Recurrent Pericarditis: diagnosis updates.

By
Dr. Ekhlas Hussein

The Pericardium

Fibrous pericardium
Serous pericardium
visceral and parietal layers.
Recurrent pericarditis

What is the problem!!!

### Rehospitalizations

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>1.7.1 Colchicine vs. control Rx</td>
<td>8</td>
<td>44</td>
<td>4</td>
<td>14</td>
<td>100.0%</td>
<td>0.56 [0.14, 2.23]</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>44</td>
<td>4</td>
<td>14</td>
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<td>0.56 [0.14, 2.23]</td>
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</table>

### Adverse Drug Effects

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
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<tbody>
<tr>
<td></td>
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<td></td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
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<tr>
<td>1.9.1 Colchicine vs. control Rx</td>
<td>5</td>
<td>60</td>
<td>0</td>
<td>60</td>
<td>45.0%</td>
<td>11.99 [0.65, 221.06]</td>
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<tr>
<td></td>
<td>3</td>
<td>42</td>
<td>1</td>
<td>42</td>
<td>54.2%</td>
<td>3.15 [0.31, 31.52]</td>
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<tr>
<td>Total events</td>
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<td>0</td>
<td>60</td>
<td>100.0%</td>
<td>5.27 [0.06, 32.76]</td>
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## Adverse Drug Effects

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events Total</th>
<th>Control Events Total</th>
<th>Odds Ratio M.H., Random, 95% CI</th>
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<tbody>
<tr>
<td>1.9.1 Colchicine vs. control Rx</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>COPE 2005</td>
<td>5</td>
<td>60</td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td>CORB 2005</td>
<td>3</td>
<td>42</td>
<td>1</td>
<td>42</td>
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<tr>
<td>Subtotal (95%) Cr</td>
<td>8</td>
<td>102</td>
<td>1</td>
<td>102</td>
</tr>
<tr>
<td>Total events</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00, Chi² = 0.52, df = 1 (P = 0.47), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect Z = 1.00 (P = 0.31)</td>
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<td></td>
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</table>

### 1.9.2 Statins vs. control Rx:

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events Total</th>
<th>Control Events Total</th>
<th>Odds Ratio M.H., Random, 95% CI</th>
<th>Odds Ratio M.H., Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Di Pasquale et al. 2007</td>
<td>1</td>
<td>28</td>
<td>0</td>
<td>27</td>
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<tr>
<td>Subtotal (95%) Cr</td>
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<td>28</td>
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<td>28</td>
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<tr>
<td>Total events</td>
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<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect Z = 0.96 (P = 0.51)</td>
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### 1.9.3 Steroids vs. control Rx:

<table>
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<th>Study or Subgroup</th>
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<th>Control Events Total</th>
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<th>Odds Ratio M.H., Random, 95% CI</th>
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<tbody>
<tr>
<td>Rashkova et al. 2003</td>
<td>1</td>
<td>11</td>
<td>0</td>
<td>10</td>
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<tr>
<td>Subtotal (95%) Cr</td>
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<td>11</td>
<td>0</td>
<td>11</td>
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<tr>
<td>Total events</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect Z = 0.15 (P = 0.88)</td>
<td></td>
<td></td>
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</table>

### 1.9.4 Steroids: low-dose vs. high-dose:

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events Total</th>
<th>Control Events Total</th>
<th>Odds Ratio M.H., Random, 95% CI</th>
<th>Odds Ratio M.H., Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Imazio et al. 2005</td>
<td>1</td>
<td>49</td>
<td>12</td>
<td>51</td>
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<tr>
<td>Subtotal (95%) Cr</td>
<td>1</td>
<td>49</td>
<td>12</td>
<td>51</td>
</tr>
<tr>
<td>Total events</td>
<td>1</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect Z = 2.53 (P = 0.01)</td>
<td></td>
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</tr>
</tbody>
</table>

Acute pericarditis is a common disorder in several clinical settings.

May be the first manifestation of an underlying systemic disease

Epidemiologic studies are lacking, and exact incidence and prevalence are unknown exactly.

0.1% of hospitalized patients

5% admission the ER for non-ischemic chest pain.

Recurrent or incessant activity of the disease has been reported in 15% to 50% of cases.

with a reasonable mean recurrence rate of 30%

Etiology always tricky

Remains idiopathic in approximately 85% of cases.

Difficult to diagnose

Requires a multimodality imaging approach.

Standard diagnostic evaluations are relatively low yield

Clinical Presentation

Chest Pain (41-100%)
Cough or dyspnea (31-57%)
Malaise (54-66%)
Weight Loss (40%)
Chills (68%)
Friction Rub (59-100%)
Gallop Rhythm (66%)
Fever (75-100%)

Laboratory testing
CBC – very high WBC (purulent pericarditis)
↑ESR
Chem-7 (uremic etiology)
↑CRP, ESR
HIV in selected cases
ANA
Rheumatoid factor
Blood cultures if febrile
Tuberculin skin testing
Viral cultures and antibody testing not indicated

Cardiac Isoenzymes - '?' helpful

MB fraction of CK and Troponin I are modestly elevated

The rise in TnI is related to the extent of myocardial inflammation.

