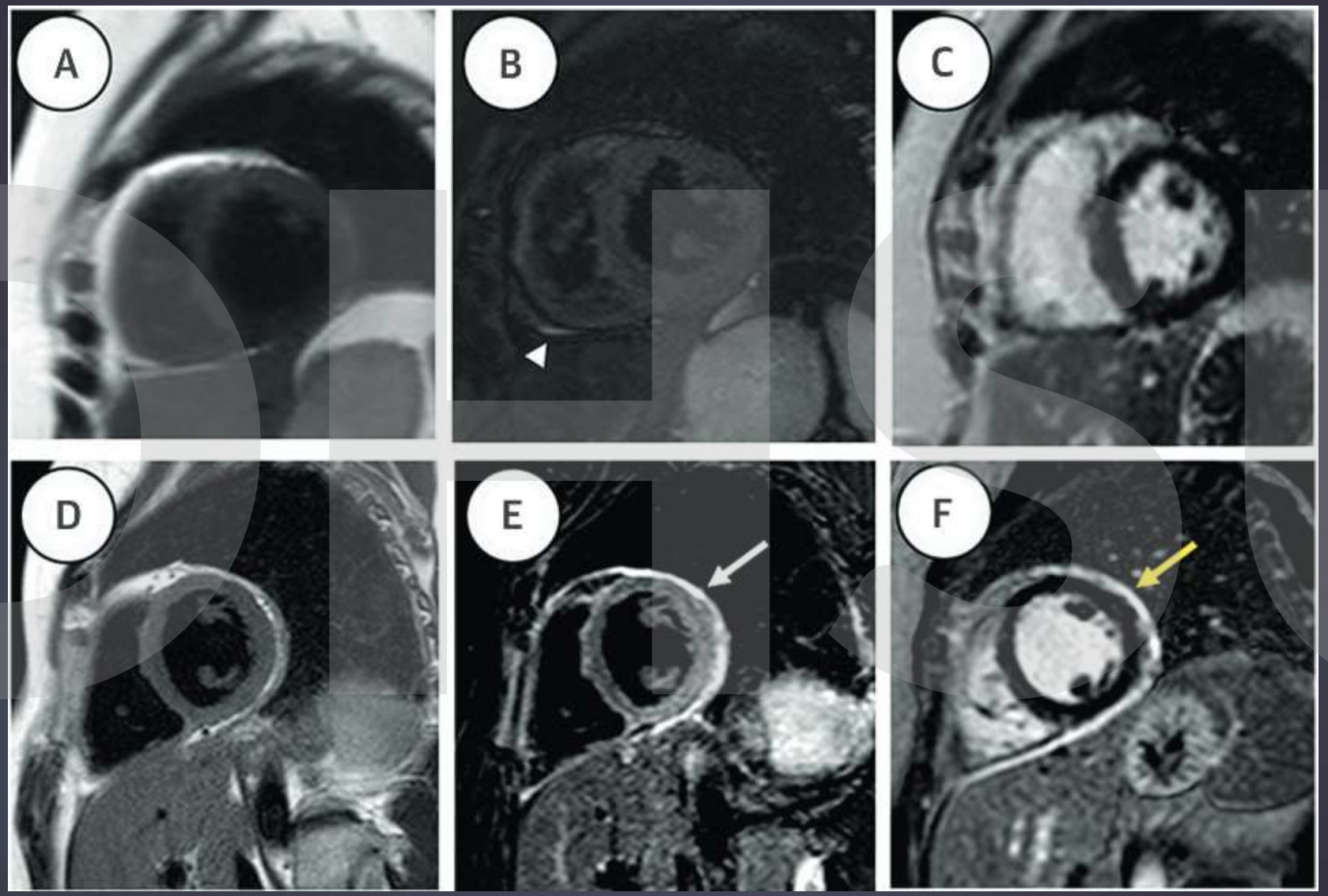
THE AMERICAN JOURNAL OF CARDIOLOGY® VOL. 94 OCTOBER 1, 2004
doi:10.1016/j.amjcard.2004.06.046

Evaluation of Complicated Pericarditis

- H&P
- ECG
- CXR
- TTE
- CRP and ESR
- CBC
- Troponin
- +/- ANA/ENA
- +/- CMR

CMR

- Allows one to answer 2 questions with greater confidence:
  - **Does this patient (still) have significant pericardial inflammation?**
    - To clarify diagnosis (e.g. recurrent pericarditic pain but no other criteria for pericarditis)
    - To guide need for and selection of more intensive therapy
    - To allow for tapering of medications
  - **Does this patient have constrictive physiology?**
- Via evaluation of:
  - Pericardial thickness (normal is < 1-2 mm, > 4 mm is definitely abnormal)
  - Pericardial edema
  - Pericardial inflammation ("late gadolinium enhancement", LGE)
  - Ventricular interdependence



JACC VOL. 68, NO. 21, 2016
NOVEMBER 29, 2016:2311–28

TABLE 2 Practical Considerations in the Current Use of CMR to Evaluate Pericarditis

Assessment	Method	Strengths	Limitations
Pericardial thickness	T_1- or T_2-weighted fast-spin echo images (36)	• Extent of pericardial thickness appreciated • Often abnormal in patients with constrictive pericarditis	• In-plane spatial resolution limits assessment of normal or mildly thickened pericardium (46) • Some patients with constrictive pericarditis may have normal pericardial thickness
Pericardial edema	T_2 short-tau inversion-recovery fast-spin echo images (36)	• Likely a specific finding for active pericarditis	• Difficult to distinguish from pericardial effusion (48)
Pericardial inflammation	Late gadolinium enhancement (36,51)	• Increased pericardial enhancement reflects increased vascularity (53) • Potential use of "ruling in" or "ruling out" pericarditis in equivocal cases (49,56)	• Correlation with different stages of pericarditis still being defined
Ventricular interdependence	Cine imaging with short-axis images at the basal level with patients instructed to breathe deeply (36)	• Relative septal excursion may be a specific finding for constrictive pericarditis (45,46)	• Patient respiratory effort can influence diagnostic yield

CMR = cardiac magnetic resonance.

Usefulness of Cardiac Magnetic Resonance–Guided Management in Patients With Recurrent Pericarditis

M. Chadi Alraies, MD[a,*], Wael AlJaroudi, MD[b], Hirad Yarmohammadi, MD, MPH[a], Teerapat Yingchoncharoen, MD[a], Andres Schuster, MD[a], Alpana Senapati, MD[a], Muhammad Tariq, MD[a], Deborah Kwon, MD[a], Brian P. Griffin, MD[a], and Allan L. Klein, MD[a]

- Single-center non-randomized study of **507** pts with recurrent pericarditis
- 257 had CMR-guided therapy
- 250 had no CMR
- Similar baseline characteristics
- CMR-guided therapy was associated with fewer subsequent recurrences, less corticosteroid use (lower HbA1c!), & fewer pericardiocenteses

Am J Cardiol. 2015; 115:542-547

CT

- In the setting of pericarditis, may demonstrate non-calcified pericardial thickening +/- effusion.
- Pericardium may enhance with administration of contrast
- Attenuation (CT values) of an effusion may help to narrow the DDx
  - Simple serous effusion : <10-25 HU
  - Exudate : > 25 HU (e.g. malignancy, myxedema, purulence)
  - Hemopericardium: > 60 HU
- May identify & characterize pericardial calcification
  - Even very small amounts of calcification are highly suggestive of constrictive pericarditis

Recurrent Pericarditis Treatment

- Physical activity restriction
- ASA/NSAIDS + colchicine
- Colchicine is typically continued at least 6 months
- ASA/NSAIDS + colchicine + low-dose corticosteroids
- Tapering is done one medication at a time, and only if symptoms have resolved and CRP normalized
- Intensity & duration of anti-inflammatory therapy guided by the phenotype (inflammatory vs. non-inflammatory)

