Pericardial Disease:
Key Concepts

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- Clinician, Educator, Textbook Author
  - Clinical focus: General and preventive cardiology, noninvasive imaging, pericardial disease
  - Research interests: Novel approaches for pericardial disease, innovations in medical education

Disclosures

Member of Data Monitoring Committee for RHAPSODY trial
(Cleveland Clinic / Kiniksa Pharmaceuticals)

Objectives

Diagnosis and management of:

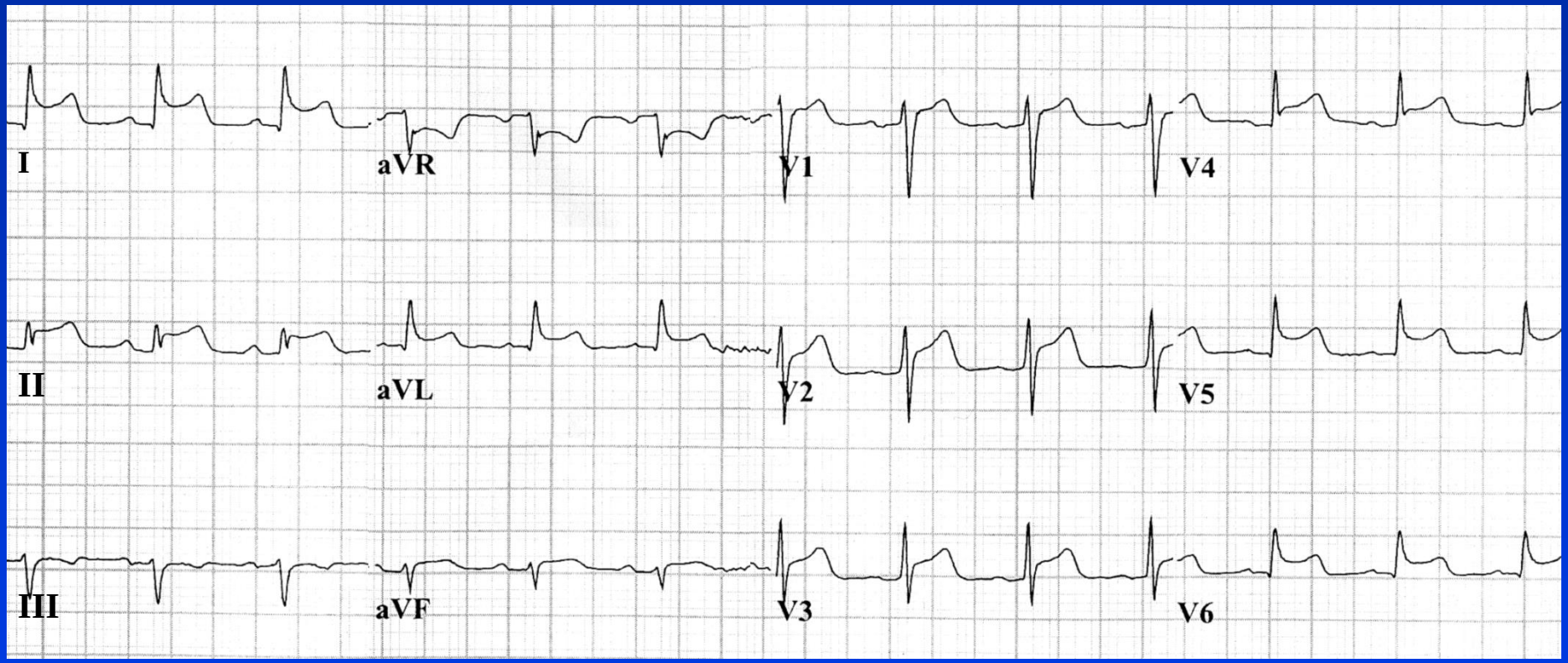
- Acute pericarditis
- Cardiac tamponade
- Constrictive pericarditis

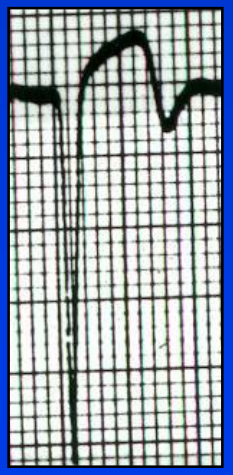
Case Presentation

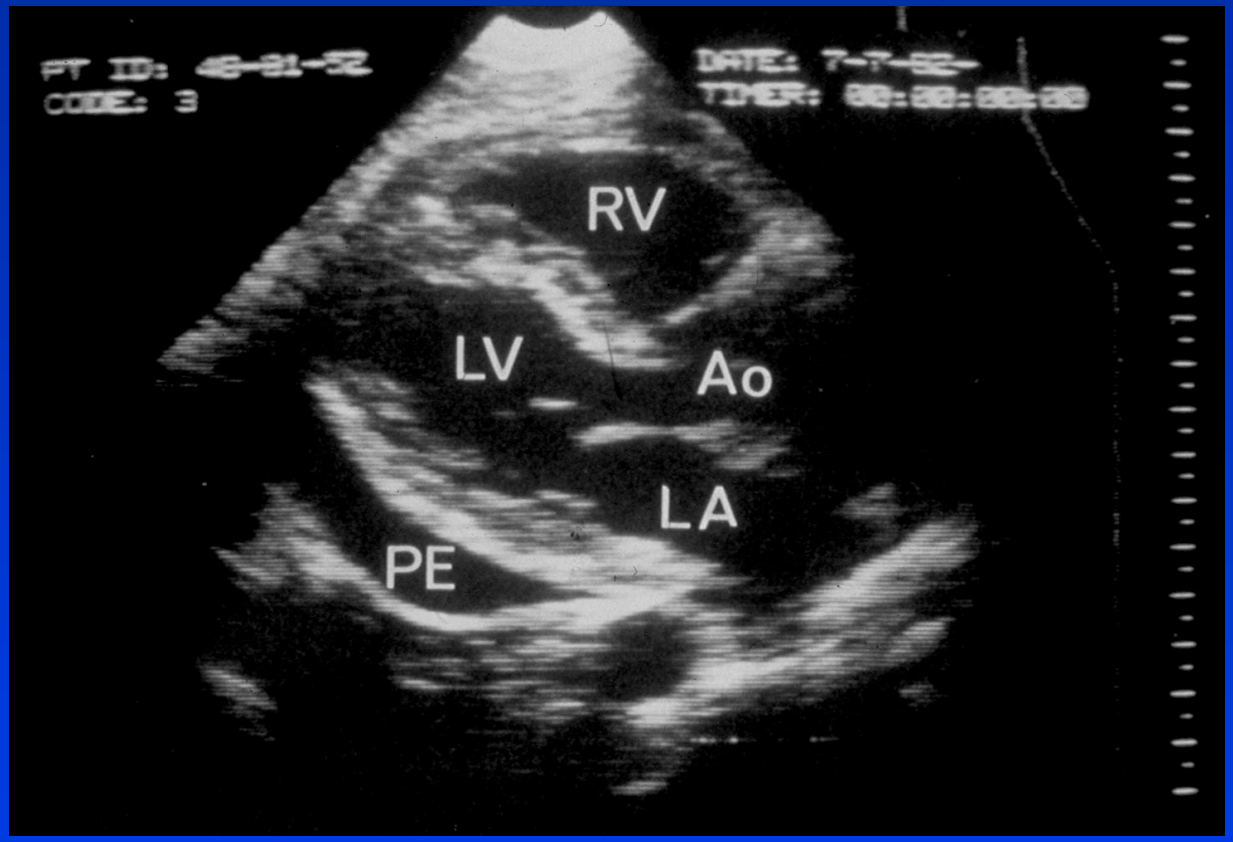
42-year-old malpractice attorney presents to the emergency department with chest pain since awakening

- No history of angina
- Father had MI at age 55
- Had uncomplicated upper respiratory tract infection one month ago

Electrocardiogram



	ST Coving	Which Leads?	ST-T Evolution	PR Segment
Pericarditis	 (STE < 5 mm)	Diffuse	Days-weeks	↓
Acute STEMI		Localized	Hours	Normal


RV
LV
Ao
LA
PE

Acute Pericarditis

- >85% post-viral / idiopathic[1]
- Usually self-limited: 1-3 weeks
- 15-30% recurrence rate[2]
- Several recent prospective trials offer evidence-based guidance

[1]*Am J Cardiol* 1995;75:378.
[2]*Circulation* 2010;121:916.

Management of Acute Pericarditis

- Aspirin and other NSAIDs
- Colchicine
- Glucocorticoids

NSAIDs

- No prospective randomized trials

Aspirin[1]	650-975 mg TID-QID
Ibuprofen	400-800 mg TID
Indomethacin	50 mg TID
Ketorolac[2]	IM or IV: 15-30 mg QID

- ~2 week course followed by taper

[1] *J Am Coll Cardiol* 2004;43:1042.

[2] *Am Heart J* 1993;125:1455.

