



# Post-cardiac injury syndrome in the Emergency Department: mini-review

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## Article Info

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## ABSTRACT

The term post-cardiac injury syndrome (PCIS) defines a group of inflammatory diseases involving predominantly the pericardium. The syndrome results from a cardiac injury and refers mainly to post-myocardial infarction pericarditis, post-pericardiotomy syndrome and post-traumatic pericarditis (including iatrogenic conditions appearing after percutaneous interventions).

Signs and symptoms are similar to those seen in acute pericarditis and pericardial effusion in other clinical settings. The diagnosis is clinical and could be challenging in the Emergency Department (ED). PCIS should be considered as an alternative diagnosis to acute pericarditis in case of unilateral right-sided, massive, or transudative pleural effusion.

Although typically a benign condition, PCIS may result in significant morbidity and potential mortality; tamponade and constrictive pericarditis represent the leading complications. Therefore, early detection is clinically relevant. Currently, a combination of nonsteroidal anti-inflammatory drugs and colchicine is the mainstay treatment for this condition. Colchicine has also appeared to be effective in primary prevention of PCIS after cardiac surgery.

The purpose of this article is to review the principle clinical characteristics of PCIS in order to achieve an early diagnosis.

## Introduction

The pericardium is a fibroelastic sac made up of visceral and parietal layers separated by a virtual space, the pericardial cavity. In healthy individuals, the pericardial cavity contains 15 to 50 mL of an ultrafiltrate of plasma. Acute pericarditis refers to inflammation of the pericardial sac; extension of this inflammation to the myocardial tissues leads to myopericarditis or perimyocarditis, depending on whether the disease is primarily myocarditic or pericarditic, respectively. The main aetiologies of pericardial effusion include infectious, neoplastic and connective tissue diseases and iatrogenic causes, but up to 50% of cases remains idiopathic.

Pericarditis with or without a pericardial effusion resulting from injury of the pericardium constitutes the post-cardiac injury syndrome (PCIS).

The PCIS appears to be produced by an initial injury to the myocardium, leading to the release of cardiac antigens that stimulate the immune response. Immune complexes are then generated and deposit in the pericardium, pleura, and lungs, eliciting an inflammatory response<sup>1</sup>. The following observations support this hypothesis:

- the discrete latent period from cardiac injury to the clinical onset of PCIS;
- the coexistence of pleural effusion and/or pulmonary infiltrates;
- a statistically significant correlation between post-operative to pre-operative ratios of anti-actin and anti-myosin antibodies and the clinical occurrence of post-cardiac injury syndrome;
- the generally excellent response to anti-inflammatory therapy, and occasional relapse after steroid withdrawal.

## Post-cardiac injury syndrome

### Clinical features

The term PCIS refers to the following principal conditions: post-myocardial infarction pericarditis, post-pericardiotomy syndrome (PPS) and post-traumatic pericarditis (either iatrogenic or not)<sup>2</sup>.

PCIS was first described after myocardial infarction by Dressler in 1956<sup>3</sup>. For this reason, late post-MI pericarditis is frequently referred to as Dressler syndrome. This disorder must be distinguished from the pericarditis and/or pericardial effusion which may occur early (< 7 days) after a transmural MI, as a result of involvement of the epicardial surface or rupture of the free wall of the left ventricle.

PPS can occur after the pericardium is opened, even though no other cardiac structures are involved (e.g., after surgery for bronchogenic lung carcinoma). Post-traumatic pericarditis can be triggered by blunt or penetrating trauma<sup>4</sup>, but it could also complicate percutaneous coronary interventions, ablation procedures and pacemaker lead insertion<sup>5</sup>.

Patients who develop PCIS present with signs and symptoms similar to those seen in acute pericarditis and/or pericardial effusion in other clinical settings.

The main features of the post-cardiac injury syndrome include:

- Predisposition and latency: this condition should be considered in patients with a history of prior injury to, or invasion of, the pericardium, myocardium, or both, who develop a pericarditis or a pericardial effusion after a latent period (typically weeks to months) from the injury.
- Signs and symptoms: a review by Imazio et al.<sup>6</sup> reported that the main clinical findings include pleuritic chest pain (56%) and fever (54%); leucocytosis and other markers of inflammation (74%) (e.g., elevated erythrocyte sedimentation rate,

elevated C-reactive protein); electrocardiographic changes (24%), classically diffuse ST-segment elevation in association with PR depression, although often absent or masked by other electrocardiogram findings; pericardial (89%) and sometimes pleural effusion (with or without a pulmonary infiltrate), pericardial rub (32%), cardiac tamponade (2%).