Anti-interleukin-1 agents

	Anakinra	Cankinumab	Rilonacept
Mechanism	Recombinant protein inhibitor of IL-1α and IL-1β	Monoclonal IgG inhibitor of IL-1β	Dimeric fusion protein inhibitor of IL-1α and IL-1β
Administration	SC/IV	SC	SC
Dosing	No loading dose 100 mg **daily** (if > 50 kg)	No loading dose 4 mg/kg or 150 mg q4-8 wks	Loading 320 mg, then 160 mg **weekly**
Renal dose adjustment	**Consider QOD dosing for eGFR < 30**	None	None
Half-life	4-6 h	26 d	7 d
Adverse effects	Injection site reactions, infections, hepatitis	Injection site reactions, infections, neutropenia	Injection site reactions, infections, dyslipidemia, neutropenia
Monitoring	Baseline TB & HBV/HCV screen, serial CBC & CRP	Baseline TB screen, serial CRP & CBC	Serial CRP & CBC
Pericarditis studies	**AIRTRIP**	n/a	**RHAPSODY**

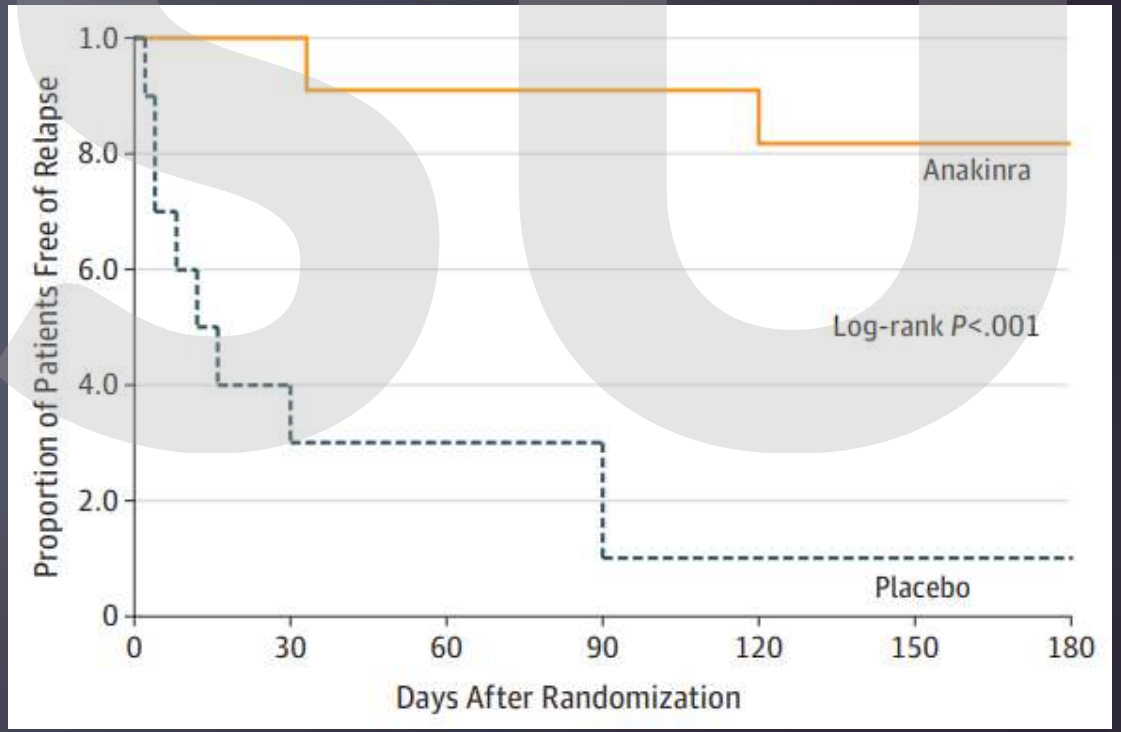
JAMA | Preliminary Communication

Effect of Anakinra on Recurrent Pericarditis Among Patients With Colchicine Resistance and Corticosteroid Dependence

The AIRTRIP Randomized Clinical Trial

Antonio Brucato, MD; Massimo Imazio, MD, FESC; Marco Gattorno, MD; George Lazaros, MD; Silvia Maestroni, MD; Mara Carraro, RN; Martina Finetti, MD; Davide Cumetti, MD; Alessandra Carobbio, MSc; Nicolino Ruperto, MD, MPH; Renzo Marcolongo, MD; Monia Lorini, MD; Alessandro Rimini, MD; Anna Valenti, MD; Gian Luca Erre, MD; Maria Pia Sormani, PhD; Riccardo Belli, MD; Fiorenzo Gaita, MD; Alberto Martini, MD

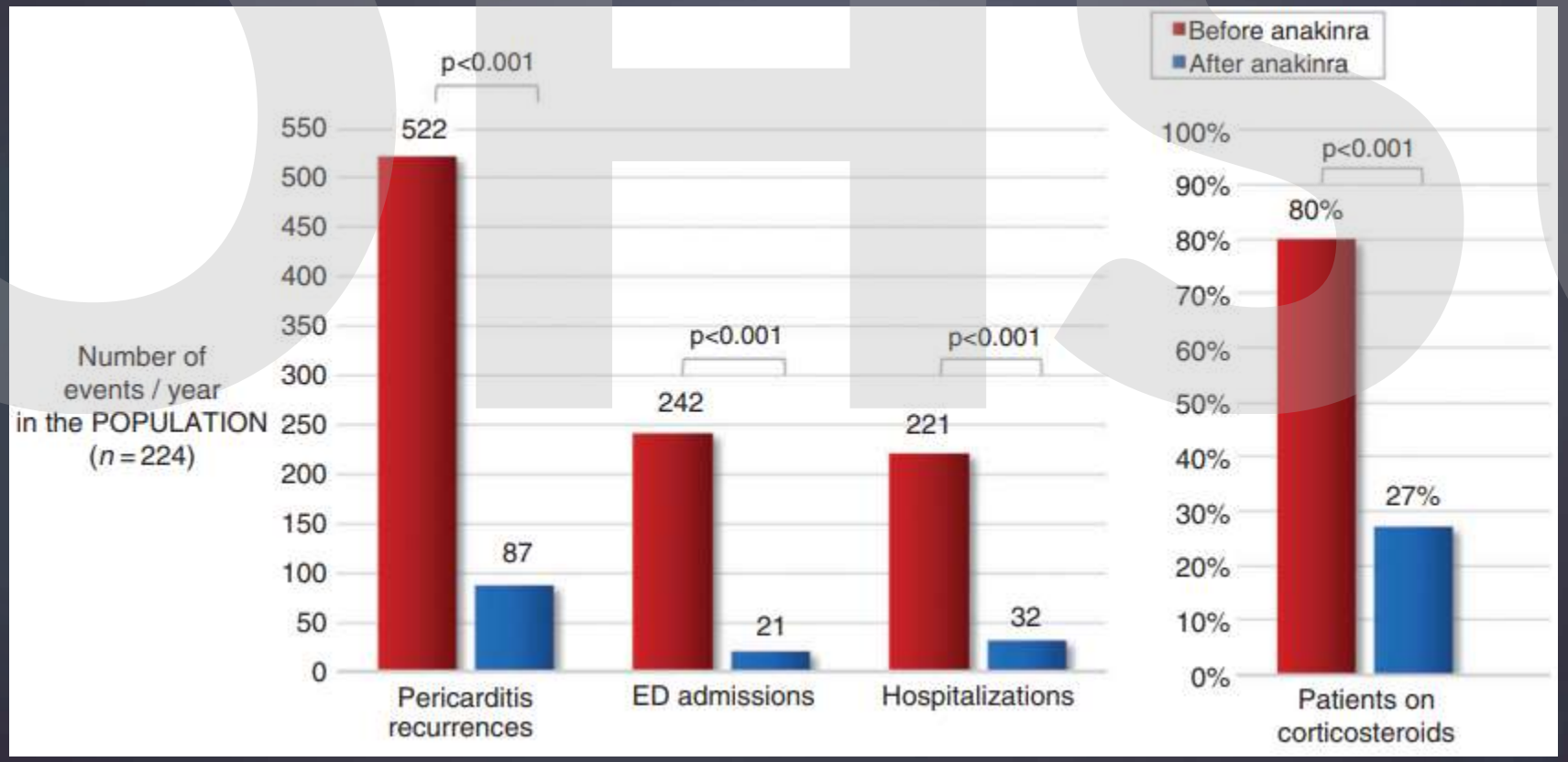
- Open-label treatment period of 60 days, then a double-blind withdrawal period where patients who had a response were randomized to continued anakinra vs. placebo x 6 months
- 21 patients were enrolled: all had recurrent idiopathic pericarditis (with ≥ 3 prior recurrences), with elevated hsCRP (> 1 mg/dl) and corticosteroid dependence
- Patients with secondary causes of pericarditis (bacterial infections, malignancy, cardiac injury, autoimmune disease) were excluded
- All 21 patients had response to anakinra (decreased pain, normalized CRP)
- Withdrawal of anakinra lead to relapse in 90% of placebo patients. 2 of 11 patients (18%) on anakinra relapsed.