NSAIDs

- If symptoms or fever persist > 1 week, consider etiologies other than post-viral / idiopathic
- Imazio et al (*J Am Coll Cardiol* 2004;43:1042)
  - 254 pts with acute pericarditis treated as outpatients
  - 221 responded rapidly – presumably idiopathic
  - 33 (13%) had persistent symptoms

    14 Autoimmune disorder[1]

    6 Tuberculosis

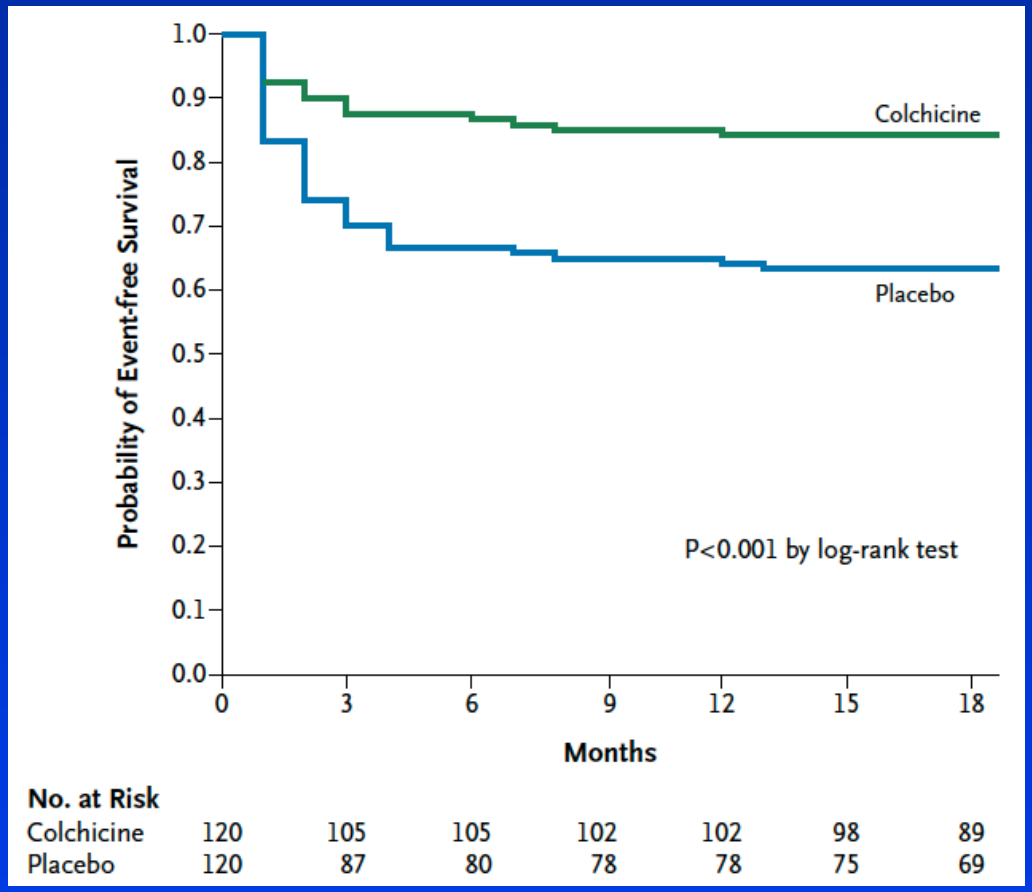
[1]Connective tissue disease or post-pericardiotomy syndrome

ICAP: Double-blinded Trial of Colchicine in Initial Acute Pericarditis

(Imazio M et al. *N Eng J Med* 2013; 369:1522)

- Multicenter study of 240 men & women with 1st episode of pericarditis (idiopathic/ viral, CTD, or post-cardiac surgery)
- Randomized to colchicine (0.5-1.0 mg/d x 3 months) vs. placebo, in addition to ASA or ibuprofen
- Primary end point: Persistent or recurrent pericarditis

ICAP: Primary Outcome Results



Outcome	RRR	*P*
Persistent or recurrent pericarditis	0.56	<0.001
Symptoms at 72 hours	0.52	=0.001

N Eng J Med 2013; 369:1522

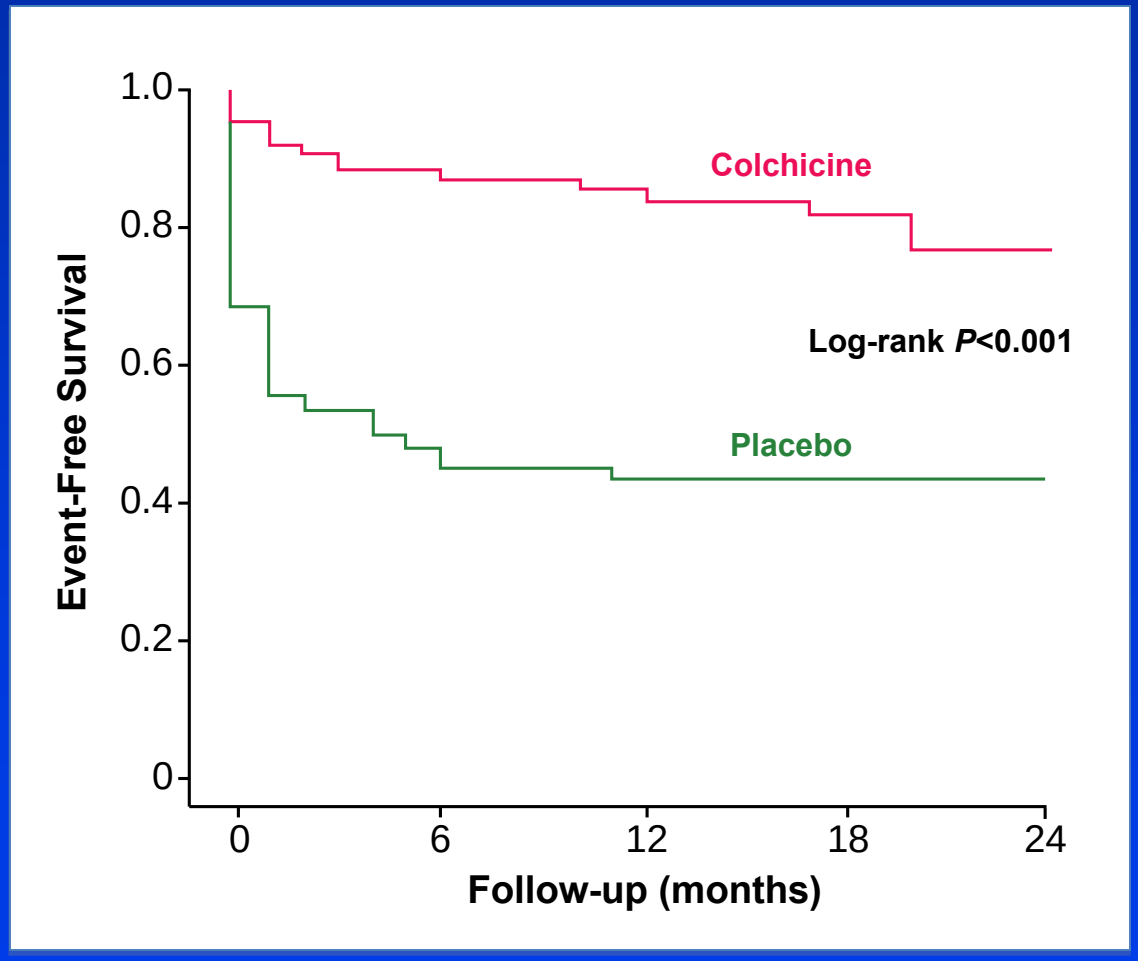
CORP: Double-blinded study of colchicine for secondary prevention

(Imazio M et al. *Ann Intern Med* 2011; 155:409)

- Prospective, placebo-controlled trial at four urban hospitals in Italy: 120 men & women with 1st recurrence of pericarditis
- Randomized to colchicine (1-2 mg x 1 day, then 0.5-1.0 mg/d x 6 months) vs. placebo, in addition to ASA or ibuprofen
- Primary end point: Recurrence of pericarditis at 18 months

