Pleural Effusions Following Cardiac Injury and Coronary Artery Bypass Graft Surgery

Richard W. Light, M.D.¹,²

ABSTRACT

This article discusses the pleural effusions that occur with the post–cardiac injury (Dressler’s) syndrome (PCIS) and those that occur after coronary artery bypass graft (CABG) surgery. The PCIS can occur after any type of cardiac injury and is thought to be due to antimyocardial antibodies. The primary symptoms are fever and chest pain, and pericarditis is frequently present. Pleural effusions are common with PCIS. The primary treatment for PCIS is a nonsteroidal anti-inflammatory agent or corticosteroids. Following CABG surgery, most patients will have a small unilateral left-sided pleural effusion, and approximately 10% of patients will have a larger effusion. These large effusions can be separated into early effusions occurring within the first 30 days of surgery that are bloody exudates with a high percentage of eosinophils, and late effusions occurring more than 30 days after surgery that are clear yellow lymphocytic exudates. The primary symptom of a patient with a pleural effusion post–CABG surgery is dyspnea; chest pain and fever are uncommon. Most patients with large pleural effusions postCABG surgery are managed successfully with one to three therapeutic thoracenteses.

KEYWORDS: Pleural effusion, CABG surgery, postcardiac injury syndrome

Objectives: Upon completion of this article, the reader should understand the etiology, diagnosis, and management of the post–cardiac injury syndrome and the pleural effusions that occur after coronary artery bypass surgery.

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Incidence

The incidence of PCIS has varied markedly from series to series. The explanation is obvious when the above mentioned definition is used. If one evaluates patients critically, most patients with cardiac trauma will meet the criteria for uncomplicated PCIS. Most patients post–cardiac trauma will have evidence of a systemic inflammatory response as evidenced by increased serum levels of interleukin-6 (IL-6). Probably there is a continuum of responses post–cardiac trauma ranging from mild fever and chest soreness to the complete Dressler’s syndrome with fever, pleuritic chest pain, pleural effusion, pericardial effusion, and parenchymal infiltrates.

When Dressler first described the syndrome following myocardial infarction, he stated that the incidence was 3 to 4%. Subsequent articles have indicated that the incidence is less than 1% following myocardial infarction. However, if the patient has pericarditis in the few days following the myocardial infarction, then the incidence of PCIS is approximately 15%. In recent years the incidence of PCIS after myocardial infarction has decreased to less than 0.5%. This has been attributed to the increased use of thrombolytics resulting in early reperfusion and less tissue damage.

The reported incidence of PCIS following cardiac surgery has varied from 15 to 30%. In a recent series of 266 children undergoing cardiac surgery, the incidence of uncomplicated PCIS was 11.2%, whereas the incidence of complicated PCIS was only 3.4%. In an older series of 966 adults undergoing cardiac surgery at Johns Hopkins Hospital, the incidence of PCIS was 17.8%. To be classified as having the PCIS in this series, patients were required to have two or three of the following signs and symptoms during their hospitalization or follow-up visit: (1) fever greater than 37.8°C, (2) significant anterior chest pain suggestive of pericardial inflammation, and (3) a two- or three-component pericardial friction rub on auscultation. The incidence of PCIS was comparable after all types of cardiac surgery. However, there was a higher incidence of PCIS if the patient had a history of pericarditis or if the patient had taken corticosteroids previously.

Etiology

The etiology of the PCIS is not completely known, but it appears to have an immunologic basis. When the myocardium is injured, cellular components, including autoantigens, are released. These autoantigens can provoke an autoimmune antibody reaction by antimyocardial antibodies. Subsequently, complement is activated, C3 and C4 levels fall, and leukocytes are mobilized.

There is a close relationship between the occurrence of PCIS and the development of antimyocardial antibodies in patients undergoing surgical procedures involving the pericardium. In one prospective study of 257 patients, 67 patients (26%) developed high titers of antimyocardial antibodies, and all 67 developed PCIS. In contrast, none of 102 patients without a rise in antibody titers and only 4 of 93 patients with intermediate titers developed the syndrome.

There is not a clear-cut relationship between the development of antimyocardial antibodies and PCIS in patients with myocardial infarction. In one study of 136 patients with myocardial infarction, there was no association between the development of the syndrome and the presence of antimyocardial antibodies.

