Indicators of Poor Prognosis of Acute Pericarditis

Massimo Imazio, MD; Enrico Cecchi, MD; Brunella Demichelis, MD; Salvatore Ierna, MD; Daniela Demarie, MD; Aldo Ghisio, MD; Franco Pomari, MD; Luisella Coda, MD; Riccardo Belli, MD; Rita Trinchero, MD

Background — The clinical search for indicators of poor prognosis of acute pericarditis may be useful for clinical triage of patients at high risk of specific causal conditions or complications. The aim of the present article is to assess the relationship between clinical features at presentation and specific causes or complications.

Methods and Results — A total of 453 patients aged 17 to 90 years (mean age 52 ± 18 years, 245 men) with acute pericarditis (post–myocardial infarction pericarditis was excluded) were prospectively evaluated from January 1996 to August 2004. A specific cause was found in 76 of 453 patients (16.8%); autoimmune in 33 patients (7.3%), neoplastic in 23 patients (5.1%), tuberculuous in 17 patients (3.8%), and purulent in 3 patients (0.7%). In multivariable analysis, women (hazard ratio [HR] 1.67, 95% confidence interval [CI] 1.03 to 2.70; P = 0.036) and patients with fever >38°C (HR 3.56, 95% CI 1.82 to 6.95; P < 0.001), subacute course (HR 3.97, 95% CI 1.66 to 9.50; P = 0.002), large effusion or tamponade (HR 2.15, 95% CI 1.09 to 4.23; P = 0.026), and failure of aspirin or of nonsteroidal anti-inflammatory drugs (HR 2.50, 95% CI 1.28 to 4.91; P = 0.008) were at increased risk of specific causal conditions. After a mean follow-up of 31 months, complications were detected in 95 patients (21.0%): recurrences in 83 patients (18.3%), tamponade in 14 patients (3.1%), and constriction in 7 patients (1.5%). In multivariable analysis, women (HR 1.67, 95% CI 1.03 to 2.70; P = 0.020) and patients with large effusion or tamponade (HR 2.51, 95% CI 1.37 to 4.61; P = 0.003) and failure of aspirin or of nonsteroidal anti-inflammatory drugs (HR 5.50, 95% CI 3.56 to 8.51; P < 0.001) were at increased risk of complications.

Conclusions — Specific clinical features (fever >38°C, subacute course, large effusion or tamponade, and aspirin or NSAID failure) may be useful to identify higher risk of specific causal conditions and complications. (Circulation. 2007;115:2739-2744.)

Key Words: pericarditis ■ pericardium ■ prognosis ■ risk factors

A acute pericarditis is a common disorder in several clinical settings, which include primary care as well as emergency and subspecialty departments, such as cardiology, rheumatology, and nephrology.1 The disease is recorded in ≈0.1% of hospitalized patients and ≈5% of patients admitted to the emergency department for nonacute myocardial infarction chest pain.2,3

Clinical Perspective p 2744

In clinical practice and with a traditional diagnostic approach, idiopathic and viral acute pericarditis is found in 80% to 90% of cases in immunocompetent patients from developed countries.4–7 Acute viral or idiopathic pericarditis typically follows a brief and benign course after empirical treatment with nonsteroidal antiinflammatory drugs (NSAID). As a result, it does not seem appropriate to perform a full diagnostic evaluation in all patients because no specific treatments exist for viral diseases.6–9 In many cases both the performance of tests to establish a specific causal diagnosis and hospitalization of patients may be unnecessary.6,9–12 On this basis, it has been proposed that a patient with simple uncomplicated acute pericarditis could undergo initial evaluation in a same-day hospital facility or clinic, and follow-up might be accomplished on an outpatient basis.5,11,12