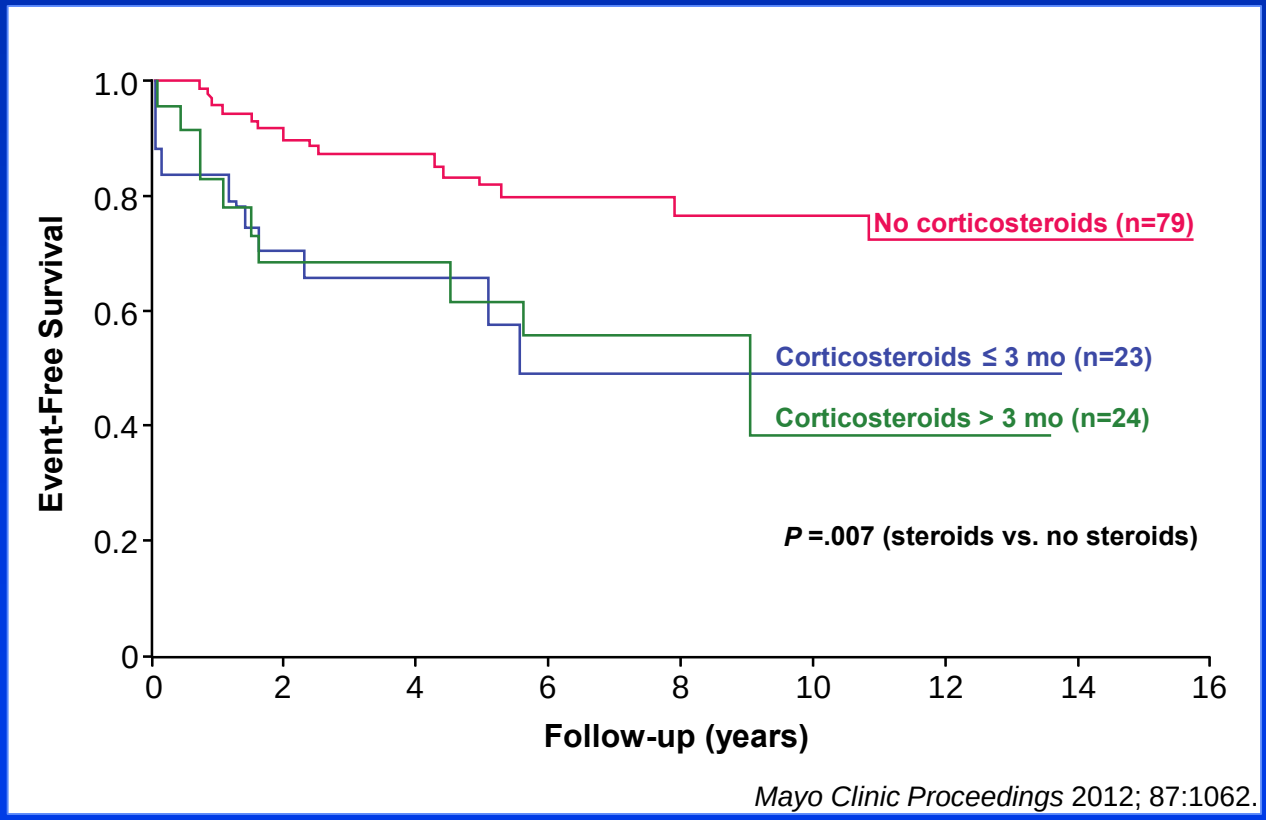
CORP: Double-blinded study of colchicine for secondary prevention

(Imazio M et al. *Ann Intern Med* 2011; 155:409)



Glucocorticoid Therapy in Pericarditis

- Rapidly improves symptoms, but should **not** be used as primary therapy for pericarditis: Increases risk of recurrences[1]



Mayo Clinic Proceedings 2012; 87:1062.

[1]Lotrionte M et al. *Am Heart J* 2010; 160:662.

Glucocorticoid Therapy in Pericarditis

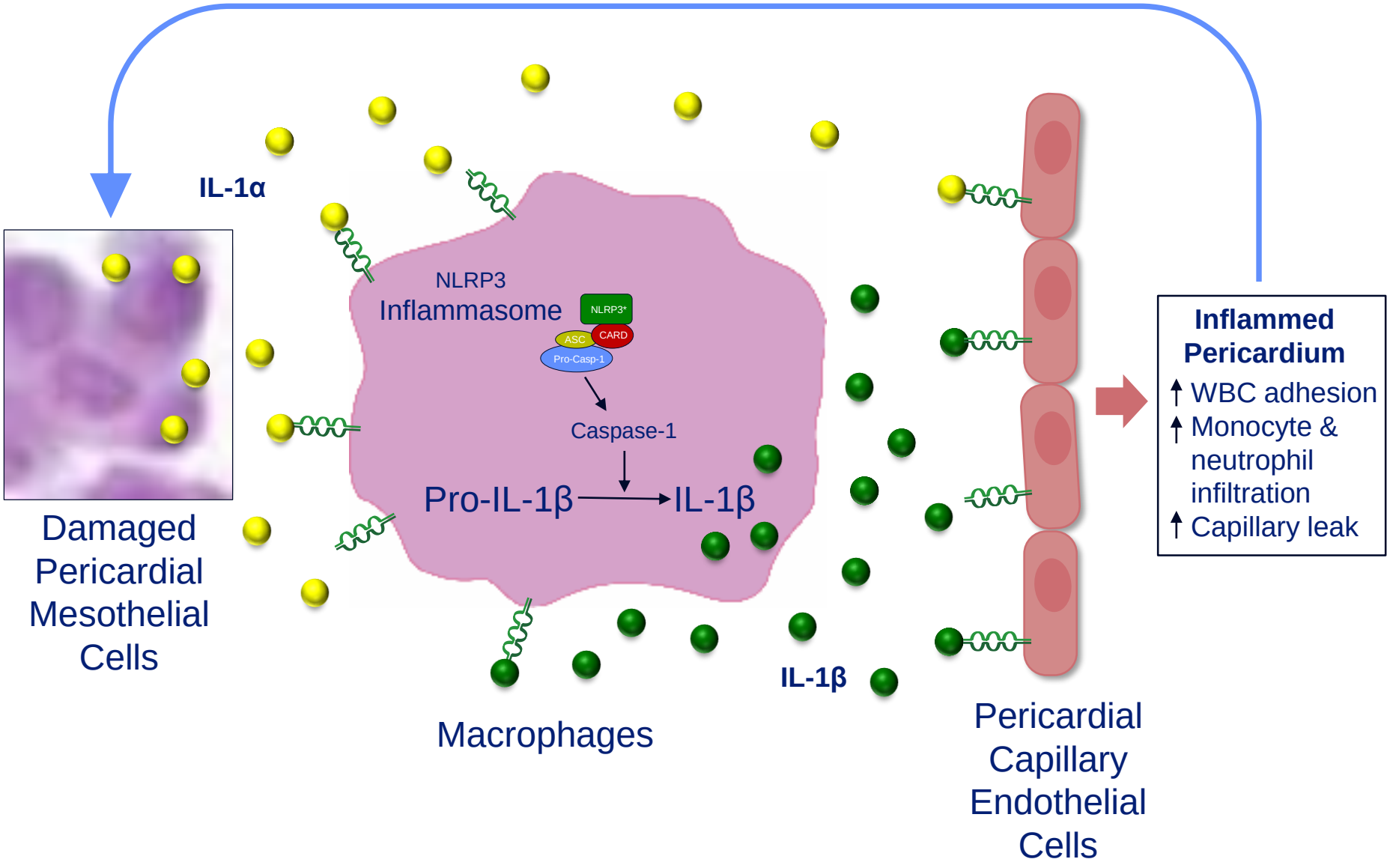
Restrict use to patients truly refractory to, or intolerant of, NSAID + colchicine

(and taper slowly)

Approach to Colchicine-Refractory or Steroid-Dependent Patients

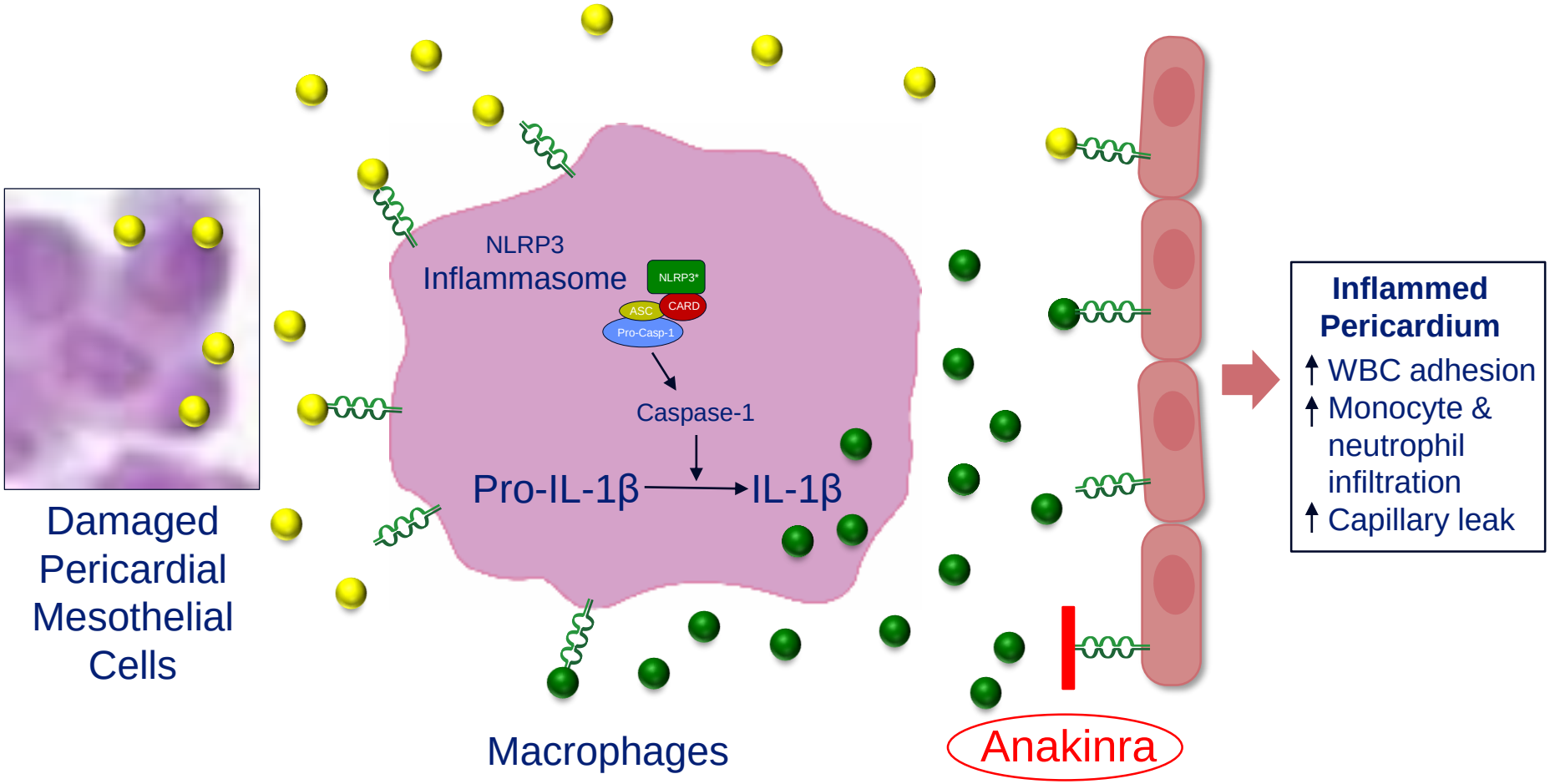
1. Confirm pericarditis is actual cause of symptoms
2. Very slow prednisone taper
3. Immunosuppressive therapy
   (case reports and nonrandomized data: methotrexate, azathioprine, mycophenolate, IV immunoglobulin)
4. IL-1 antagonist therapies
5. Pericardiectomy

Role of IL-1 in Pericarditis



Adapted from: *Am Heart J* 2020;228:81, *J Am Coll Cardiol* 2016;68:2311, and *Nat Rev Drug Discov* 2012;11:633.