Mores in younger age, male gender, presence of effusion.

Enzyme rise is transient, resolving within the first week

Not reliable to differentiate MI vs pericarditis

## Acute Pericarditis - Stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>PR segment</th>
<th>ST segment</th>
<th>T wave</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Depressed</td>
<td>Elevated</td>
<td>Upright (normal)</td>
</tr>
<tr>
<td>II</td>
<td>Normal</td>
<td>Normal</td>
<td>Upright (normal) or flattened</td>
</tr>
<tr>
<td>III</td>
<td>Normal</td>
<td>Normal</td>
<td>Inverted</td>
</tr>
<tr>
<td>IV</td>
<td>Normal</td>
<td>Normal</td>
<td>Upright</td>
</tr>
</tbody>
</table>

Spodick DH, Pericardial Disease. Braunwald 6th
Acute PCARD – Stage I

Pericarditis - Stage III
Pericarditis-Stage II

Imaging modalities
Chest X-ray

Recommended in all cases

Typically normal

Enlarged cardiac silhouette in effusion

Echocardiography

Normal unless there is an effusion

Presence of effusion supports the diagnosis, but absence does not exclude it.

The ACC/AHA/ASE all recommend to obtain an echo in any suspected pericardial disease.
Cardiac CT/MRI
• The normal pericardial thickness is considered **2 mm** while a thickness of over **4 mm** suggests a pericarditis.
Pericarditis due to specific conditions
Viral Pericarditis

Can occur in all ages but usually young adults

Simultaneous development of fever and precordial pain 10 – 12 days after a viral illness

Rising viral titers in sera may be obtained for confirmation of diagnosis

Hyperimmunoglobulin for CMV pericarditis.

Immunoglobulin for adeno- and parvovirus B19.

Interferon alpha or beta for Coxsackie B pericarditis
Viral pericarditis pericardioscopy

(B) epicardial in situ hybridisation positive for cytomegalovirus; (C) cytology of pericardial effusion; (D) epicardial immunofluorescence staining.

Bacterial Pericarditis

Staph., Strep.pneumoniae, B-hemolytic streptococci, Mycobacterium tuberculosis. Usually direct result from pulmonary infection. Patients often present in a critically ill state. Lab, Inflammatory marker, blood culture, fluid analysis, search for the primary sources of infection.
Dressler’s syndrome

It is an autoimmune attack on the pericardium that can occur 1-2 months post MI.

Myocardial antigens are exposed to the circulation after the MI.

the immune system sees these myocardial antigens as being “foreign”.


<table>
<thead>
<tr>
<th>Pericarditis</th>
<th>MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST segment</td>
<td></td>
</tr>
<tr>
<td>Diffuse, concave elevation in all leads except aVR, V6 w/o reciprocal changes</td>
<td>Localized, convex, with reciprocal changes in infarct</td>
</tr>
<tr>
<td>Height Not &gt; 5mm</td>
<td>Height may be &gt; 5 mm</td>
</tr>
<tr>
<td>PR depression</td>
<td></td>
</tr>
<tr>
<td>Frequent</td>
<td>Almost never</td>
</tr>
<tr>
<td>Q waves</td>
<td></td>
</tr>
<tr>
<td>Not usual, unless with infarct</td>
<td>Common with q wave infarct</td>
</tr>
<tr>
<td>T waves</td>
<td></td>
</tr>
<tr>
<td>Inverted after J returns to baseline</td>
<td>Inverted while ST still elevated</td>
</tr>
<tr>
<td>T inversions and ST ↑ are not seen simultaneously on the same EKG</td>
<td>T inversions and ST ↑ can be seen simultaneously on the same EKG</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td>Frequent</td>
</tr>
<tr>
<td>Conduction disturbances</td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td>frequent</td>
</tr>
</tbody>
</table>
Pericarditis

Acute apical infarction  Early Repolarisation

Tuberculosis

common in developing countries.

Either direct, lymphatic or hematogenous spread

Commonly have associated pleural effusions.

Subacute presentation/non-specific symptoms (fever, night sweats, fatigue)

Diagnosis if acid-fast bacilli found elsewhere

PCR for DNA of mycobacteria, adenosine deaminase, interferon-γ in pericardial fluid.

Ureamia

Uremic pericarditis is from toxins irritating and causing inflammation of the pericardium.

5% of people with advanced acute or chronic renal failure

More common in younger patients.

Uremic Pericarditis/Pericardial Effusion

Pericarditis for Other Reasons

Pericarditis from renal failure is a definite indication for dialysis.

Malignancy

Metastasizes to the pericardium, the cells can cause damage/inflammation.

most common followed by lymphomas and lung cancer.

Pericardial metastasis is a bad sign and indicates a very poor prognosis for survival.