Although no absolute clinical features exist that will definitely differentiate between specific and idiopathic pericarditis,6 possible “indicators of poor prognosis” of acute pericarditis have been reported.6,11,12 These negative clinical features are considered more frequently associated with an increased risk of short-term complications or a specific diagnosis. They included fever >38°C, subacute onset, immunodepression, trauma, oral anticoagulant therapy, myopericarditis, large pericardial effusion, and cardiac tamponade. Further studies have also reported that the lack of initial response to aspirin could identify a group of patients at greater risk of relapses and complications,13,14 and corticosteroids have been found as possible risk factor for recurrences in acute pericarditis.15 Although previous findings5 have
shown that the clinical subsets of patients with unfavorable clinical evolution after medical therapy and cardiac tamponade may have a higher probability of a specific cause, all other features have been derived from literature review but are not validated by prospective cohort studies. Acute pericarditis risk stratification based on clinical and echocardiographic evaluation is important in clinical practice, because it could be useful to select the appropriate care setting (outpatient versus hospitalization) as well as to identify high-risk cases to be admitted and thoroughly investigated. The aim of the present study is to verify the validity and clinical utility of proposed indicators of poor prognosis of acute pericarditis in a prospective cohort study.

Methods

Patients

All consecutive cases of acute pericarditis, excluding post-myocardial infarction pericarditis, were prospectively enrolled in a cohort study from January 1996 to August 2004. Acute pericarditis was diagnosed according to available published criteria. Diagnostic criteria have included pericarditic typical chest pain, pericardial friction rubs, widespread ST segment elevation or PR depressions not previously reported, and new or worsening pericardial effusion. A clinical diagnosis of acute pericarditis was made when at least 2 of these criteria were present. Additional evidence of active inflammation was recorded in all cases and included detection of elevated erythrocyte sedimentation rate and C-reactive protein. A clinical diagnosis of myopericarditis was performed in patients with diagnostic criteria for acute pericarditis and 1 of the following features: evidence of elevated cardiac enzymes (creatinine kinase-MB fraction, or troponin I or T) or new onset of focal or diffuse depressed left ventricular function by echocardiography. Coronary artery disease was excluded in all cases by means of coronary angiography and nuclear stress perfusion scan.

The following classification of pericardial effusion reported by Weitzman et al16 has been adopted: A small effusion is an echo-free space (anterior plus posterior) of <10 mm, a moderate effusion is an echo-free pericardial space of 10 to 20 mm, and a severe effusion is an echo-free space >20 mm. Pericardial effusion echo-free spaces are measured at the onset of the QRS complex in diastole. For circumferential effusions, the parasternal long-axis view was selected to measure the size of the pericardial effusion. For small and loculated effusions, the pericardium was visualized from as many planes as possible and included off-axis views. To facilitate the correct definition of the effusion size and to allow follow-up studies, the largest size as well as the site and view were recorded.

The clinical diagnosis of cardiac tamponade was established from the combination of physical and echocardiographic findings (patients with clinical signs of elevated jugular venous pressure and/or pulsum paradoxus plus evidence of pericardial effusion with echocardiographic signs of tamponade) in the absence of other cardiac diseases. Data were collected on the final causal diagnosis and complications during follow-up.

Poor Prognostic Predictors

According to literature review,6,11,12 the following clinical features were considered to be more frequently associated with an increased risk of short-term complications or a specific diagnosis: fever >38°C,17–19 subacute onset (symptoms that develop during a period of several days or weeks),20 immunodepression,20,21 trauma,20,22 oral anticoagulant therapy,22,23 myopericarditis (pericarditis with clinical or serologic evidence of myocardial involvement),24–27 large pericardial effusion (effusion with a diastolic echo-free space >20 mm wide) or cardiac tamponade,4,5,8 lack of initial response to aspirin or NSAID within 1 week,6,13 and corticosteroid use.6 On this basis they were considered “indicators of poor prognosis” of acute pericarditis.