Role of IL-1 in Pericarditis



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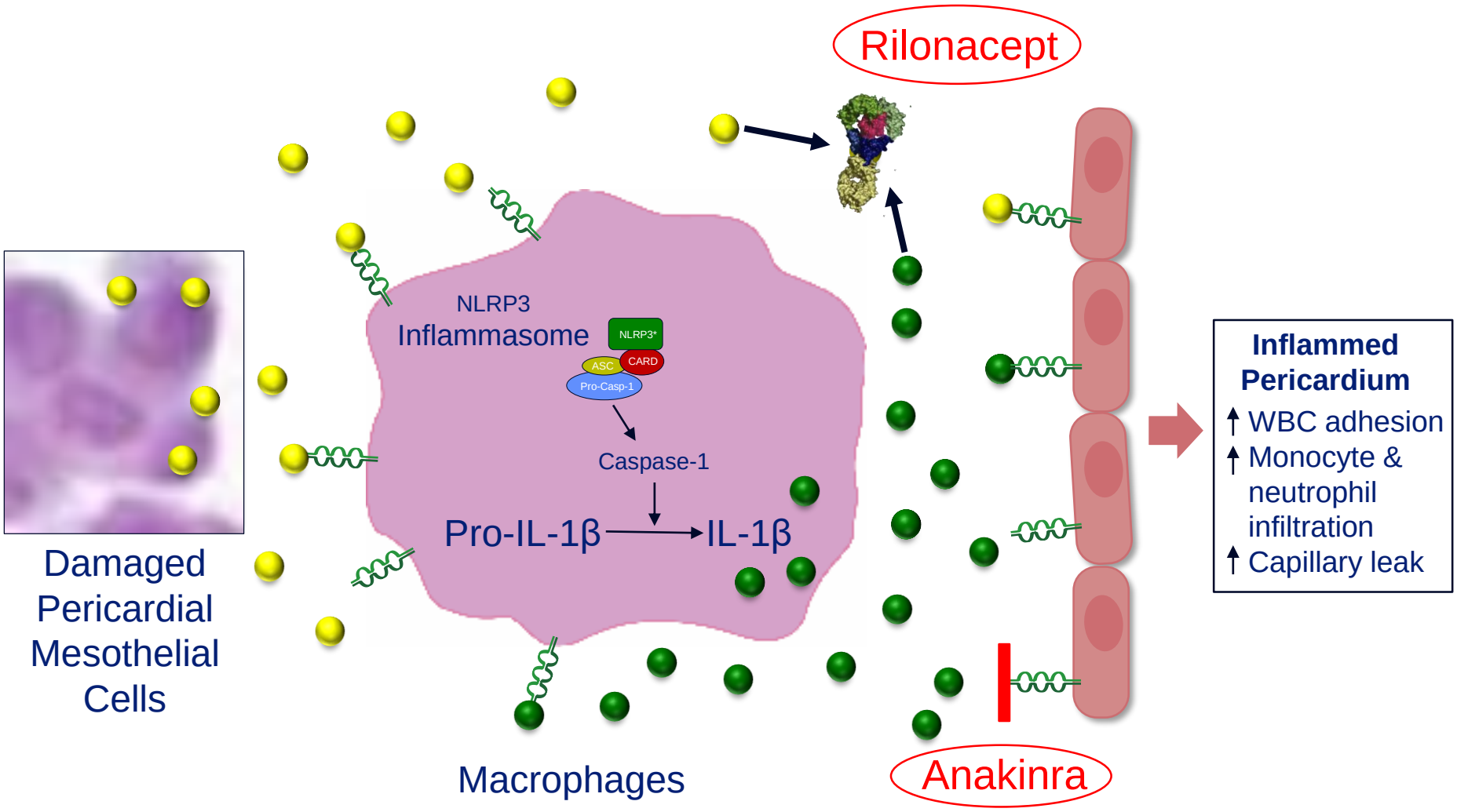
Role of IL-1 in Pericarditis

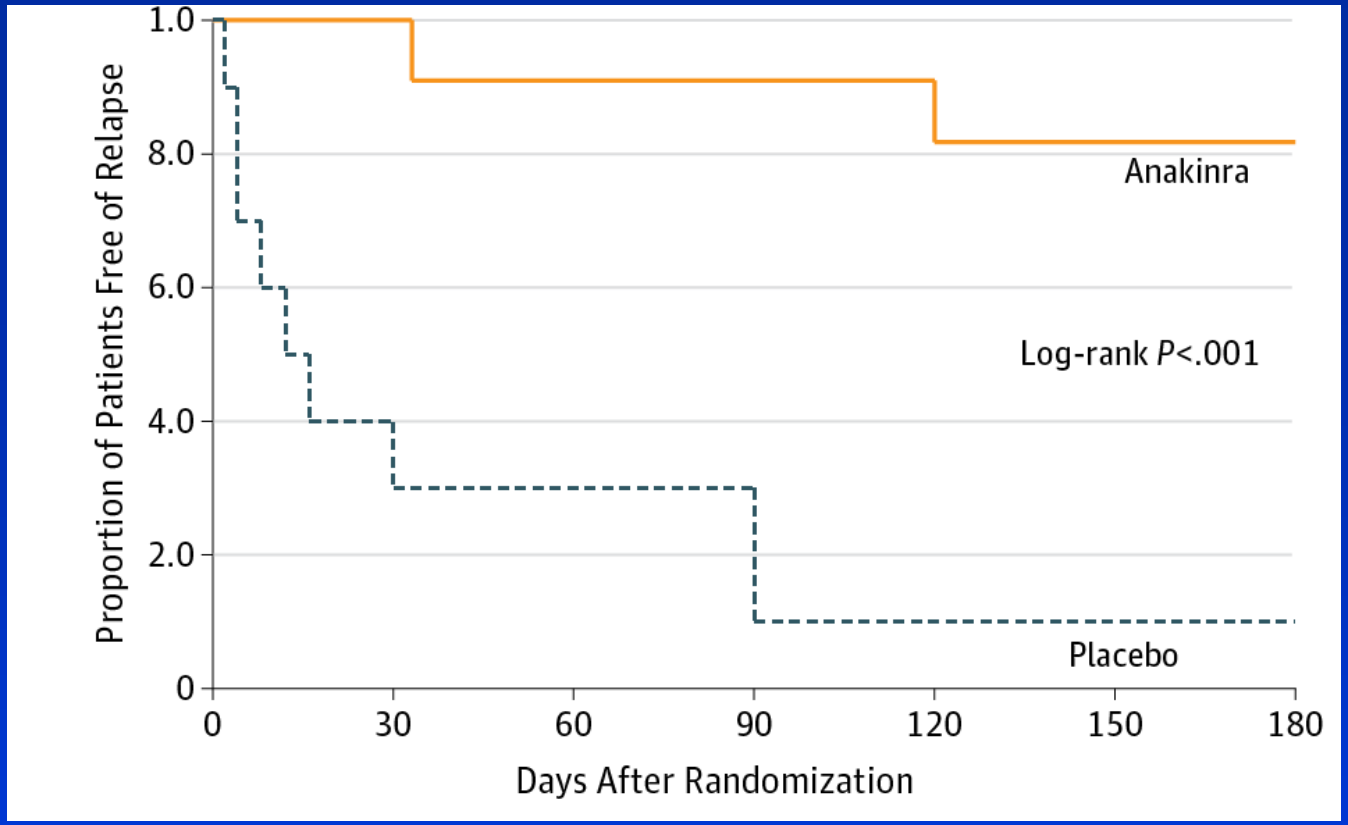


Adapted from: *Am Heart J* 2020;228:81, *J Am Coll Cardiol* 2016;68:2311, and *Nat Rev Drug Discov* 2012;11:633.