Radiation Pericarditis

Usually occurs within the first year after exposure but can be delayed for many years

Recurrence effusions and constriction are common
Neoplastic pericarditis

Hodgkin’s disease:
(A) pericardioscopy findings;
(B) epicardial histology;
(C) cytology
of pericardial effusion;
(D) immunofluorescence

Recurrent pericarditis and systemic autoimmune diseases

Most of rheumatic diseases involve the pericardium.
SLE, Rh A, progressive SS, Sjögren's Syndrome, PAN, and other systemic vasculitides.

Prognosis for acute idiopathic pericarditis

Good long-term prognosis

Cardiac tamponade with specific etiologies

Constrictive pericarditis in about 1% of patients

Recurrent or incessant disease in 15-30% of patients

Recurrent pericarditis

The most troublesome complications of acute pericarditis. Two clinical forms:
(1) The intermittent type with symptom-free intervals without therapy.
(2) The incessant type: in which the discontinuation of anti-inflammatory therapy.

Idiopathic Recurrent acute Pericarditis (IRAP)

The evidence for this is the presence of pro-inflammatory cytokines such as IL-6, IL-8 and INF-gamma in pericardial fluid (these mediators are absent in the plasma, suggesting a local inflammatory reaction).

Presence of ANA antibodies in the sera of these patients, and the good response to anti-inflammatory.

C-reactive protein and erythrocyte sedimentation rate.

The long term outcome of IRAP is good.

Antonio Brucato et al Recurrent pericarditis: Infectious or autoimmune Autoimmunity Reviews Volume 8, Issue 1, October 2010, Pages 44–47

Pathophysiology

Autoimmune responses in predisposed individuals following several exogenous triggers lead to the development of autoimmune responses.

Immunity Products of bacteria and viruses, termed PAMPs (pathogen associated molecular patterns), can interact with the toll like receptors (TLRs), molecules expressed at the cell surface of dendritic cells (DCs) and in endosomes of DCs, that function to discriminate “self” from microbial “non self”

DCs are antigen presenting cells and may promote primary T and B cell responses.

Man BL, Mok CC Serositis related to systemic lupus erythematosus: prevalence and outcome. Lupus 14:822–826
Natural killer (NK) cells, are involved via cytokine secretion and cytolytic activity, may play a role in autoimmune responses by interacting and providing stimulatory signals for DCs and T cells (loss of self recognition).

NK cells may either prevent/limit autoimmune responses or may have a permissive role in autoimmunity through suppression and lysis of DCs or activated T cells, on one hand, and their inappropriate activation on the other hand.


Recurrent pericarditis and monogenic auto-inflammatory disorders

Group of conditions characterized by spontaneously relapsing and remitting attacks of systemic inflammation without apparent involvement of antigen-specific T cells or significant production of auto-antibodies.

Usually manifest in the pediatric population.

familial Mediterranean fever (FMF) and tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS)

Tumor necrosis factor receptor-associated periodic syndrome TRAPS

patients with TRAPS mutations had more frequently a positive family history for pericarditis and periodic fever syndromes (p<0.001), a higher mean number of recurrences after the first year of colchicine treatment (p<0.001), and a higher need immunosuppressive therapies (p<0.001).
TNF receptor (TNFR) signaling pathway

Genomic structure of TNFRSF1A gene and TRAPS disease related sequence variants.
Familial Mediterranean fever

FMF the incidence of pericardial involvement 1.4% but the incidence rises to 27% in echocardiographic studies.


<table>
<thead>
<tr>
<th>Diseases</th>
<th>Gene</th>
<th>Chromosome position</th>
<th>Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary periodic fevers</td>
<td>FMF</td>
<td>MEVF 16p13.3</td>
<td>AR</td>
</tr>
<tr>
<td>TRAPS</td>
<td>TNFRSF1A 12p13</td>
<td>p55 TNF-α receptor</td>
<td>AD</td>
</tr>
<tr>
<td>Cryopyrinopathies</td>
<td>NLRP3 1q44</td>
<td>Cryopyrin</td>
<td>AD</td>
</tr>
</tbody>
</table>

Anti-heart autoantibody (AHA) immunofluorescence patterns.

Autoreactive Pericarditis
Diagnostic Criteria

Pericardial fluid revealing >5000/mm³ mononuclear cells or antisarcolemmal antibodies

Inflammation in epicardial/endomyocardial biopsies by >14 cells/mm²

Exclusion of active viral infection both in pericardial effusion and endocardial/epicardial biopsies

Exclusion of tuberculosis, borrelia burgdorferi, chlamydia pneumoniae and other bacterial infection

Absence of neoplastic infiltration in effusion and biopsy samples

Exclusion of systemic, metabolic disorders and uremia

(A) pericardioscopy findings and aimed biopsy, (B) epicardial histology, (C) cytology of pericardial effusion, (D) epicardial immunofluorescence.
Take-home messages

The etiology and pathogenesis of idiopathic recurrent acute pericarditis stand like a bridge that crosses infectious, autoimmune and auto-inflammatory pathways.

Precise diagnosis need extensive work with low yield.

Follow your clinical sense as worthy efforts may not be applied in the appropriate direction.