Corticosteroid therapy (generally prednisone at the dose of 1.0 to 1.5 mg/kg per day for 2 to 4 weeks and then gradually tapered) was restricted as initial therapy to patients with aspirin or NSAID contraindications (oral anticoagulant therapy, allergy, history of peptic ulcer or gastrointestinal bleeding). Corticosteroid therapy was considered after intolerance or failure of aspirin or NSAID. To assess the real relative importance of these clinical features to predict at presentation a possible specific cause or an increased risk of complications during follow-up, all cases were prospectively evaluated by recording specific etiologies as well as complications during follow-up.

Follow-Up

Follow-up visits were performed at 1 week, 1 month, 3 months, 6 months, 1 year, and then annually, if the course was uncomplicated. Follow-up data included at least focused history, physical examination, and echocardiogram, whereas ECG and laboratory tests were considered if necessary by clinical judgment.

Statistical Analysis

Continuous data were reported as means±SD and compared with unpaired t test. Categorical variables were expressed as proportions or percentages and compared using χ² test. Time-to-event distributions were estimated by the Kaplan-Meier method and compared with the log-rank test. The Cox proportional hazards model was used to identify independent risk factors for specific causal conditions and complications. A stepwise selection procedure was adopted. A probability value of <0.05 was considered to show statistical significance. Statistical analysis was performed with the SPSS 13.0 software (Chicago, Ill.).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline Features

A total of 453 patients aged 17 to 90 years (mean age 52±18 years, 245 men) were included in the study period. A specific cause (nonviral/idiopathic) was found in 76 of 453 patients (16.8%): autoimmune (pericardial injury syndromes and connective tissue diseases) in 33 patients (7.3%), neoplastic in 23 patients (5.1%), tuberculous in 17 patients (3.8%), and purulent in 3 patients (0.7%). A specific cause was recorded in 34 of 245 men (13.9%) and in 42 of 208 women (20.2%); this difference showed a trend toward statistical significance (P=0.097). Corticosteroid therapy was prescribed as initial therapy in 62 of 453 (13.7%), and after failure of aspirin and NSAID in 44 patients. Corticosteroids were prescribed as initial therapy in 25 patients with a specific cause.

Mean age was similar in patients with or without a specific cause (55.1±16.5 years versus 51.4±18.3 years; P=0.103). In single-predictor analysis (Table 1), a higher rate of the following features was found in patients with a specific cause: fever >38°C (42.1% versus 9.3%), subacute onset (14.5% versus 1.1%), large effusion (23.7% versus 0.8%), cardiac tamponade (17.1% versus 8.8%), and aspirin failure (57.9% versus 11.1%) (P<0.001 for all groups). A rise of cardiac troponin I was mainly found in patients with ST segment elevation (90 of 104 patients; 86.5%) and with idiopathic/viral pericarditis (26.5% versus 5.2%; P<0.001). In multivariable analysis (Table 2), women (HR 1.67, 95% CI 1.03 to 2.70; P=0.036), patients with fever >38°C (HR 3.56, 95% CI 1.82 to 6.95; P<0.001), subacute course (HR 3.97, 95% CI 1.66 to 9.50; P=0.002), large effusion or tamponade...
(HR 2.15, 95% CI 1.09 to 4.23; P = 0.026), and aspirin or NSAID failure (HR 2.50, 95% CI 1.28 to 4.91; P = 0.008) were at increased risk of specific causal conditions. On the contrary, patients with elevation of cardiac troponin I had a lower risk of a specific causal condition (HR 0.37, 95% CI 0.14 to 0.97; P = 0.042).

Follow-Up Data
After a mean follow-up of 31 months, complications were detected in 95 patients (21.0%): recurrences in 83 patients (18.3%), cardiac tamponade in 14 patients (3.1%), and constrictive pericarditis in 7 patients (1.5%). Compared with patients diagnosed with idiopathic or viral pericarditis, patients with a specific cause showed a higher rate of complications (38.2% versus 18.0%; P = 0.001), which included recurrences (27.6% versus 16.5%; P = 0.032), cardiac tamponade (14.5% versus 0.8%; P = 0.001), constrictive pericarditis (5.3% versus 0.8%; P = 0.017), and a shorter event-free survival (Figure 1).