JAMA. 2016;316(18):1906-1912. doi:10.1001/jama.2016.15826

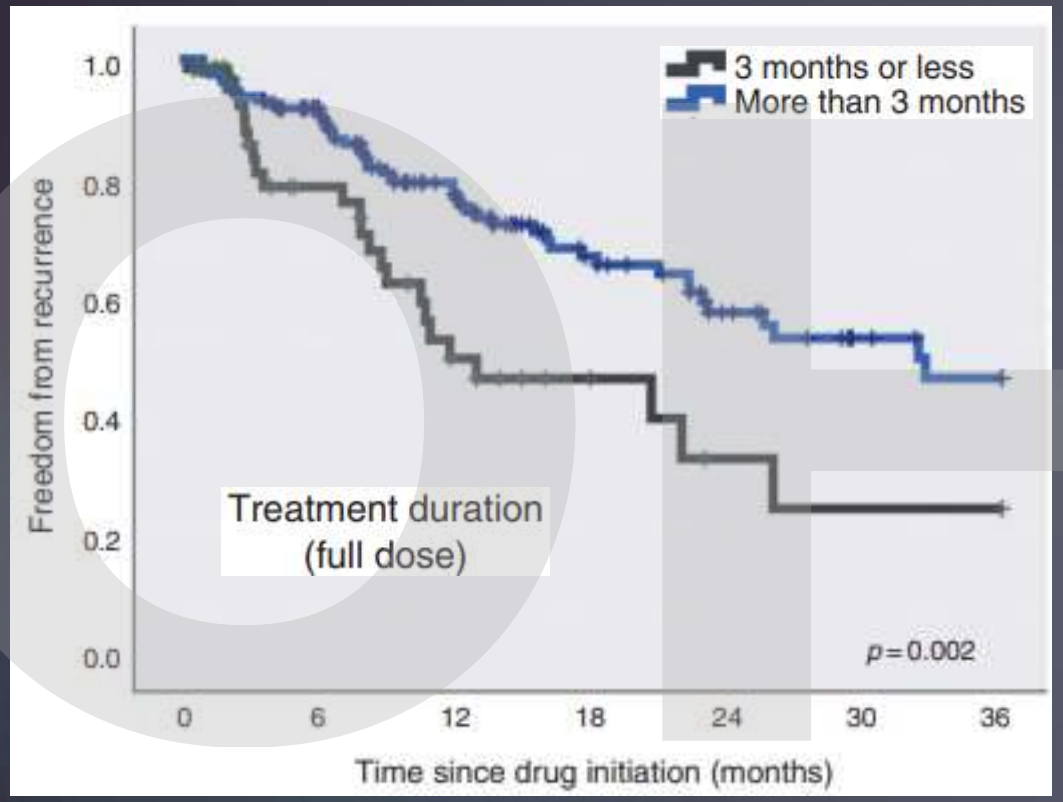
IRAP (International Registry of Anakinra for Pericarditis)

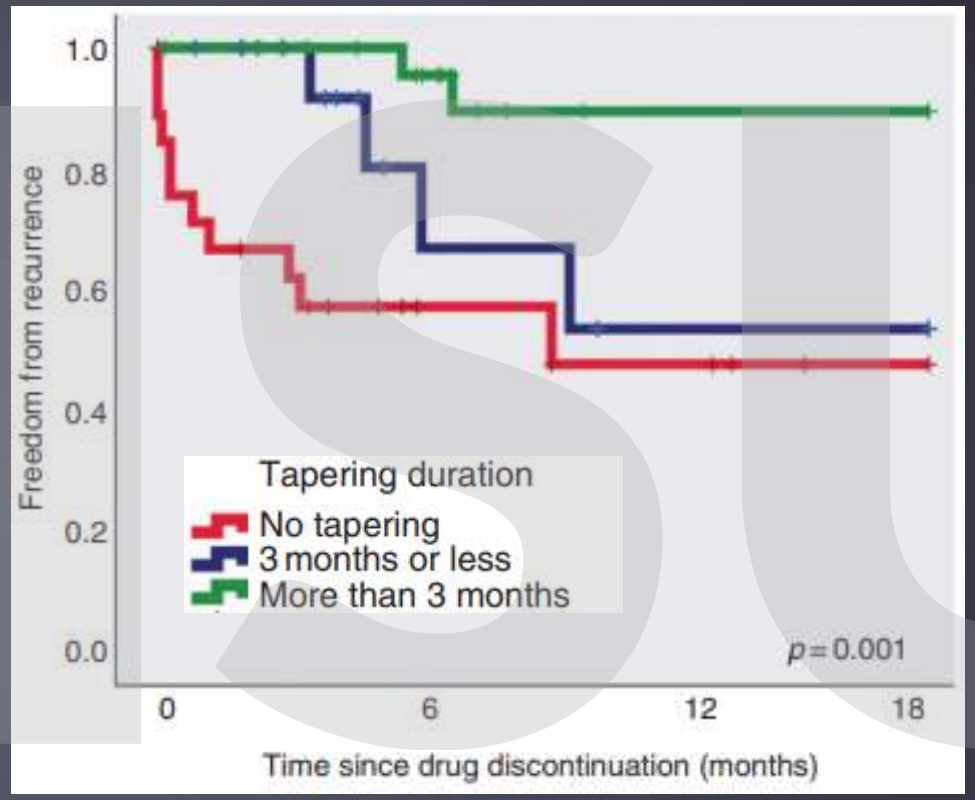
- International registry of anakinra use in pericarditis (all patients with colchicine-resistant, corticosteroid-dependent recurrent pericarditis, with at least 2 recurrences).