- Treatment: diagnosis is suggested by an excellent response to non-steroidal anti-inflammatory drugs, colchicine, and glucocorticoids.
- Tendency to recur.

### Epidemiology

The incidence of PCIS is not entirely clear. Studies performed in post-MI patients in the era prior to reperfusion therapies reported different rates of PCIS, with incidences between almost 0% and 3%<sup>7,8</sup>. Currently, Dressler syndrome seems to have largely disappeared in patients undergoing reperfusion strategies, perhaps due to decreased infarct size<sup>9</sup>. In a cohort study of 201 consecutive patients with acute MI treated with fibrinolysis, only one patient developed post-cardiac injury syndrome, and this patient had no evidence of reperfusion<sup>10</sup>. In a study by Imazio et al., of 743 patients with ST-segment elevation acute myocardial infarctions treated with primary percutaneous coronary intervention, early post-MI pericarditis was diagnosed in 31 patients (4.2%), while Dressler syndrome was recorded in only 1 patient (0.1%); both the conditions were associated with a larger ischemic area and/or late reperfusion<sup>11</sup>.

PPS has been reported to occur in 10 to 40% of patients after cardiac surgery<sup>5</sup>, but the incidence is variable depending on the population studied. Van Osch D et al. in an observational study, reported an incidence of 14.5% of PCIS in 822 patients undergoing non emergent valve surgery<sup>4</sup>, while in another study of 688 patients undergoing coronary artery bypass grafting (CABG), the authors reported an incidence of 9%, with 22% of patients requiring pleural drainage, and 5% pericardiocentesis<sup>12</sup>.

PCIS following electronic cardiac device implantation is a rare complication with a reported incidence of <5%<sup>13</sup>. In an observational study reviewing 4,705 medical records of patients subjected to device implantations, though, the incidence of PCIS was reported to be lower (1.61 cases per 1,000 procedures)<sup>14</sup>.

### Etiopathogenesis

The exact pathogenesis of PCIS remains uncertain. PCIS seems to be an autoimmune phenomenon mediated by a combined activation of both cell-mediated and humoral mechanisms<sup>15</sup>. Some observations supporting this association are the latent period between cardiac

injury and the onset of PCIS, the correlation between titers of different antibodies (particularly the elevated levels of anti-actin and anti-myosin antibodies) and the clinical occurrence of PCIS and the excellent response to anti-inflammatory therapy. However, the significance of these antibodies and their relation to the severity of myocardial injury is still unclear<sup>15</sup>.

Nowadays, PCIS is regaining importance and interest as an emerging cause of pericarditis, especially in developed countries, due to a great and continuous increase in the number and complexity of percutaneous cardiologic procedures<sup>16</sup>.

### PCIS in the Emergency Department

In the ED the major challenge is the early diagnosis of PCIS. The diagnostic evaluation of all patients with suspected post-cardiac injury syndrome includes:

- laboratory testing: complete blood count (CBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and troponin. Most, but not all, patients will have an elevation of white blood cell counts and inflammatory markers (CRP and ESR);
- 12-lead electrocardiogram (ECG): a 12-lead ECG should be performed in all patients with suspected PCIS, although it is difficult to make the diagnosis based on ECG findings alone. The ECG is most often abnormal in case of myocardial infarction or other forms of cardiac surgery;
- chest radiograph: in PCIS typical findings on chest X-ray include pleural effusion and an increase in heart size, due to the presence of pericardial effusion; pulmonary infiltrates are occasionally seen. More than 15% of PCIS patients have right-sided pleural effusion (except for Dressler syndrome), 25% have an opacification of half or more of the hemithorax, and nearly two-thirds present hemotorax. The majority of pleural fluids met Light's exudative criteria (97%) in which lymphocytes predominated (74%)<sup>17</sup>. Nevertheless, it is not possible to definitively make the diagnosis based on these findings alone;
- echocardiogram: the main echocardiographic finding in PCIS is pericardial effusion. Echocardiography should document the size of the effusion and provide echocardiographically-derived hemodynamic data, in order to evaluate the presence of cardiac tamponade. In patients with limited imaging window, transoesophageal echocardiography may be required.