Mean age was similar in patients with or without complications (53.1 ± 17.5 years versus 51.7 ± 18.2 years; P = 0.502). In single-predictor analysis (Table 3), the following features were more common in patients with complications: female gender (62.1% versus 41.6%; P < 0.001), fever >38°C (29.5% versus 10.9%; P < 0.001), subacute onset (10.5% versus 1.4%; P < 0.001), oral anticoagulants (14.7% versus 4.0%; P < 0.001), large effusion (14.7% versus 1.7%; P < 0.001) or cardiac tamponade (14.7% versus 0.6%; P < 0.010), aspirin or NSAID failure (55.8% versus 9.2%; P < 0.001), and corticosteroid use (36.8% versus 7.5%; P < 0.001).

In multivariable analysis (Table 4), women (HR 1.65, 95% CI 1.08 to 2.52; P = 0.020), patients with large effusion or tamponade (HR 2.51, 95% CI 1.37 to 4.61; P = 0.003), and aspirin or NSAID failure (HR 5.50, 95% CI 3.56 to 8.51; P < 0.001) were at increased risk of complications during follow-up. Corticosteroids were associated with an increased rate of complications in idiopathic or viral pericarditis (48.4% versus 14.1%; P < 0.001) (Figure 2).

Discussion
Causes of Pericarditis
The present study confirms that the majority of unselected cases of acute pericarditis (80% to 85%) in immunocompetent patients from developed countries have idiopathic or viral causes (Table 5). In Europe and the US, the main specific causes to consider are autoimmune (pericardial injury syndromes and connective tissue diseases), neoplastic, and tuberculous. Bacterial pericarditis other than tuberculosis is rare (<1%). Although the relative frequency of tuberculous pericarditis seems almost unchanged over years in western countries, the causes of acute pericarditis are completely different in developing countries with a high prevalence of specific forms related to tuberculosis (eg, 70% to 80% of cases in sub-Saharan Africa, and even up to >90% when pericarditis is associated with HIV-infection). The incidence

#### TABLE 1. Baseline Frequencies of Poor Prognostic Predictors in Patients With or Without a Specific Cause

<table>
<thead>
<tr>
<th>Feature</th>
<th>Idiopathic or Viral (n=377)</th>
<th>Specific Cause (n=76)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender (n=208)</td>
<td>166 (44.0)</td>
<td>42 (55.3)</td>
<td>0.093</td>
</tr>
<tr>
<td>Fever &gt;38°C (n=67)</td>
<td>35 (9.3)</td>
<td>32 (42.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Subacute course (n=15)</td>
<td>4 (1.1)</td>
<td>11 (14.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Immunodepression (n=22)</td>
<td>15 (4.0)</td>
<td>7 (9.2)</td>
<td>0.103</td>
</tr>
<tr>
<td>Trauma (n=8)</td>
<td>7 (1.9)</td>
<td>1 (1.3)</td>
<td>0.909</td>
</tr>
<tr>
<td>Oral anticoagulants (n=28)</td>
<td>21 (5.6)</td>
<td>7 (9.2)</td>
<td>0.354</td>
</tr>
<tr>
<td>Rise of cardiac troponin I (n=104)</td>
<td>100 (26.5)</td>
<td>4 (5.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Large pericardial effusion (n=21)</td>
<td>3 (0.8)</td>
<td>18 (23.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac tamponade (n=16)</td>
<td>3 (0.8)</td>
<td>13 (17.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ASA or NSAID failure at 1 week (n=86)</td>
<td>42 (11.1)</td>
<td>44 (57.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed as n (%). ASA indicates acetylsalicylic acid.