Anakinra in Recurrent Pericarditis

(AIRTRIP Trial *JAMA* 2016; 316:1906)

- Double-blind, placebo-controlled, randomized withdrawal trial (n=21, mean age 45.4 y)
- Patients with ≥ 3 recurrences (colchicine resistant, glucocorticoid dependent, elevated CRP)
- Initial open label treatment with daily subcutaneous anakinra: All patients able to stop steroids, CRP normalized
- At 60 days: randomized to continued anakinra vs. placebo x 6 months
- Primary end point: Recurrent pericarditis



18% recurrence

90% recurrence

Anakinra side effects:

- Local skin reaction common (resolved with topical Rx)
- 3 pts: transaminitis (<2xULN), reversed with ↓dose

Conclusion:

- Anakinra allows rapid withdrawal from steroids
- Prolonged therapy is necessary

JAMA 2016; 316:1906

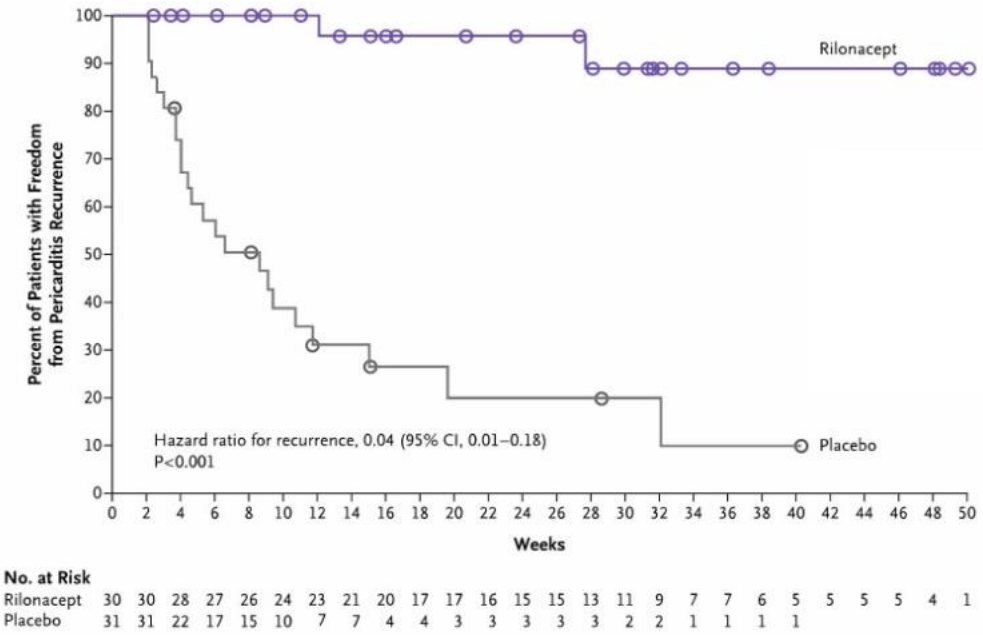
Rilonacept in Recurrent Pericarditis

(RHAPSODY Trial *N Engl J Med* 2021; 384:31)

- Double-blind, placebo-controlled, randomized withdrawal trial (n=61, mean age 44.7 y)
- Patients with ≥2 recurrences and elevated CRP (~47% on glucocorticoid therapy)
- Initial open label treatment with weekly subcutaneous rilonacept: All patients able to wean off steroids, colchicine
- At 12 weeks: randomized to continued rilonacept vs. placebo
- Primary end point: Recurrent pericarditis

RHAPSODY: Time to the First Adjudicated Pericarditis Recurrence

Primary Efficacy Endpoint (Randomized Withdrawal Period; n = 61)



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Klein AL et al. *N Engl J Med* 2021;384:31.

RHAPSODY AEs:

Event	Run-In Period	Randomized Withdrawal Period				
	Rilonacept (N = 86)	Rilonacept, Including Bailout (N = 30)	Placebo, Including Bailout (N = 31)	Rilonacept, Before Bailout (N = 30)	Placebo, Before Bailout (N = 31)	Total (N = 86)
Any AE	69 (80)	24 (80)	22 (71)	24 (80)	13 (42)	74 (86)
Serious AE	1 (1)	1 (3)	3 (10)	1 (3)	1 (3)	5 (6)
Cancer	0	1 (3)	0	1 (3)	0	1 (1)
Injection-site reaction	28 (33)	6 (20)	2 (6)	5 (17)	0	29 (34)
Infection or infestation	14 (16)	12 (40)	7 (23)	12 (40)	3 (10)	29 (34)
URTI	12 (14)	7 (23)	2 (6)	7 (23)	0	19 (22)

Klein AL et al. *N Engl J Med* 2021;384:31.

Complications of Acute Pericarditis

Cardiac tamponade
(Pericardial fluid under pressure)

Constrictive pericarditis
(Scarred, rigid Pericardium)

Impaired diastolic ventricular filling

Elevated venous pressures

↓

Jugular venous distension
&
Pulmonary congestion

Reduced stroke volume

↓

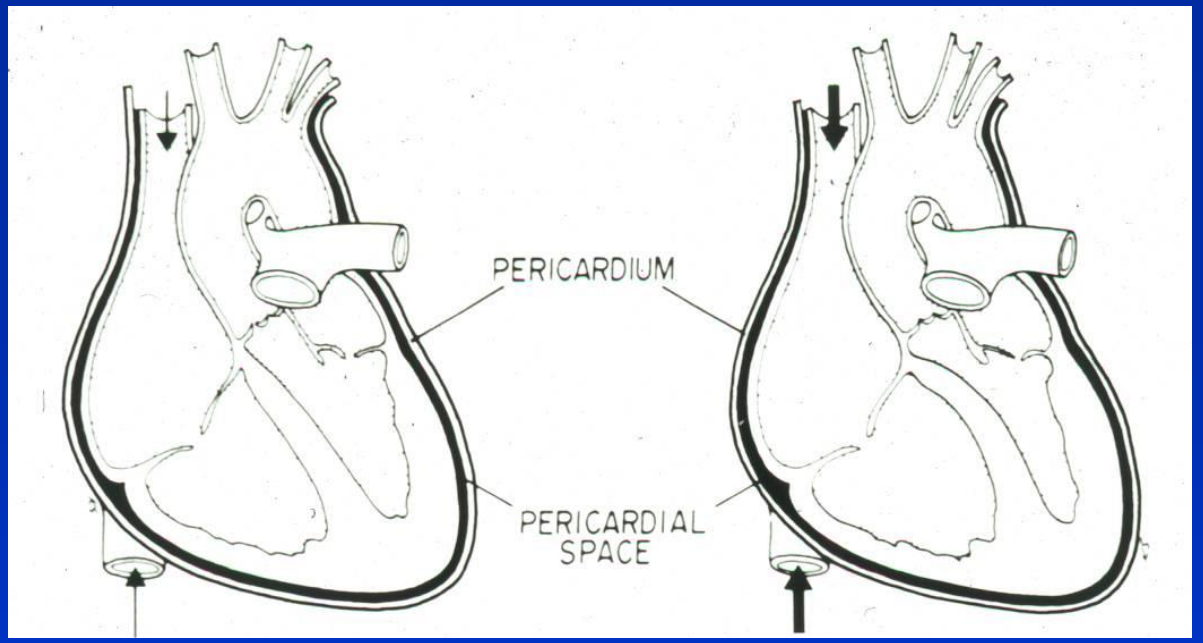
Decreased Cardiac output

Cardiac Tamponade
(Beck, 1935)