Epidemiological studies have indicated that there are other factors that appear to be associated with the development of the post–cardiac injury syndrome. There is a seasonal variation in the post–cardiac injury syndrome, with the highest incidence corresponding to the time of the highest prevalence of viral infection in the community. De Scheerder and coworkers have hypothesized that a concurrent viral infection may trigger the immune response.

Clinical Manifestations

The clinical manifestations of PCIS include fever, chest pain, pericarditis, pleuritis, and/or pneumonitis. As commented upon previously in this article, however, many patients are given the diagnosis of PCIS with only two of the five manifestations. Following myocardial infarction, the symptoms usually develop in the second or third week; an occasional patient develops symptoms within the first week, whereas a larger percentage develop symptoms only after the third week. Following cardiac surgery, the syndrome is seen at an average of 3 weeks but can occur any time between 3 days and 1 year.

The two cardinal symptoms of PCIS are chest pain and fever. The chest pain often precedes the onset of fever and varies from crushing and agonizing, mimicking myocardial ischemia, to a dull ache to pleuritic chest pain. A pericardial friction rub is present in almost all patients and a pericardial effusion is present in the majority. Laboratory evaluation reveals a peripheral leukocytosis and an elevated erythrocyte sedimentation rate (> 100 mm/hr) in most patients. The chest radiograph reveals pulmonary infiltrates in the majority of patients. Approximately 80% of the patients will have a pleural effusion, and the effusions are bilateral in approximately 50%. When the effusions are unilateral, they are more commonly on the left than on the right. The pleural fluid is an exudate with a normal pH and a normal glucose level. The pleural fluid is frankly bloody in about 30% of patients, and the differential cell count may reveal predominantly polymorphonuclear leukocytes or mononuclear cells depending upon the acuteness of the process.
Diagnosis
The diagnosis of PCIS should be considered in any patient who develops a pleural effusion following trauma to the heart and who is febrile and has chest pain. Since there are no specific tests with which to establish the diagnosis, the diagnosis is made by excluding other diseases that can produce identical symptoms in the patient post–cardiac injury. The main diagnoses to exclude are pleural effusions post–coronary artery bypass (CABG) surgery, congestive heart failure, pulmonary embolism, and pneumonia with a parapneumonic effusion or empyema. Pleural effusions due to PCIS and those due to CABG surgery are distinguished primarily by the patient’s symptoms; patients with pleural effusions due to PCIS invariably have chest pain and fever, whereas those with pleural effusions post–CABG surgery have dyspnea, but no chest pain or fever. Congestive heart failure is excluded if the pleural fluid is an exudate. The possibility of pulmonary embolism can be evaluated with a spiral computed tomography (CT) scan or with a perfusion lung scan. It is important not to mistakenly diagnose the PCIS as a pulmonary embolism. Anticoagulation is contraindicated with the PCIS syndrome because patients with the syndrome are positive or the pleural fluid is purulent. One report suggested that the diagnosis of the syndrome could be established by demonstrating a high titer of antimitochondrial antibody and a low complement level in the pleural fluid.

Prevention and Treatment
There is no known means by which to prevent the development of PCIS. Mott and coworkers randomized 246 children who were undergoing cardiac surgery with cardiopulmonary bypass to receive intravenous methylprednisolone (1 mg/kg) or saline prior to cardiopulmonary bypass and 6 hours for four doses post-surgery. They found that the incidence of PCIS was identical in the two groups. Possibly a different result would have been obtained if the corticosteroids had been given for a longer duration.

Once the syndrome has developed, it usually responds to treatment with anti-inflammatory agents such as aspirin or indomethacin. My choice is indomethacin 25 to 50 mg every 8 hours. Although a single episode of the PCIS is usually self-limited, recurrences are frequent. Recurrent episodes become progressively more resistant to treatment with nonsteroidal anti-inflammatory agents, but usually respond to corticosteroid therapy. Prednisone is administered orally in doses of 40 to 60 mg daily with rapid tapering over 8 to 10 days. If symptoms recur when the prednisone is tapered, additional courses are indicated.

One report suggested that the development of the PCIS postoperatively in patients who had undergone CABG surgery was a very serious event because the grafts were likely to be occluded by the inflammatory process. When 31 subsequent patients were treated with prednisone, 30 mg per day for a week and tapering doses for 5 weeks thereafter, in addition to aspirin 600 mg qid, only 16% of the grafts became occluded. However, it should be noted that this report has not been validated since it was originally published in 1976.