Difficulty or total failure in visualizing pacemaker wires is not rare if the spatial orientation of the echocardiography two-dimensional beam does not cut across the path of the

wire<sup>18</sup>; thus, if PCIS following electronic cardiac device implantation is suspected, Computed Tomography scans may accomplish the diagnosis of lead perforation<sup>19</sup>.

According to the 2015 European Society of Cardiology (ESC) guidelines for the diagnosis and management of pericardial diseases<sup>2</sup> in patients with a history of previous myocardial injury (most commonly 1 week to 3 months before the presentation), the diagnosis of PCIS is made if the patient meets two of these five criteria: fever without an alternative explanation, pericardial and/or pleuritic chest pain, pleural or pericardial rubs, pericardial and/or pleural effusion, typical laboratory findings including elevated white blood counts and increased CRP.

The differential diagnosis of PCIS includes several conditions: infectious or malignant pleuropericarditis, pulmonary embolism, blunt chest wall trauma, oesophageal rupture, pneumothorax and connective tissue disorders. Although typically rather benign, PCIS may result in significant morbidity and potential mortality due to fatal arrhythmias and cardiac tamponade. Therefore, its early detection is clinically relevant<sup>20</sup>.

### Treatment

Nonsteroidal anti-inflammatory drugs (NSAIDs), preferably aspirin or ibuprofen, are the first-line treatment, often combined with gastrointestinal protector. The 2015 ESC guidelines suggest that NSAIDs selection should be based on criteria other than efficacy, such as likelihood of side effects or other aspirin indications (e.g., patients already on antiplatelet therapy or in PCIS after MI)<sup>2</sup>.

Colchicine should also be considered in addition to aspirin or other NSAIDs for the therapy of PCIS. The duration of therapy is at least of three to four weeks and is based on the persistence of symptoms<sup>2</sup>. In case of incomplete response to the therapy, the addition of systemic corticosteroids to colchicine may be considered, once a specific cause of pericarditis has been excluded, in order to achieve a better control of symptoms. It must be taken into account, though, that the use of corticosteroids in pericardial diseases has been associated with a higher rate of chronicity and more recurrences<sup>6</sup>.

Moreover, therapeutic thoracentesis may be considered in moderate to large pleural effusions to improve respiratory symptoms.

Most experts suggest to recheck inflammatory markers after symptoms resolution to ensure the inflammation is resolved prior to tapering or discontinuing therapy.

### Prevention

The widespread use of early reperfusion therapy and cardiac medications with anti-inflammatory properties may have reduced the incidence of PCIS<sup>21</sup>. Several strategies

(aspirin, corticosteroids, colchicine) have been examined in clinical trials for primary prevention of post-pericardiotomy syndrome<sup>22</sup>. In the COLchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS) trial colchicine appeared to be safe and efficacious in the prevention of the PPS and its related complications<sup>23</sup>; this results were confirmed by the following COLchicine for Prevention of the Post-pericardiotomy Syndrome and Post-operative Atrial Fibrillation (COPPS-2) trial<sup>24</sup>. Consequently, a 30-day course of colchicine beginning one to three days following surgery (0.5 mg twice daily for patients  $\geq$  70 kg, 0.5 mg daily for those <70kg) should be considered according to the latest ESC guidelines for the prevention of PPS<sup>2</sup>.

### Prognosis and follow-up

The prognosis of the PCIS is relatively good for most patients; however, 10 to 15% of cases will experience a recurrence<sup>5</sup>. A long-term follow-up with echocardiography every 6–12 months is needed due to the small but distinct risk of developing constrictive pericarditis<sup>2</sup>.

### Conclusions

PCIS should be included in the differential diagnosis of chest pain in the Emergency Department, because it is one of the most common forms of acquired pericardial diseases. This diagnosis should be considered in all patients with a history of a recent cardiac surgery or procedure, presenting after a latent period (weeks to months) with pleuritic chest pain and fever. In this context, the auscultation of a pericardial rub, the concomitant presence of pericardial effusion on imaging tests, and increased value of CRP and white blood cells are all features that strongly suggest a diagnosis of PCIS.

Most patients respond satisfactorily to the combination of a NSAID and colchicine. Corticosteroids can be considered when NSAIDs are contraindicated or ineffective. The post-operative use of colchicine may also prevent the development of PCIS in patients undergoing cardiac surgery. Since pleural involvement is frequent, therapeutic thoracentesis may be considered in order to hasten resolution of symptoms in moderate to large pleural effusions.

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### Conflicts of interest

There are no conflicts of interest.

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