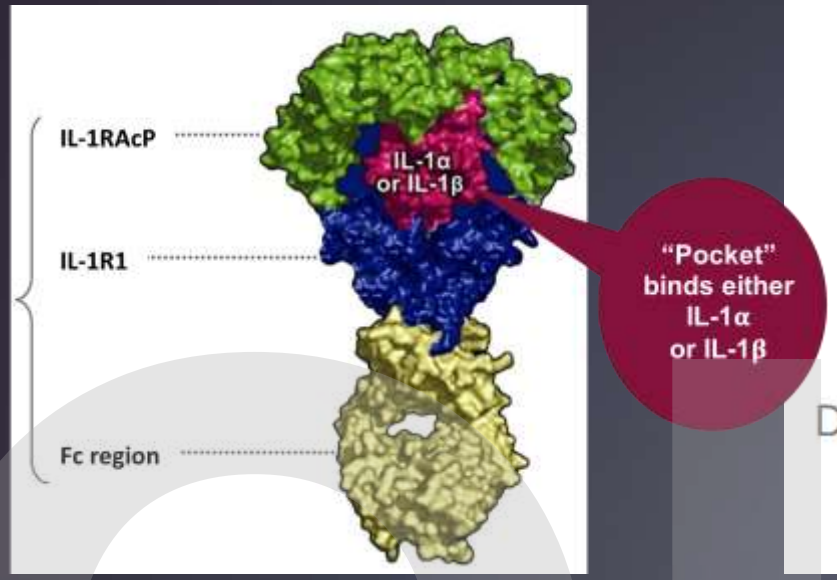
European Journal of Preventive Cardiology
2020, Vol. 27(9) 956–964

How long to continue?





- Treatment duration > 3 months (full dose) is associated with lower relapse risk
- Slow taper (> 3 months on reduced dose) is associated with lower relapse risk

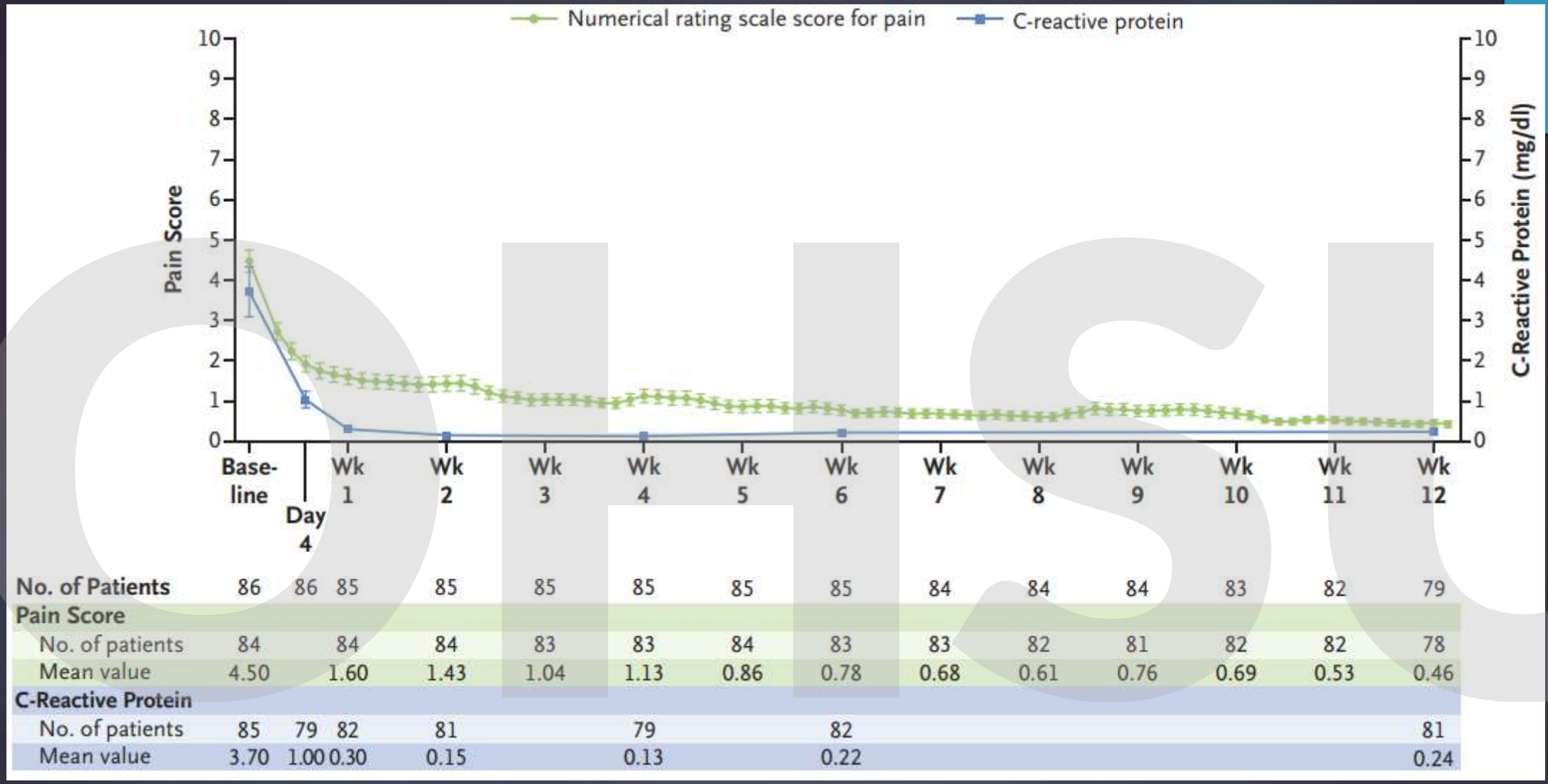


Phase 3 Trial of Interleukin-1 Trap Rilonacept in Recurrent Pericarditis

Allan L. Klein, M.D., Massimo Imazio, M.D., Paul Cremer, M.D., Antonio Brucato, M.D., Antonio Abbate, M.D., Ph.D., Fang Fang, Ph.D., Antonella Insalaco, M.D., Martin LeWinter, M.D., Basil S. Lewis, M.D., David Lin, M.D., Sushil A. Luis, M.B., B.S., Stephen J. Nicholls, M.B., B.S., Ph.D., Arian Pano, M.D., Alistair Wheeler, M.D., and John F. Paolini, M.D., Ph.D., for the RHAPSODY Investigators*