- Jugular venous distention
- “Small, quiet heart”
- Hypotension


EXP.
INSP.
Ao
RV
L.G
100
90
80
70
60
50
40
30
20
10
0

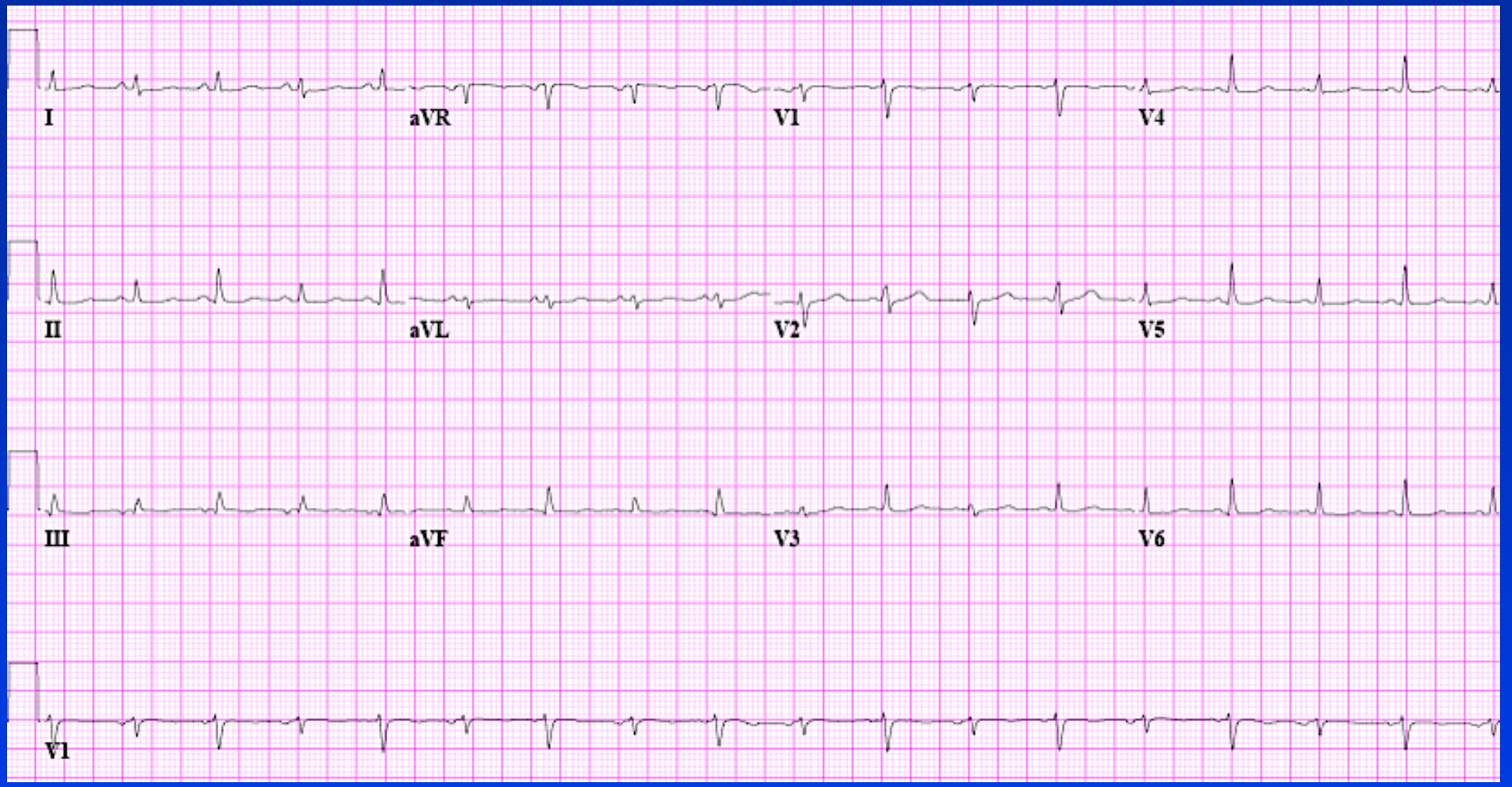
Normal



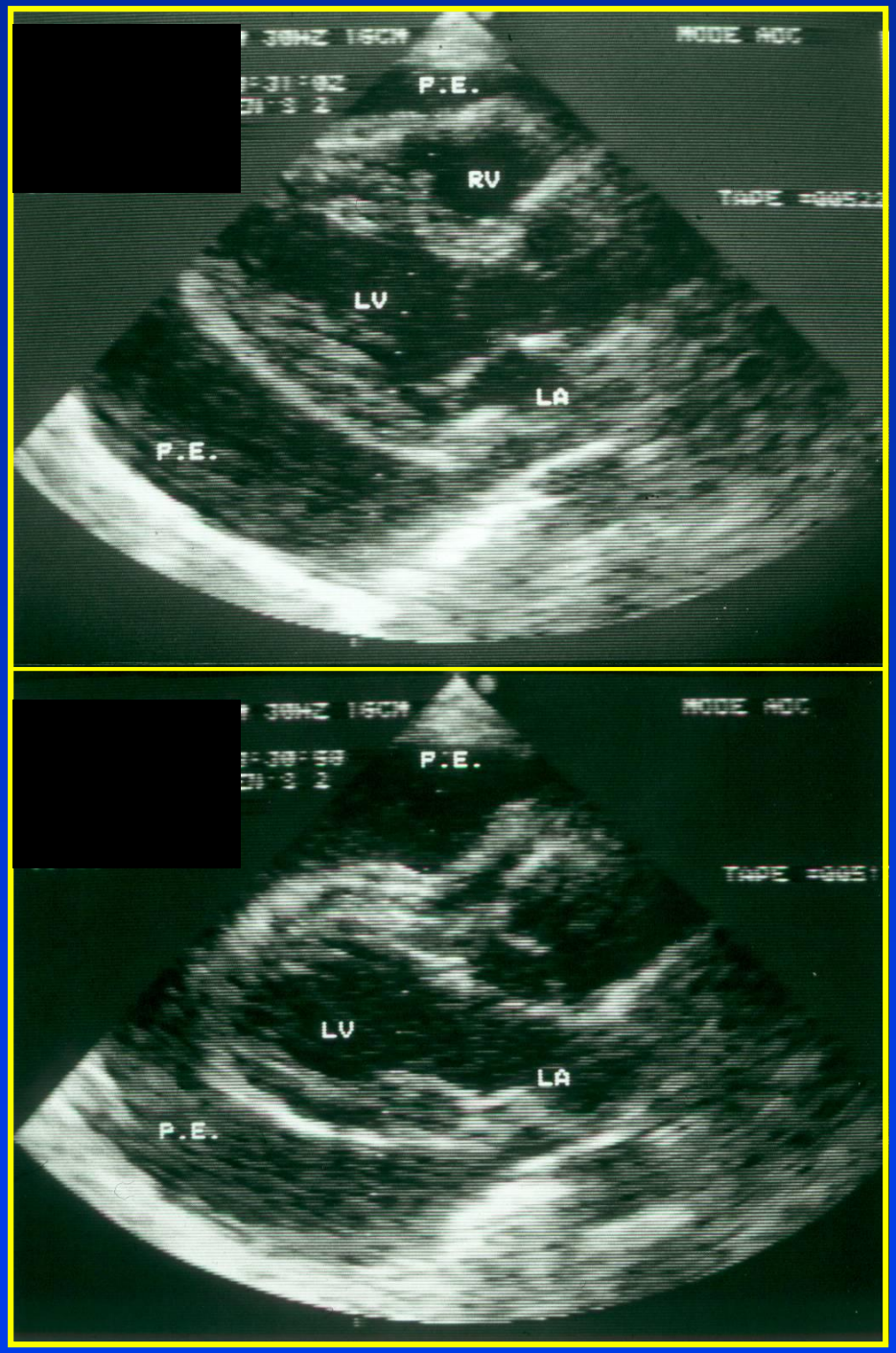
Expiration

Inspiration

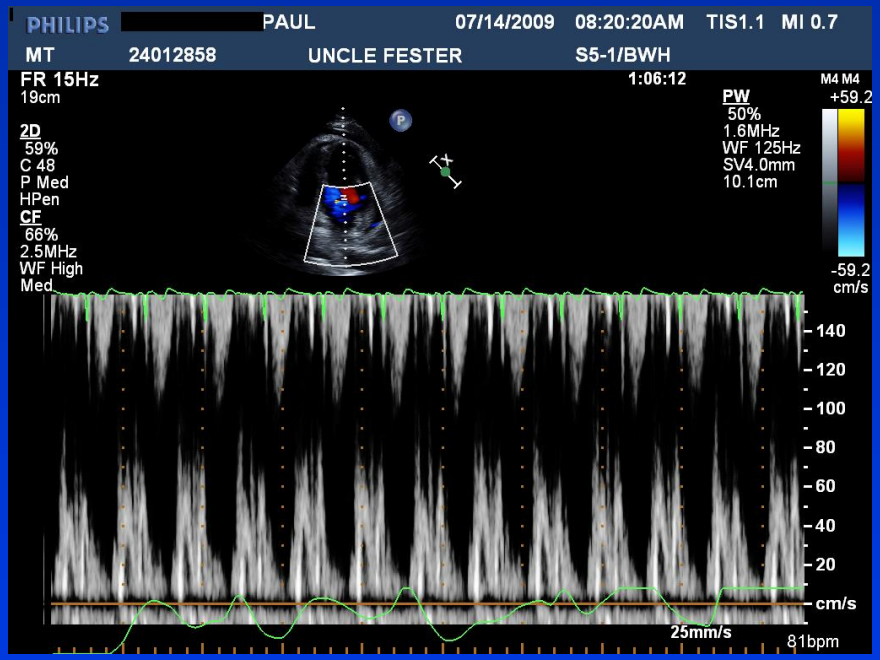
Cardiac Tamponade



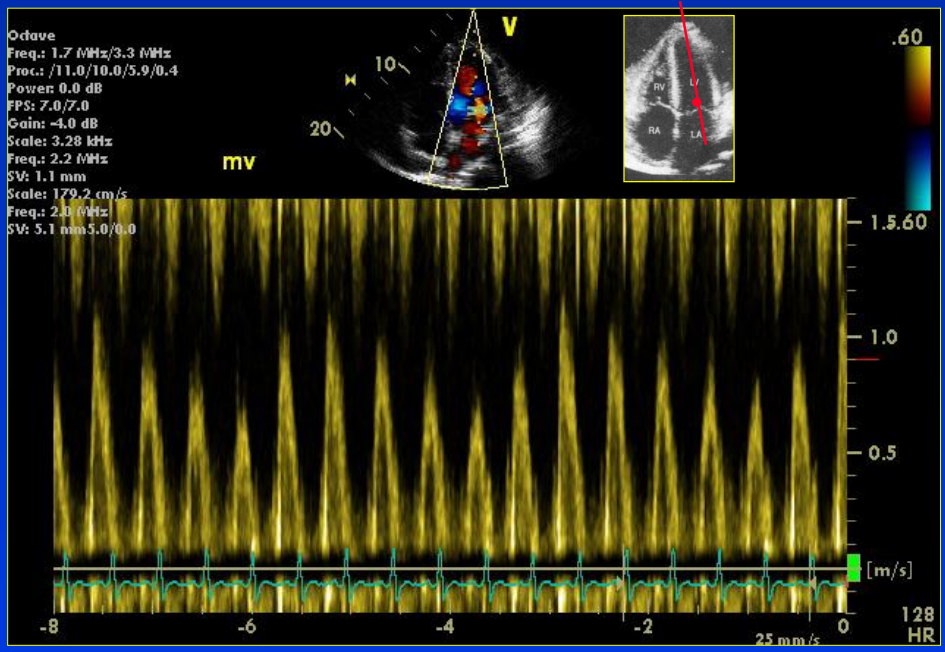
- Low limb lead voltage
- Electrical alternans


P.E.
RV
LV
LA
P.E.
P.E.
LV
LA
P.E.