PLEURAL EFFUSIONS POST–CORONARY ARTERY BYPASS SURGERY
More than 600,000 patients undergo CABG surgery in the United States each year. Given that approximately 10% of the patients who undergo CABG surgery will develop a pleural effusion occupying more than 25% of the hemithorax in the subsequent month, CABG surgery is one of the more common causes of pleural effusions in the United States.

Incidence
Many patients who undergo CABG surgery will develop a small, left-sided pleural effusion in the first few days postoperatively. In one study of 122 patients, the incidence of pleural effusion on the routine chest radiograph 6 days postoperatively was 42%. In this study, the incidence of pleural effusion was nearly identical in patients who received internal mammary artery (IMA) graphs (43%) and in those that received only saphenous vein grafts (SVG) (41%). Approximately 80% of the effusions in this series were small (occupying less than one intercostal space) and were unilateral left-sided. In a second study the same investigators performed chest ultrasound at 7, 14, and 30 days postoperatively on 47 patients and reported that the prevalence of pleural effusion was 89% at 7 days, 77% at 14 days, and 57% at 30 days. The higher incidence of effusion in this latter series was attributed to the increased sensitivity of ultrasound as compared with the chest radiograph at detecting pleural fluid. The majority of the pleural effusions were unilateral and left sided in this series. In contrast to the previous study, the prevalence of pleural effusions was higher in this series if the patients received an IMA graft. In a third study, Landymore and Howell reported that at the time of discharge from the hospital, the incidence of pleural effusion was 91% in 34 patients who had received an IMA graft and had the pleura opened, whereas the incidence of pleural effusion was
58% in 33 patients who had received an IMA graft but in whom the pleura was not opened.22

The natural history for the small, unilateral, left-sided effusions is gradual resolution.21,22 However, in certain patients, the effusion enlarges and produces symptoms. Hurlbut and associates23 obtained chest radiographs 8 weeks postoperatively on 76 patients who had received IMA grafts and reported that 5 of 55 patients (9.1%) who underwent pleurotomy and 3 of 21 patients (14.5%) who had an IMA without pleurotomy had a pleural effusion at the 8-week follow-up visit. Four of these 76 patients underwent thoracentesis. In a recent prospective study from our institution,19 the prevalence of pleural effusions at approximately 30 days post-operatively on chest radiographs in 349 patients who had undergone CABG surgery was 63%. Although most of the effusions were small, 34 of the 349 patients (9.7%) had a pleural effusion that occupied more than 25% of the hemithorax. The incidence of large effusions was higher in the 282 patients who received an IMA graph (10.9%) than in the 67 patients that received only SVG graphs (4.5).

**Etiology**

The pathogenesis of the pleural effusions following CABG surgery is not definitely known. The early, small, left-sided effusions are probably related to the trauma of surgery including phrenic nerve injury and atelectasis. Large effusions (those occupying more than 25% of the hemithorax) can be divided into two categories: those occurring within the first 30 days and those occurring after the first 30 days.24,25 The early effusions are usually bloody with a median hematocrit above 5%. The likely etiology of these effusions is trauma from the surgery and postoperative bleeding into the pleural space.25

The etiology of the effusions occurring later is unclear. These effusions tend to be clear with a predominance of lymphocytes in the pleural fluid.24,25 It has been suggested that these effusions are manifestations of the PCIS.26 However, it is unlikely that these effusions represent the PCIS because the two main clinical manifestations of the PCIS are chest pain and fever; both symptoms are very uncommon in patients with pleural effusions more than 30 days after surgery.19

The observation that the pleural fluid associated with the late effusions post–CABG is lymphocytic suggests an immunological etiology. To my knowledge there have been no studies of the serum levels of antimyocardial or antimesothelial cell antibodies in these individuals. Antimyocardial antibody was detected in the pleural fluid and in the serum of one patient with a pleural effusion secondary to PCIS post–CABG surgery. However, we could detect no antimyocardial antibody in the pleural fluid of 25 patients with pleural effusions post–CABG (unpublished observations) who did not have fever and chest pain.