#### TABLE 2. HRs for Specific Causes in the Cox Proportional Hazards Model

<table>
<thead>
<tr>
<th>Feature</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>1.67</td>
<td>1.03 to 2.70</td>
<td>0.036</td>
</tr>
<tr>
<td>Fever &gt;38°C</td>
<td>3.56</td>
<td>1.82 to 6.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Subacute course</td>
<td>3.97</td>
<td>1.66 to 9.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rise of cardiac troponin I</td>
<td>0.37</td>
<td>0.14 to 0.97</td>
<td>0.042</td>
</tr>
<tr>
<td>Large effusion/tamponade</td>
<td>2.15</td>
<td>1.09 to 4.23</td>
<td>0.026</td>
</tr>
<tr>
<td>ASA or NSAID failure</td>
<td>2.50</td>
<td>1.28 to 4.91</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Variables included in the full model: age, female gender, fever >38°C, subacute course, immunodepression, trauma, oral anticoagulants, rise of cardiac troponin I, large pericardial effusion or cardiac tamponade, and ASA or NSAID failure. ASA indicates acetylsalicylic acid. A stepwise selection procedure was used.
of tuberculous pericarditis is increasing in Africa as a result of the HIV epidemic. In developed countries, tuberculous pericarditis is less frequent, but a possible increase may be expected in the near future as a result of immigrants from areas with a high prevalence of tuberculosis and HIV-infected patients. On this basis, knowledge of the epidemiological data is essential for the development of a rational management program for the disease. The varied causes of pericarditis suggest that the diagnostic approach should be targeted at the individual patient and background.

**Clinical Poor Prognostic Predictors**

Presumptive indicators of poor prognosis of acute pericarditis (fever >38°C, subacute onset, immunodepression, trauma, oral anticoagulant therapy, myopericarditis, large pericardial effusion, and cardiac tamponade), derived from literature review, have been proposed to identify patients who should be admitted to a hospital and submitted to a full etiological search. However, additional risk factors may be considered. Another important feature of high risk may be the lack of response to a NSAID after at least 1 week of therapy. In fact, failure to respond to a NSAID may imply the possibility of a specific cause. For instance, the lack of response to NSAID, an incessant or recurrent course, and cardiac tamponade at presentation were found to be risk factors for neoplastic origin of acute pericardial disease. A recent open-label study on the use of colchicine in acute pericarditis has shown that corticosteroid use was a risk factor for recurrences, and so corticosteroids may also be considered within poor prognostic predictors.

To the best of our knowledge, no prospective cohort studies have tested the possible clinical validity of all these predictors. The major finding of this work is that some features can truly be considered indicators of a possible specific cause: fever >38°C (HR 3.56), subacute course (HR 3.97), large effusion or tamponade (HR 2.15), and aspirin or NSAID failure (HR 2.50). Large effusion or tamponade (HR 2.51) and aspirin or NSAID failure (HR 5.50) are also useful indicators of complications during follow-up. Women are at increased risk of a specific causal condition (HR 1.67) or complications (HR 1.65).

Although a potential study limitation is the possible underestimation of the risk associated with specific features such as trauma with a low frequency in the studied population, this study demonstrates that corticosteroids were associated with an increased rate of complications in idiopathic or viral pericarditis (48.4% versus 14.1%; P<0.001). Main differences are recorded within the first 18 months.
work also reassesses the relative importance of other presumed negative predictors. Elevation of cardiac troponin I and myopericarditis, immunodepression, use of oral anticoagulants, and a recent trauma are not associated with an increased risk of complications, although it seems reasonable in clinical practice to consider admission for patients with these features to monitor clinical evolution at least in the first days. Patients with these features should be reassured about the possible risk of complications and prognosis. Although corticosteroids should not be considered as a risk factor in a general population of patients with acute pericarditis, corticosteroids were associated in this study with an increased rate of complications in idiopathic or viral pericarditis (48.4% versus 14.1%; \(P<0.001\)) (Figure 2).