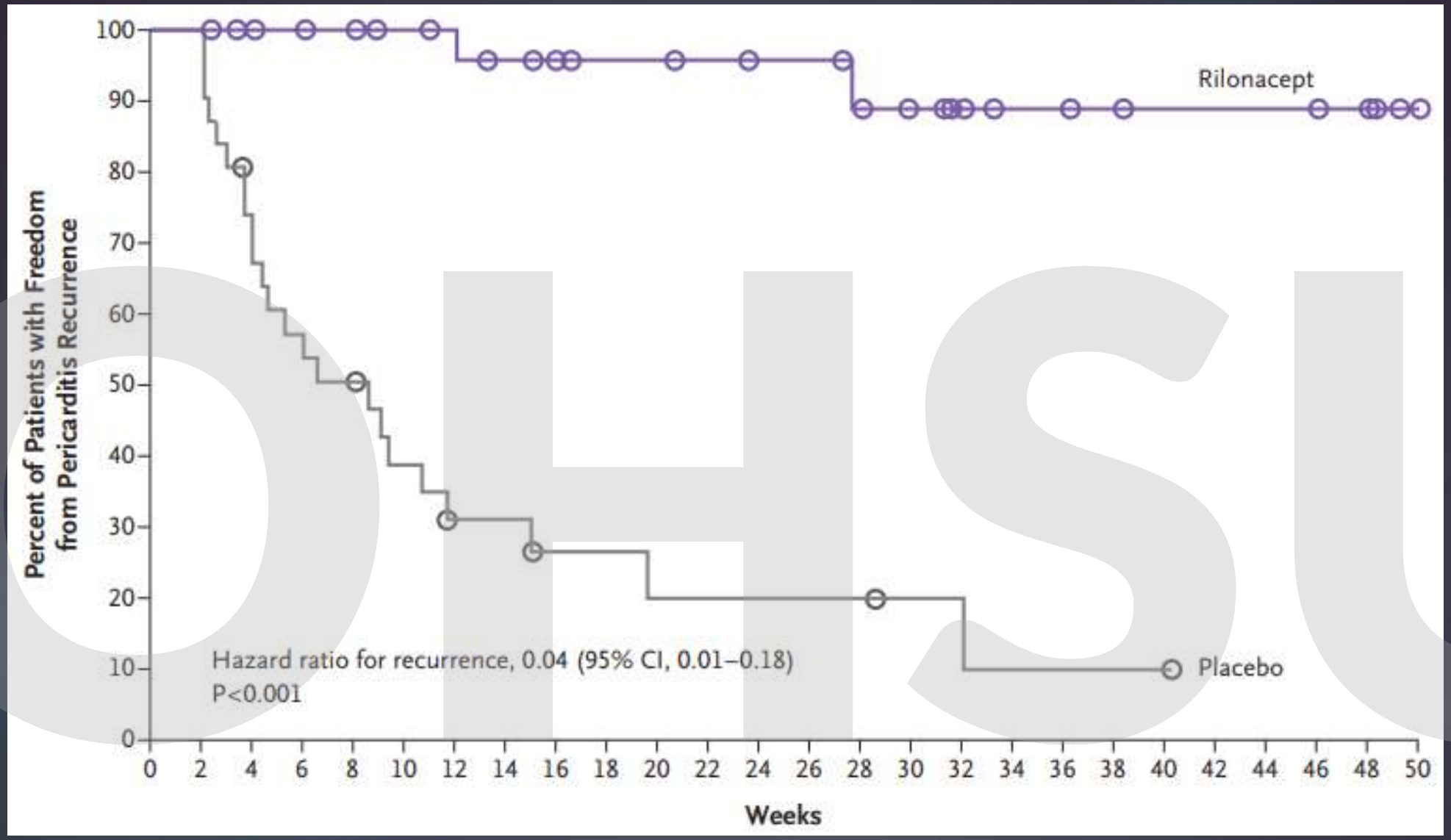
- Patients had a history of multiple recurrences (≥2) and were experiencing a recurrence at the time of enrolment, despite treatment with NSAIDs, colchicine, or corticosteroids (in any combination), and also had an hsCRP > 1 mg/dl
- Trial consisted of a 4 week screening period, 12 week run-in period (all patients received rilonacept & had other meds tapered during this period), and a randomized withdrawal period (rilonacept vs. placebo)
- 141 patients were screened and 86 patients enrolled and 61 completed the withdrawal period

N Engl J Med 2021;384:31-41.
DOI: 10.1056/NEJMoa2027892



No. of Patients	86	86	85	85	85	85	85	85	84	84	84	83	82	79
Pain Score														
No. of patients	84		84	84	83	83	84	83	83	82	81	82	82	78
Mean value	4.50		1.60	1.43	1.04	1.13	0.86	0.78	0.68	0.61	0.76	0.69	0.53	0.46
C-Reactive Protein														
No. of patients	85	79	82	81		79		82						81
Mean value	3.70	1.00	0.30	0.15		0.13		0.22						0.24

- Rapid, sustained response in almost all patients during run-in period



- Rilonacept was very effective in preventing recurrence. 7% in the rilonacept arm and 74% in the placebo arm
- Adverse effects were generally mild – most commonly URIs and injection site reactions. LDL and TG rose modestly.

Others

- AZA
- IVIG
- Cyclophosphamide
- Cyclosporine
- Methotrexate
- HCQ
- Anti-TNF agents
- Pericardiectomy

Other Pericardial Syndromes

PERICARDIAL EFFUSION , TAMPONADE, AND CONSTRICTION

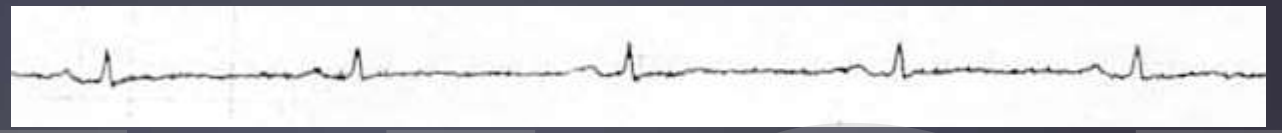
Pericardial Effusion

- Normal pericardium contains up to 50 ml of pericardial fluid
- Pericardial fluid may accumulate due to an inflammatory process (pericarditis), increased systemic venous pressure, or impaired lymphatic function
- Effusions are classified by **timing/onset, size, distribution, and composition**
- Many cases are asymptomatic, incidental findings

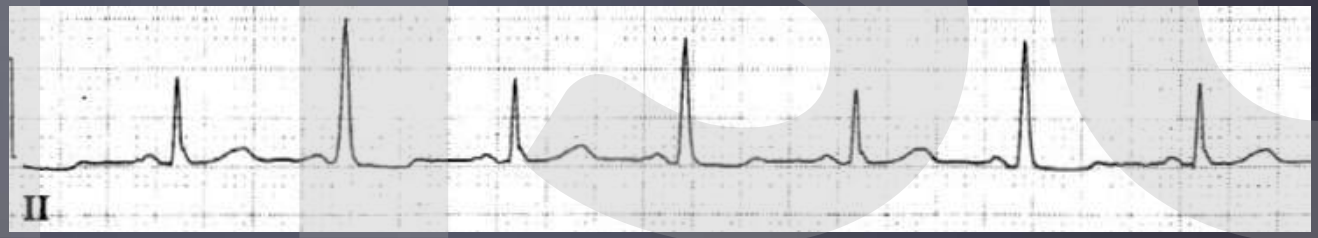
Onset	Acute Subacute Chronic (>3 months)
Size	Mild <10 mm Moderate 10–20mm Large >20 mm
Distribution	Circumferential Loculated
Composition	Transudate Exudate

- May also present w/ progressive DOE, orthopnea, nausea, dysphagia, hoarseness, hiccups

The ECG in pericardial effusions



- **Low voltage**
  - Caused by insulating effect of pericardial fluid
  - Typically defined as a QRS amplitude < 0.5 mV in the limb leads and < 1.0 mV in the precordial leads
  - **Not specific** for pericardial effusion: wide DDx including obesity, amyloidosis, prior infarction(s), constrictive pericarditis, myxedema, etc.