When pleural specimens from patients undergoing thoracoscopy for persistent post-CABG pleural effusions are examined, there is an intense lymphocytic pleuritis with little fibrosis within the first few months of surgery (Fig. 1).27 Immunohistochemical analysis demonstrates that there is a mixed population of lymphocytes with a predominance of B cells.27 As time goes on, there is a gradual decrease in the cellular infiltrate and a gradual increase in the degree of fibrosis.27 After 1 year or more, the pleura is markedly thickened with increased amounts of dense fibrous tissue (Fig. 2). The fibrous component is typically paucicellular, but it does contain collections of entrapped cells that are cytokeratin immunoreactive, compatible with mesothelial cells.27

The occurrence of pleural effusions post–CABG surgery is increased if the patient receives topical hypothermia at the time of surgery with iced slush. Nikas and coworkers studied 505 nonrandomized consecutive patients undergoing CABG surgery and reported that 60% of the 191 patients who received topical hypothermia had a pleural effusion, whereas only 25% of the 314 patients who did not receive topical hypothermia developed a pleural effusion.28 Moreover, 25% of those in the hypothermia group required a thoracentesis, whereas only 8% of those in the control group required a thoracentesis.28 In a second study, Allen and associates reported that the incidence of pleural effusion was 50% in 50 patients who received topical hypothermia but only 18% in 50 patients who did not receive topical hypothermia.29 These data suggest that cold injury to the phrenic nerve resulting in atelectasis may cause the pleural effusion.

As mentioned previously, patients who receive an IMA graft are more likely to develop a large pleural effusion than are those who receive only SVG. In addi-
tion, the type of chest drain used postoperatively may influence the development of pleural effusions. Robinowitz-Elins and associates reported that a thoracentesis was required in only 2 of 295 patients (1%) who received a Blake Drain (19F) postoperatively compared with 48 of 1547 (3.1%) who received a conventional chest tube (32F).30 We recently reported that patients who underwent CABG surgery off pump (without cardiopulmonary bypass) had a lower incidence of large pleural effusion 4 weeks postoperatively than did those who underwent CABG surgery with cardiopulmonary bypass.31

Clinical Manifestations
The primary symptom of patients with pleural effusion post–CABG is dyspnea. In a recent study from our institution, 22 of 29 patients (75.9%) with an effusion occupying more than 25% of the hemithorax complained of dyspnea, but only 3 (10.3%) complained of chest pain and only 1 (3.4%) complained of fever.19 It should be noted that almost every patient with the PCIS syndrome has both chest pain and fever.

The pleural effusions that occur after CABG surgery tend to be unilateral on the left side. In the study from our institution in which chest radiographs were obtained approximately 4 weeks post-surgery, 196 of 349 patients (62%) had pleural effusions.19 The effusions were unilateral or larger on the left in 155 (73.4%), whereas they were unilateral on the right or larger on the right in only 14 (7.2%).19

As mentioned previously, the larger pleural effusions that occur after CABG can be divided into those that occur within the first 30 days of surgery and those that occur more than 30 days after surgery.25,26 The pleural fluid from the early effusions is bloody with a median red blood cell count of > 700,000 cells mm$^3$ (Table 1).25 The pleural fluid is frequently eosinophilic with median eosinophil percentage of nearly 40.25 The median pleural fluid lactate dehydrogenase (LDH) level is approximately twice the upper limit of normal for serum.25 Because the pleural fluid is bloody, it is likely that the LDH in the pleural fluid is LDH-1, which is the LDH from the red blood cells. The pleural fluid protein is in the exudative range, and the pleural fluid glucose is not reduced.25

The pleural fluid from the late-appearing pleural effusions is quite different from the bloody fluid with the high eosinophil count and the high LDH level seen in the early effusions. The fluid from the late effusions is usually a clear yellow exudate that contains predominantly lymphocytes. In one series the median lymphocyte percentage in 26 pleural fluids from late effusions was 68%, whereas the median eosinophil percentage was 0.25. The median level of LDH is approximately the upper normal limit for serum. The pleural fluid protein is in the exudative range, and the pleural fluid glucose is not reduced.25 The pleural fluid adenosine deaminase is below 40 IU/L.32

| Table 1 | Comparison of the Characteristics of the Pleural Fluid in Patients with the PCIS Syndrome, Early Effusions Post–CABG Surgery and Late Effusions Post–CABG Surgery |
| --- | --- | --- |
| **Appearance** | Bloody or serosanguineous | Bloody | Clear Yellow |
| **Differential WBC** | PMNs or Mononuclear cells | Neutrophils and Eosinophils | Small lymphocytes |
| **Protein** | Exudative range | Exudative range | Exudative range |
| **LDH** | Exudative range | ~2× upper limit normal | ~1× upper limit normal |
| **Glucose** | Normal | Normal | Normal |
| **pH** | Normal | Normal | Normal |
| **Antimyocardial antibody** | High titer | Absent | Absent |