This finding confirms the evidence that corticosteroid therapy is a risk factor for recurrent pericarditis in patients with viral or idiopathic origin of pericarditis. Corticosteroid therapy given in the index attack can favor the occurrence of recurrences, probably because of its deleterious effect on viral replication and clearance such as that reported in animal studies.\(^{11,15}\) Moreover, frequent and prolonged administration of these drugs may lead to serious complications.\(^{11,15}\)

A risk stratification of acute pericarditis can be performed at presentation on a clinical basis (history, physical examination, routine blood chemistry that includes markers of myocardial lesion, chest x-ray, and echocardiography). Patients without indicators of poor prognosis of acute pericarditis may be considered at low risk and can be assigned to outpatient treatment with aspirin or NSAID and gastroprotection without a specific search for causation (Figure 3). Complications such as cardiac tamponade and constriction are rare in this low-risk population (<1%), and outpatient treatment is safe. In many such patients, even an extensive diagnostic evaluation is likely to prove negative for an underlying cause.\(^{6,7,9}\) Even viral studies should not be considered, because the yield is low and management is not altered.\(^{7,9}\)

Patients with \(\geq 1\) “indicators of poor prognosis” of acute pericarditis could be considered high-risk cases to be admitted to hospital for monitoring and a specific search for a cause should be considered. Complications such as cardiac tamponade and constriction are more common in these patients and a close follow-up is warranted.

The clinical triage of acute pericarditis is probably not only safe and efficacious but also cost-effective for the reduction of hospitalization rates and management costs. These data may be particularly valuable in the reduction of costs associated with pericarditis in the United States and Europe, because many patients are admitted to a hospital for initial evaluation and treatment rather than managed as outpatients.\(^{6,7,9}\)

**Acknowledgments**

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**Disclosures**

None.

**References**

In developed countries, idiopathic and viral pericarditis is found in 80% to 90% of unselected immunocompetent patients with acute pericarditis. These patients typically follow a brief and benign course after empirical treatment with nonsteroidal antiinflammatory drugs. Thus, it does not seem appropriate to perform a full diagnostic evaluation in all patients because no specific treatments exist for idiopathic and viral pericarditis. Although no absolute clinical features will definitely differentiate between specific and idiopathic pericarditis, possible “indicators of poor prognosis” have been reported (fever >38°C, subacute course, immunodepression, trauma, oral anticoagulant therapy, myopericarditis, large pericardial effusion, cardiac tamponade, failure of aspirin or of nonsteroidal antiinflammatory drugs, and corticosteroid use) but not validated in prospective studies. They are considered to be more frequently associated with an increased risk of complications or cardiac tamponade, failure of aspirin or of nonsteroidal antiinflammatory drugs, and corticosteroid use.

The major finding of this work is that fever >38°C (hazard ratio [HR] 3.56), subacute course (HR 3.97), differentiates between specific and idiopathic pericarditis, possible “indicators of poor prognosis” have been reported (fever >38°C, subacute onset, immunodepression, trauma, oral anticoagulant therapy, myopericarditis, large pericardial effusion, cardiac tamponade, failure of aspirin or of nonsteroidal antiinflammatory drugs, and corticosteroid use) but not validated in prospective studies. They are considered to be more frequently associated with an increased risk of complications or specific diagnoses. The major finding of this work is that fever >38°C (hazard ratio [HR] 3.56), subacute course (HR 3.97), large effusion or tamponade (HR 2.15), and failure of aspirin or of nonsteroidal antiinflammatory drugs (HR 2.50) can truly be considered indicators of a possible specific cause, whereas large effusion or tamponade (HR 2.51) and failure of aspirin or of nonsteroidal antiinflammatory drugs (HR 5.50) are useful indicators of complications. Women are at increased risk of specific causal conditions (HR 1.67) or complications (HR 1.65). Acute pericarditis triage based on clinical and echocardiographic evaluation is feasible and useful to select high-risk cases to be admitted and thoroughly investigated. 

These data may be particularly valuable in the reduction of costs associated with pericarditis in the United States and Europe, where many patients are admitted to a hospital rather than managed as outpatients.

**CLINICAL PERSPECTIVE**

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