Excessive Respiratory Variation (Flow velocity paradox)



No Tamponade

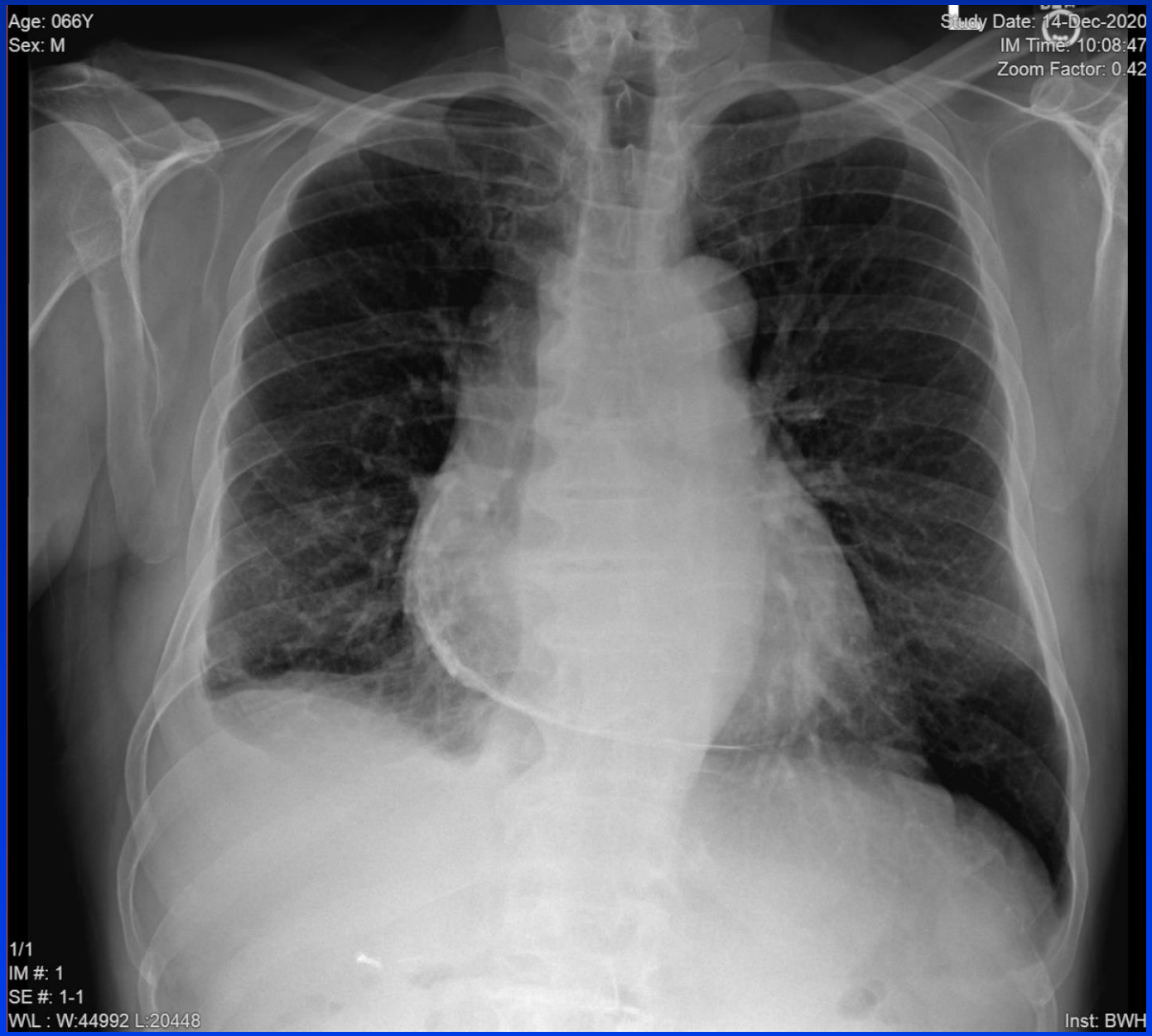


Tamponade

Cardiac Tamponade

1. Pericardial pressure elevated
2. Equalization of diastolic pressures:

Pericardial pressure = RA
= RV
= PCW
= LV


Age: 066Y
Sex: M
Study Date: 14-Dec-2020
IM Time: 10:08:47
Zoom Factor: 0.42
1/1
IM #: 1
SE #: 1-1
W\L : W:44992 L:20448
Inst: BWH

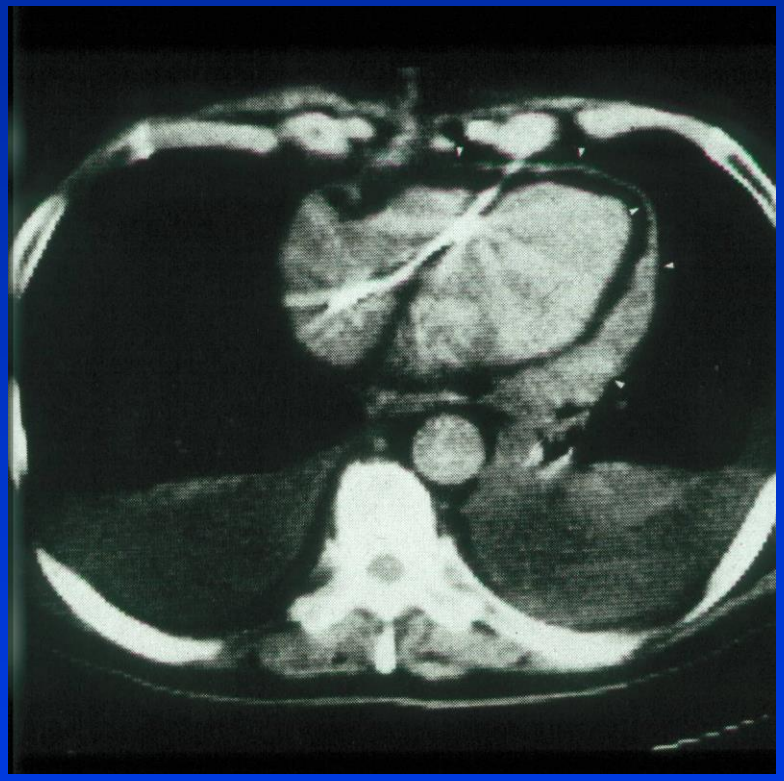
Constrictive Pericarditis Etiologies

(Cleveland Clinic Series; n=163)

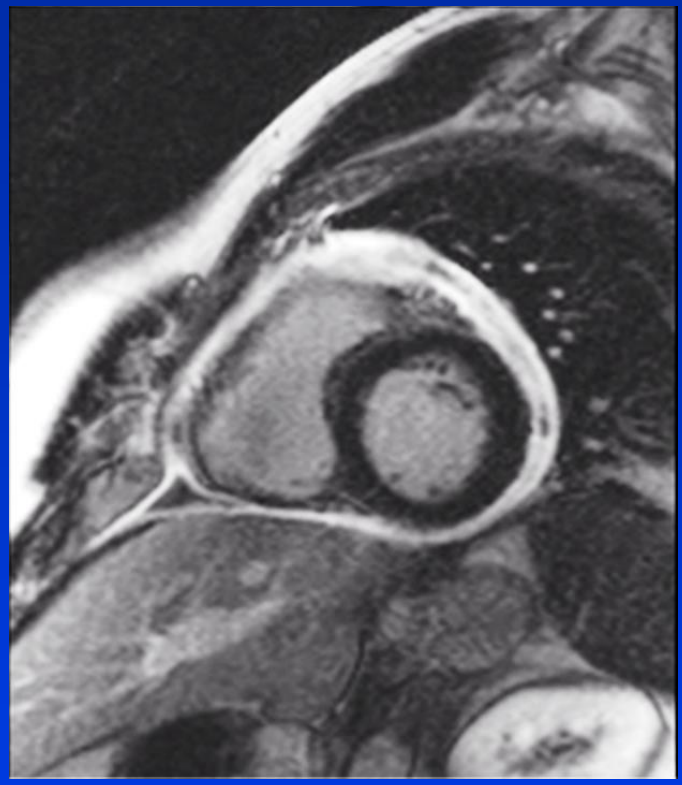
Postviral / idiopathic	46%
Post–cardiac surgical	37%
Mediastinal irradiation	9%
Miscellaneous (e.g., collagen vascular disease)	8%

J Am Coll Cardiol 2004;43:1445.