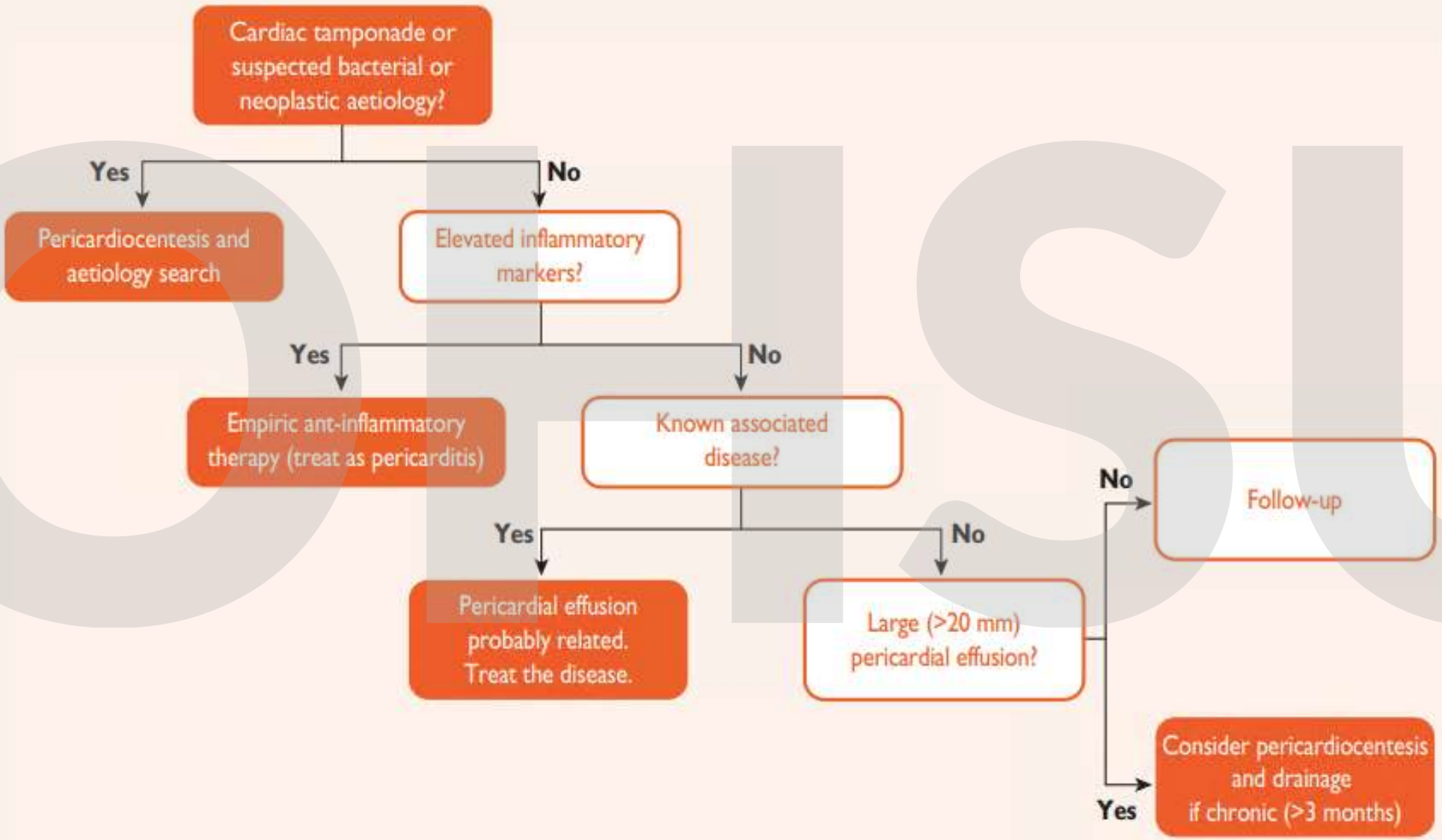


- **Electrical alternans**
  - Caused by changes in cardiac position due to increased motion within the pericardial space
  - **Low sensitivity** for pericardial effusions, but suggestive of cardiac tamponade when present

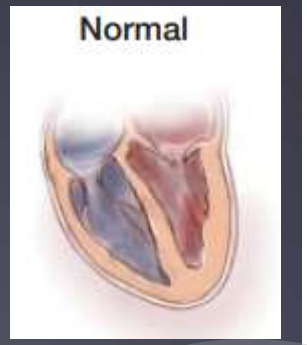
Etiology of Pericardial Effusions

- In asymptomatic/incidental cases, in developed countries:
  - 50% idiopathic
  - 10-25% malignant
  - 15-30% infections
  - 15-30% iatrogenic
  - 5-15% autoimmune
- In developing countries where TB is endemic, >60% are due to TB.

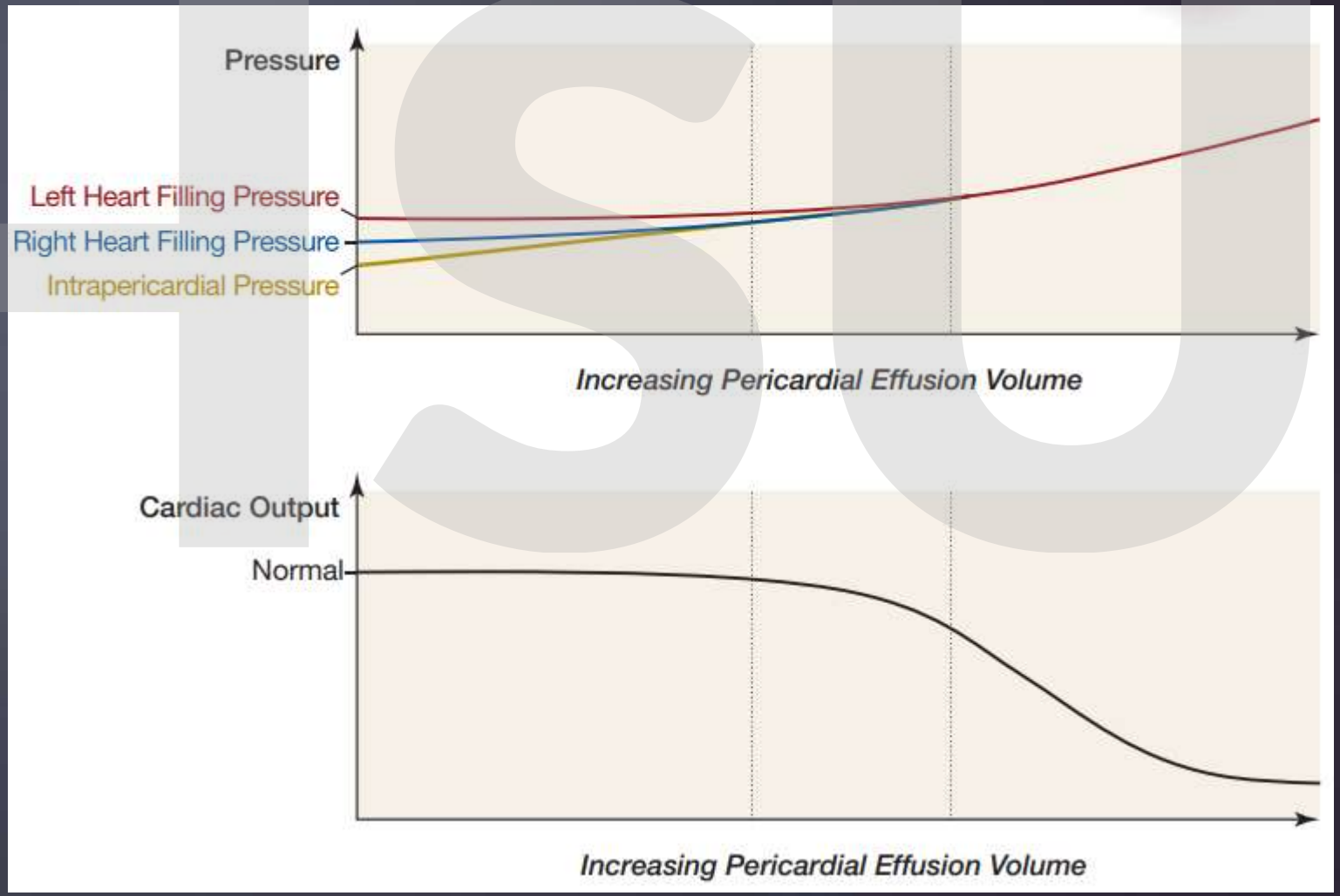
Empiric anti-inflammatory therapies should be considered if a missed diagnosis of pericarditis is presumed.



Cardiac Tamponade



- Occurs when a pericardial effusion accumulates rapidly enough or becomes large enough such that intra-pericardial pressure is greater than or equal to intra-cardiac pressures
- Initially affects RA, then RV, then LA and LV



Beck's Triad

TWO CARDIAC COMPRESSION TRIADS

CLAUDE S. BECK, M.D.