Figure 2 Pleural specimen from a patient 12 months post–coronary artery bypass graft (CABG) surgery with a persistent pleural effusion. Note the dense fibrous tissue.
**Diagnosis**
When a patient is seen with a pleural effusion post-CABG surgery, there are several other diagnoses to consider in addition to the pleural effusion secondary to CABG surgery. The main diagnoses to exclude are congestive heart failure, pulmonary embolus, parapneumonic effusions, the PCIS, and chylothorax. The work-up of the patient is influenced by the patient’s symptoms. If the patient is asymptomatic and the effusion is predominantly left-sided and occupies less than 25% of the hemithorax, it can be attributed to the coronary artery surgery without performing a thoracentesis. If the patient is febrile or has chest pain, a thoracentesis should be performed to rule out a pleural infection. In this situation, consideration should also be given to the possibility of a pulmonary embolism. If dyspnea is out of proportion to the size of the effusion, the possibility of a pulmonary embolism should also be considered. If the effusion is large, the patient should undergo a therapeutic thoracentesis to verify if a chylothorax is not present and to alleviate dyspnea if the patient is dyspneic. If the effusion is a late effusion with lymphocytes predominating in the pleural fluid, the diagnosis of tuberculosis should be excluded. This is most easily done by measuring the level of ADA (adenosine deaminase) in the pleural fluid since the pleural fluid ADA level is almost always above 40 with tuberculous pleuritis but is almost always less than 40 with the pleural effusion post–CABG surgery.

**Treatment**
There are no controlled studies that address the treatment of the pleural effusion due to CABG surgery. If the effusion is small and the patient is asymptomatic, no treatment is necessary because such effusions virtually always resolve. If the effusion is larger and the patient is symptomatic, a therapeutic thoracentesis should be performed. If a symptomatic effusion recurs after the initial therapeutic thoracentesis, a second therapeutic thoracentesis should be considered. If the effusion recurs, many patients are also given non-steroidal anti-inflammatory agents or prednisone, but there are no controlled studies documenting the efficacy of this approach. In like manner, chemical pleurodesis has been successful in some patients. It is important to realize that the great majority of patients with large pleural effusions will do well with only therapeutic thoracentesis. In our prospective study, we followed 30 patients who had a pleural effusion occupying more than 25% of their hemithorax for 12 months. Eight of the patients (27%) received no invasive treatment for their pleural effusion, 16 (53%) were treated with a single therapeutic thoracentesis, 2 (7%) required two thoracenteses, and 4 (13%) required three or more thoracenteses. One patient was still receiving periodic thoracentesis 12 months post-CABG.

In rare instances, the patient continues to be symptomatic despite several thoracenteses. Over the past few years we have subjected eight such patients to thoracoscopy. At thoracoscopy, several patients had thin sheets of fibrous tissue that coated the lung and prevented it from expanding. We hypothesize that this sheet of fibrous tissue “trapped” the lung and prevented it from reexpanding (Fig. 3). The incidence of trapped lung after CABG surgery is not known, but is probably very low. At our hospital, where ~2500 CABG surgeries are performed annually, only four cases of trapped lung were seen during a recent 2-year period. The diagnosis of trapped lung can be established by measuring...
the pleural pressure as fluid is withdrawn. If the pleural pressure is initially below \(-10\) cm H\(_2\)O or if the pleural pressure falls more than \(20\) cm H\(_2\)O per 1000 mL fluid removed, the diagnosis is strongly supported.\(^{33}\) After the fibrous tissue coating the visceral pleura was removed, the lung expanded, and the effusion did not recur. However, given that most of the patients had a mechanical or a chemical pleurodesis at the time of thoracoscopy, it is not clear that the decortication itself was responsible for the resolution of the pleural effusion.\(^{27}\)

Thoracoscopy is recommended for an effusion after CAGB that continues to recur for several months despite several therapeutic thoracenteses. At thoracoscopy, any fibrous tissue coating the visceral pleura should be removed and the parietal pleura should be abraded to create a pleurodesis.

**REFERENCES**

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