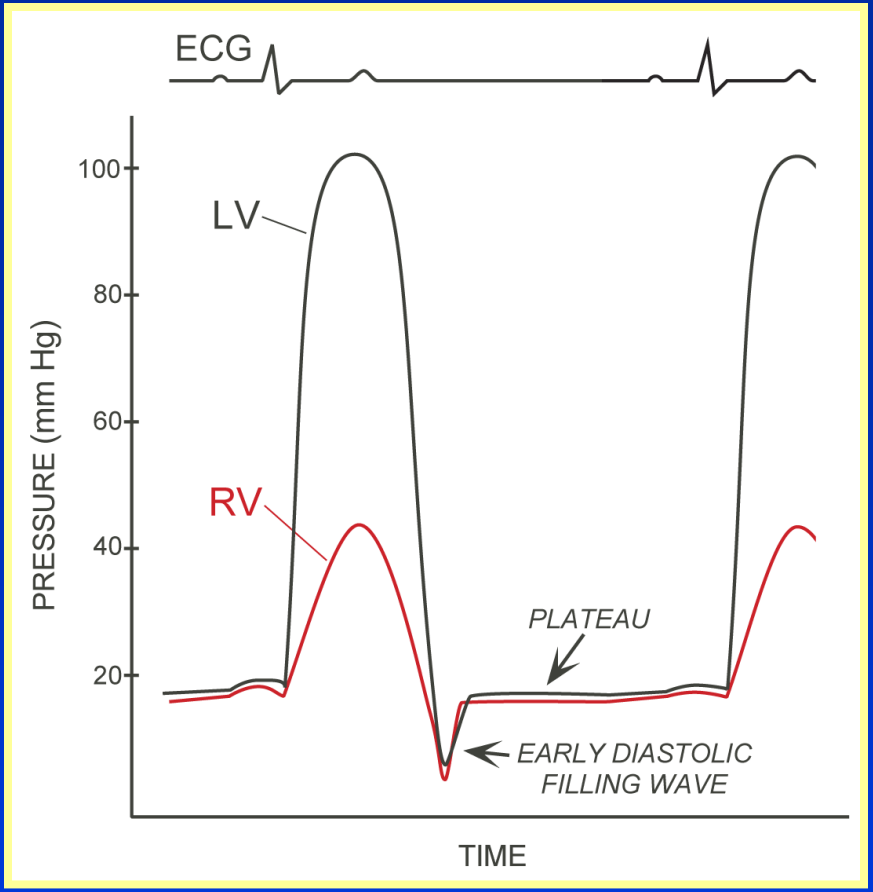
	Constrictive pericarditis	Cardiac tamponade
Pulsus paradoxus	+	+++
Kussmaul Sign	+++	+



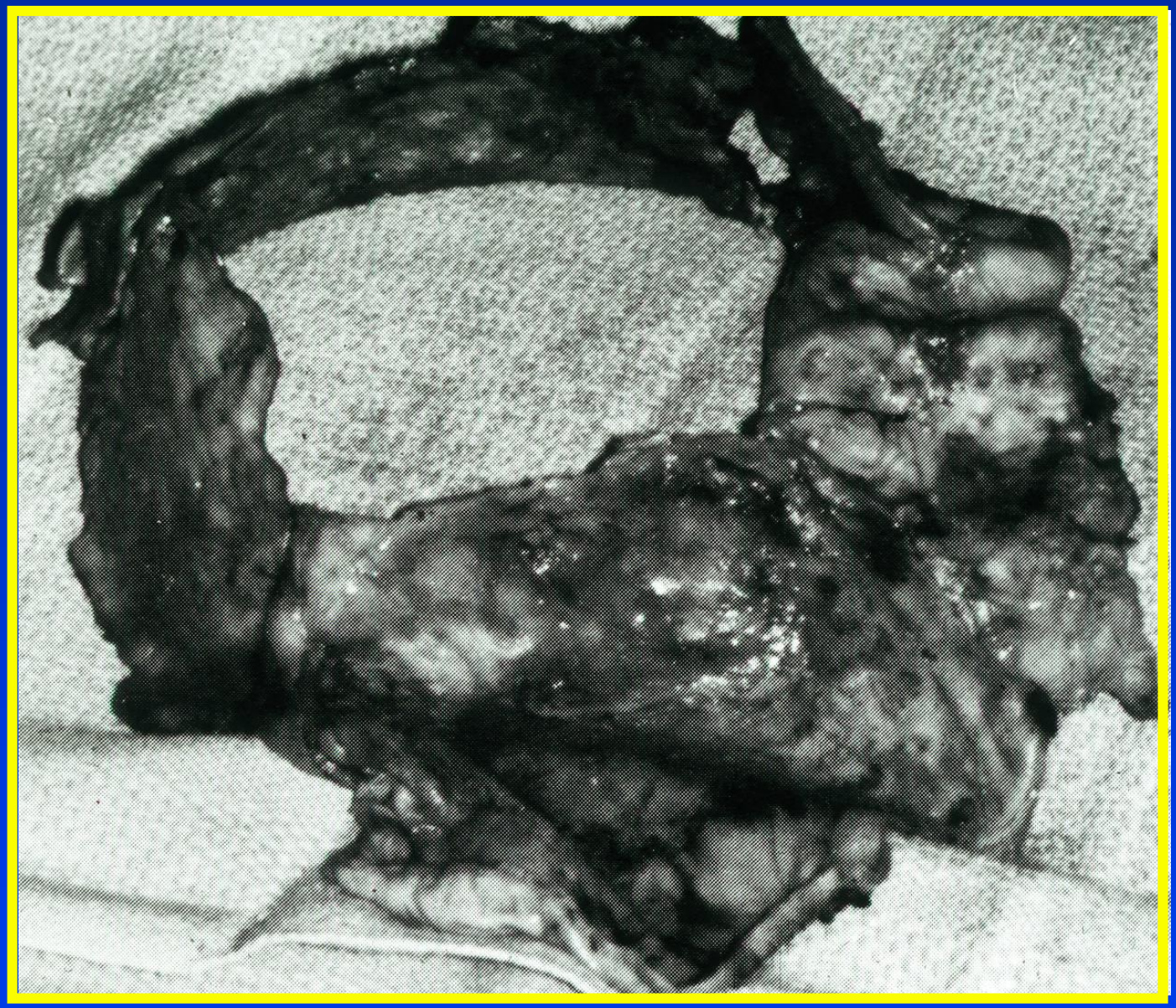
CT



CMR



1. Elevation of diastolic pressure in ventricles
2. Equalization of diastolic pressure in ventricles
3. “Dip and plateau” pressure pattern



Question #1

38 year old woman, previously healthy, presents with fever, pleuritic anterior chest pain and a pericardial friction rub.

ECG shows diffuse ST elevation and PR segment depression.

Echocardiography demonstrates a small posterior pericardial effusion, without cardiac chamber compression.

Which of the following is correct?

A. Glucocortocoid therapy is indicated to prevent progression of the effusion
B. A bacterial etiology is most likely responsible
C. The relapse rate is > 15%
D. Kussmaul sign is an expected physical finding

Which of the following is correct?

A. Glucocortocoid therapy is indicated to prevent progression of the effusion
B. A bacterial etiology is most likely responsible
C. The relapse rate is > 15%
D. Kussmaul sign is an expected physical finding

Question #2

56 year old man presents with exertional dyspnea, marked jugular venous distention and peripheral edema; no pulsus paradoxus.

History of Hodgkin Disease 18 years earlier, treated with chemotherapy and thoracic radiation therapy.

As part of evaluation, right-sided heart catheterization was performed:

Chamber	*Pressure (mm Hg)*	*Normal (mm Hg)*
Right atrium (mean)	16	≤ 8
Right ventricle	30/17	≤ 30/8
Pulmonary wedge (mean)	16	≤ 10

Which of the following is true?

A. Pericardiocentesis should be performed urgently
B. Therapy should include diuretic, ACE inhibitor and beta-blocker
C. CT scan would be more helpful than echocardiography in confirming diagnosis
D. Sinus bradycardia is likely present

Which of the following is true?

A. Pericardiocentesis should be performed urgently
B. Therapy should include diuretic, ACE inhibitor and beta-blocker
C. CT scan would be more helpful than echocardiography in confirming diagnosis
D. Sinus bradycardia is likely present

Additional Reading

1. Adler Y, Charron P, Imazio M, et al. 2015 ESC guidelines for the diagnosis and management of pericardial diseases. *Eur Heart J* 2015;36:2921-64.
2. Brucato A, Imazio M, Gattorno M, et al. Effect of anakinra on recurrent pericarditis among patients with colchicine resistance and corticosteroid dependence: the AIRTRIP randomized clinical trial. *JAMA* 2016;316:1906-12.
3. Chiabrando JG, Bonaventura A, Vecchié A, et al. Management of acute and recurrent pericarditis: JACC state-of-the- art review. *J Am Coll Cardiol* 2020;75:76-92.
4. Cremer PC, Kumar A, Kontzias A, et al. Complicated Pericarditis: Understanding Risk Factors and Pathophysiology to Inform Imaging and Treatment. *J Am Coll Cardiol* 2016 (68):2311–28
5. Klein AL, Imazio M, Cremer P, et al. Phase 3 trial of interleukin-1 trap rilonacept in recurrent pericarditis. *N Engl J Med* 2021;384:31.
6. Lilly LS. Treatment of acute and recurrent idiopathic pericarditis. *Circulation* 2013;127:1723.
7. Leung, YY, Yao Hui LL, Kraus VB. Colchicine--Update on mechanisms of action and therapeutic uses. *Semin Arthritis Rheum* 2015 Dec;45(3):341-50.
8. LeWinter M, Kontzias A, Lin D et al. Burden of Recurrent Pericarditis on Health-Related Quality of Life. *Am J Cardiol* 2021 (141): 113-119.