CLEVELAND

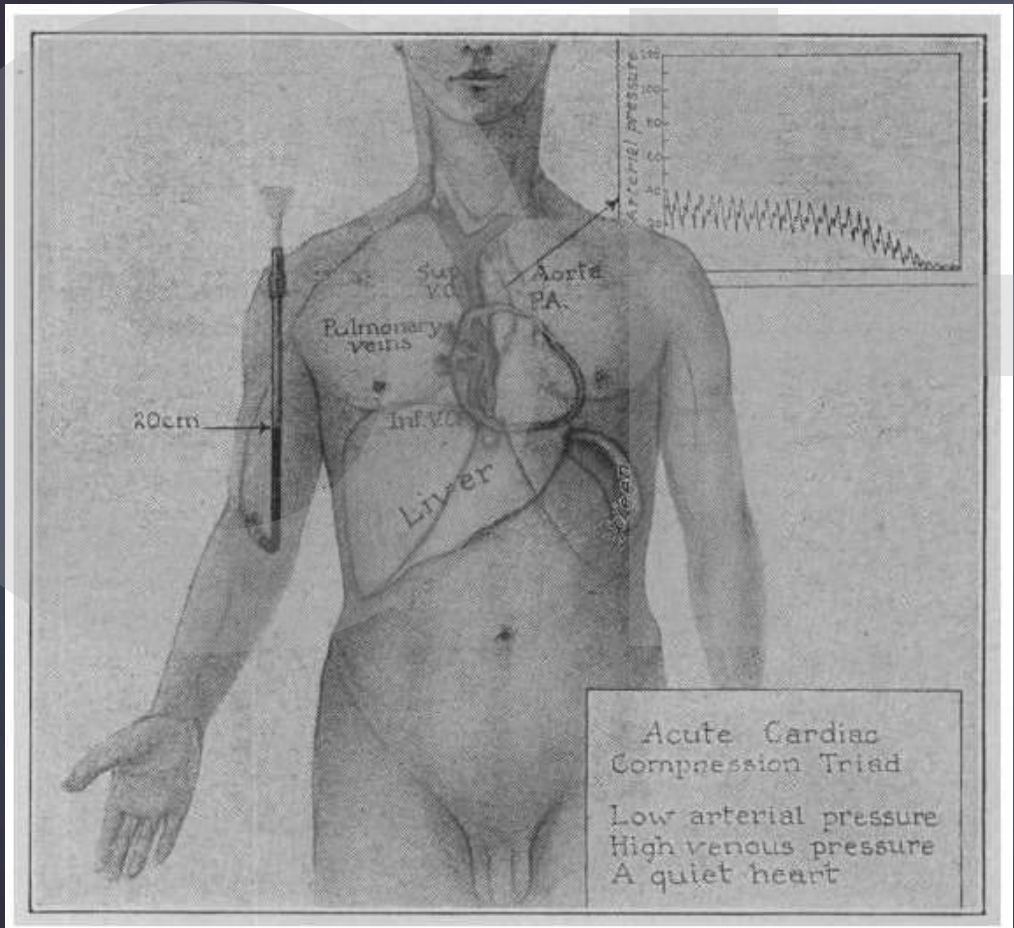


Fig. 2.—Acute cardiac compression triad.

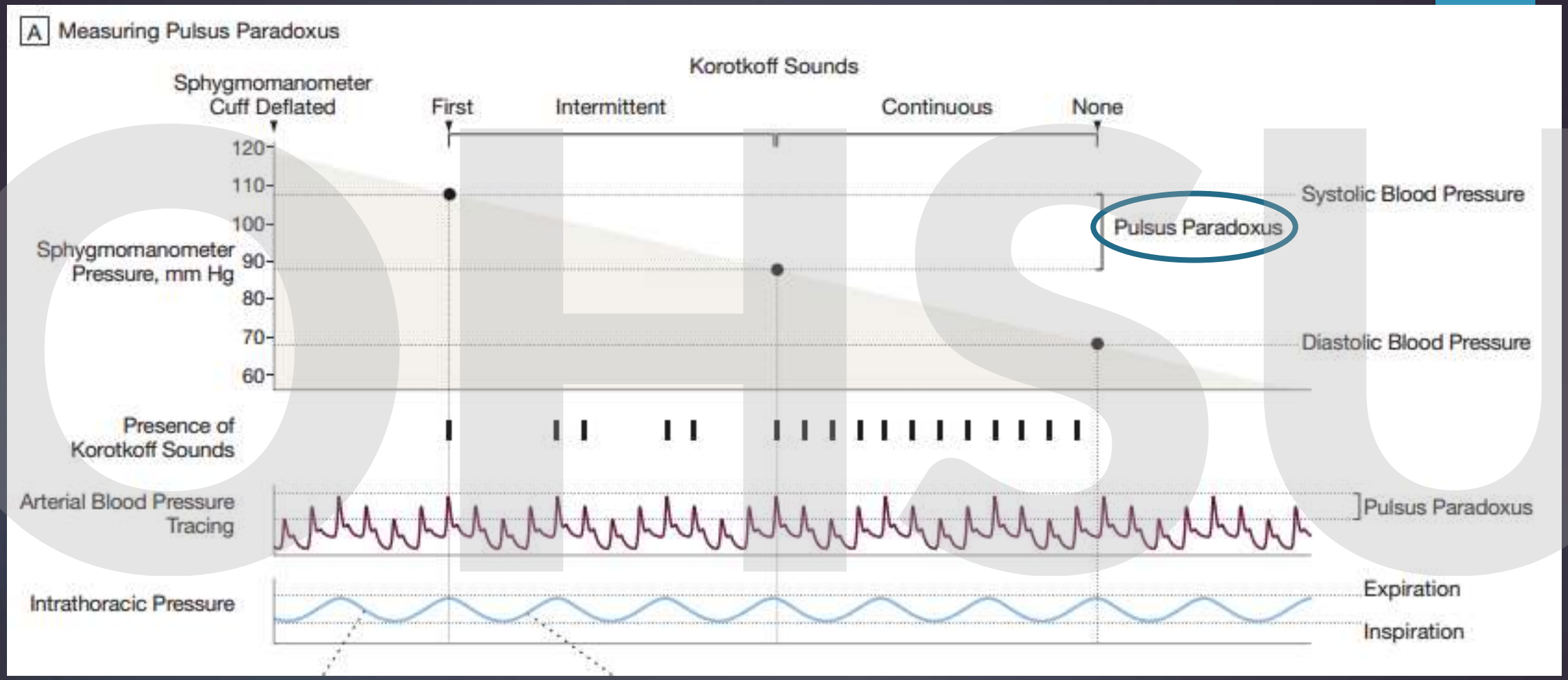
- Described by Beck in 1935.
- Made a distinction between the effects of acute and chronic pericardial effusions.
- Described a triad associated with acute compression:
  - "A falling arterial pressure" (hypotension)
  - "A rising venous pressure" (jugular venous distention)
  - "A small quiet heart" (muffled heart sounds)

JOUR. A. M. A.
MARCH 2, 1935

Cardiac Tamponade & Physical Examination

- Claude Beck – performed the 1st successful defibrillation in 1947 (in Cleveland) on a 14 year-old boy who experienced VF on the operating room table, after 45 minutes of open chest cardiac massage

Pulsus Paradoxus



- Exaggeration of the normal inspiratory decrease in blood pressure (ventricular interdependence).
- BP cuff is slowly deflated. Kortokoff sounds respirophasic, then continuous.

JAMA, April 25, 2007—Vol 297, No. 16

JAMA, April 25, 2007—Vol 297, No. 16

More Useful than Beck's Triad

	Sensitivity	+LR	-LR
Hypotension	26%	1.4	0.9
Jugular venous distention	**76%**	5.2	0.1
Diminished heart sounds	28%	-	0.8
Dyspnea	**87-88%**		
Tachycardia	**77%**	2.7	0.2
Tachypnea	**80%**		
Pulsus paradoxus > 10-12 mmHg	**82-98%**	3.3-5.9	0.03
Low voltage on ECG	42%		
Electrical alternans	16-21%		
Cardiomegaly on CXR	**89%**		

Echocardiographic Diagnosis

- Diastolic RV collapse
- Systolic RA collapse
- Abnormal ventricular septal motion
- Exaggerated respirophasic variation in mitral inflow velocity (>25%)
- Inspiratory decrease & expiratory increase in pulmonary vein diastolic flow
- Respirophasic variation in LV and RV size
- Echocardiographic pulsus paradoxus (variation in LVOT Doppler SV)
- Inferior vena cava dilation

Constrictive Pericarditis

- **Heart failure** due to pericardial restraint – a thickened, scarred, inelastic (often calcified) pericardium decreases the compliance of the cardiac chambers (impeding diastolic filling).
- Wide variety of etiologies, but thought to be due repeated cycles of injury. Risk of CP is related to underlying etiology. Of note, idiopathic recurrent pericarditis do NOT often develop CP
  - 42-49% idiopathic/viral
  - 11-37% post-cardiac surgery
  - 9-31% chest irradiation
  - 3-7% autoimmune
  - 3-6% bacterial/mycobacterial
- Classically associated with pericardial thickening and calcifation, but these may be absent in up to 20%

CP - continued

- The diagnosis of CP should be considered in ALL patients with "HFpEF" – it is a potentially curable cause of HF

Diagnostic evaluation	Constrictive pericarditis
Physical findings	Kussmaul sign, pericardial knock
ECG	Low voltages, non-specific ST/T changes, atrial fibrillation.
Chest X-ray	Pericardial calcifications (1/3 of cases).
Echocardiography	• Septal bounce. • Pericardial thickening and calcifications. • Respiratory variation of the mitral peak E velocity of >25% and variation in the pulmonary venous peak D flow velocity of >20% • Colour M-mode flow propagation velocity (Vp) >45 cm/sec. • Tissue Doppler: peak e' >8.0 cm/s.
Cardiac Catheterization	'Dip and plateau' or 'square root' sign, right ventricular diastolic, and left ventricular diastolic pressures usually equal, ventricular interdependence (i.e. assessed by the systolic area index >1.1).[a]
CT/CMR	Pericardial thickness >3–4 mm, pericardial calcifications (CT), ventricular interdependence (real-time cine CMR).

Recommendations	Class[a]	Level[b]	Ref.[c]
Transthoracic echocardiography is recommended in all patients with suspected constrictive pericarditis	I	C	
Chest X-ray (frontal and lateral views) with adequate technical characteristics is recommended in all patients with suspected constrictive pericarditis	I	C	
CT and/or CMR are indicated as second-level imaging techniques to assess calcifications (CT), pericardial thickness, degree and extension of pericardial involvement	I	C	
Cardiac catheterization is indicated when non-invasive diagnostic methods do not provide a definite diagnosis of constriction	I	C	

Echocardiographic Features of Constriction

- Respirophasic septal shift
- Annulus reversus
- Annulus paradoxus
- Significant respiratory variation in mitral & tricuspid inflow
- Preserved longitudinal strain
- Strain reversus
- Dilated inferior vena cava
- Prominent hepatic vein diastolic expiratory flow reversal

Forms of Constrictive Pericarditis

Syndrome	Definition	Therapy
Transient constriction (d.d. permanent constrictive pericarditis, restrictive CMP).	Reversible pattern of constriction following spontaneous recovery or medical therapy.	A 2–3-month course of empiric anti-inflammatory medical therapy.
Effusive-constrictive pericarditis (d.d. cardiac tamponade, constrictive pericarditis).	Failure of the right atrial pressure to fall by 50% or to a level below 10 mmHg after pericardiocentesis. May be diagnosed also by non-invasive imaging.	Pericardiocentesis followed by medical therapy. Surgery for persistent cases.
Chronic constriction (d.d. transient constriction, restrictive CMP).	Persistent constriction after 3–6 months.	Pericardiectomy, medical therapy for advanced cases or high risk of surgery or mixed forms with myocardial involvement.

- Early CP (transient CP) may be reversible with anti-inflammatory therapy. **CMR** may be useful to identify persistent inflammation.
- **CT** may be useful to identify pericardial calcifications, which may suggest chronicity, less likelihood to respond to anti-inflammatory Rx.
- Radical pericardiectomy is the treatment of choice for chronic CP

CMR in CP

- Pericardial LGE is associated with a reversible CP phenotype
- However, CMR to assess for inflammation is not necessary in every patient with CP
  - If there is HF but no chest pain, and there is already prominent calcification on CXR or CT, CMR is unlikely to add value and CP will not likely be reversible with anti-inflammatory therapy
  - If there is typical pericarditic pain and elevated inflammatory markers, anti-inflammatory therapy is indicated and CMR is also not needed

CP - Therapy

Recommendations	Class[a]	Level[b]	Ref.[c]
The mainstay of treatment of chronic permanent constriction is pericardiectomy	I	C	
Medical therapy of specific pericarditis (i.e. tuberculous pericarditis) is recommended to prevent the progression of constriction	I	C	
Empiric anti-inflammatory therapy may be considered in cases with transient or new diagnosis of constriction with concomitant evidence of pericardial inflammation (i.e. CRP elevation or pericardial enhancement on CT/CMR)	IIb	C	

- Pericardiectomy operative mortality may be as high as 6-12%
- Predictors of poor outcome with pericardiectomy:
  - Cachexia
  - Hypoalbuminemia
  - Low CO
  - Atrial fibrillation
  - Radiation heart disease
  - Child-Pugh class B or C
  - CKD-3+
  - Older age
  - Pulmonary hypertension

Post-cardiac injury syndromes

- Includes post-myocardial infarction pericarditis, post-pericardiotomy syndrome, and post-traumatic pericarditis
- Presumed autoimmune pathogenesis related to initial damage to pericardial tissue, with latent period until appearance of first manifestations
- Typically responds well to NSAIDs/ASA and colchicine

Tuberculous pericarditis

- <4% of pericarditis in the developed world, but accounts for >70% of cases in developing countries (>90% in pts with HIV)
- Often presents with pericardial effusion, effusive-constrictive pericarditis, or constrictive pericarditis
- High mortality of 17-40% at 6 months
- Treatment with antimycobacterial antibiotics (typically RIPE x2 mo then RI x 4 months) reduces the likelihood of chronic constriction from 50% to 17-40%
- Adjunctive steroids may be helpful in HIV-negative TB-pericarditis to reduce the risk of chronic constriction

Pericarditis in Autoimmune Disease

- Approximately 5-15 % of acute & recurrent pericarditis cases may be due to underlying autoimmune disease:
  - SLE, RA, Scleroderma, Sjogren syndrome, Behcet's, vasculitides, sarcoidosis, IBD (most will have already been diagnosed)
- Pericarditis occurs in 20-50% of SLE patients, typically during acute flares
  - Even greater involvement is seen at autopsy
- Also frequency occurs in RA, but is rarely symptomatic (<10%)

Pericardial Cyst

- Benign unilocular mass, usually an incidental finding on CXR or CT
- Most commonly seen at the R costophrenic angle (70%) or L costophrenic angle (20%)
- Rare congenital abnormality
- Accounts for 13-17% of all mediastinal cysts
- Rarely can have associated symptoms due to cardiac compression

Congenital absence of the pericardium

- Extremely rare congenital anomaly
- May be partial or complete
- Usually asymptomatic; rarely associated with symptoms when cardiac structures (e.g. LA appendage, coronary artery, etc.) are compressed or incarcerated within a partial defect
- 1/3 of cases are associate with other congenital anomalies

Resources

2015 ESC Guidelines for the diagnosis and management of pericardial diseases

The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)