

Prevalence of C-Reactive Protein Elevation and Time Course of Normalization in Acute Pericarditis

Implications for the Diagnosis, Therapy, and Prognosis of Pericarditis

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Background—The role of inflammatory markers is not well defined for either diagnosis or treatment of pericarditis. The aim of this study is to prospectively evaluate the frequency of high-sensitivity C-reactive protein (hs-CRP) elevation in patients with acute pericarditis, its time course of normalization, and the possible importance for diagnosis, therapy, and prognosis.

Methods and Results—Two hundred consecutive patients with viral or idiopathic acute pericarditis (mean age, 53 ± 15.5 years; 103 men) were studied from August 2005 to August 2007 in 2 Italian referral centers. Hs-CRP was determined at presentation and then every week until normalization. Hs-CRP elevation was recorded in 156 of 200 cases (78%) at presentation. Recognized causes of a negative hs-CRP at presentation were early assessment in 15 of 44 cases (34%) and previous anti-inflammatory therapies in 22 of 44 cases (50%). Hs-CRP normalization was achieved with the following time course: 120 of 200 (60%) at week 1, 170 of 200 (85%) at week 2, 190 of 200 (95%) at week 3, and all cases (100%) at week 4. In multivariable analysis, incomplete response to empirical anti-inflammatory therapy at week 1 (hazard ratio, 2.98; 95% confidence interval, 1.80 to 4.94; $P < 0.001$), corticosteroid therapy (hazard ratio, 2.80; 95% confidence interval, 1.59 to 4.95; $P < 0.001$), and the presence of elevated hs-CRP at week 1 (hazard ratio, 2.36; 95% confidence interval, 1.32 to 4.21; $P = 0.004$) were independent risk factors for recurrence.

Conclusions—Hs-CRP is elevated at the initial presentation in ≈ 3 of 4 cases of acute pericarditis, identifies patients at higher risk of recurrence, and could be used to monitor disease activity and select appropriate therapy length. (*Circulation*. 2011; 123:1092-1097.)

Key Words: C-reactive protein ■ diagnosis ■ pericarditis ■ prognosis ■ therapy

There are no universally accepted criteria for the diagnosis of pericarditis. In clinical practice, some criteria are usually adopted (chest pain, pericardial rubs, PR depression and diffuse ST-segment elevation on ECG, pericardial effusion; at least 2 of 4 should be present for the diagnosis), and the role of inflammatory markers (eg, C-reactive protein [CRP]) is not well defined.¹⁻⁵

Clinical Perspective on p 1097

Pericarditis is an inflammatory disease, and evidence of elevated markers of inflammation could support the diagnosis. Moreover, the same length of therapy is empirical, and markers of inflammation (ie, CRP) may be a useful guide for treatment because it can be assumed that anti-inflammatory therapy should be continued until the inflammation is extinguished. On this basis, persistent elevation of inflammatory markers, as evidence of disease activity, could be associated with a worse prognosis.

The aim of the present study is to prospectively evaluate the frequency of high-sensitivity CRP (hs-CRP) elevation in patients with acute pericarditis, its time course of normalization, and the possible importance for diagnosis, therapy, and prognosis.

Methods

Patients

All consecutive cases of acute pericarditis within 24 hours from symptom onset were screened for inclusion in a prospective cohort study from August 2005 to August 2007. A final diagnosis of idiopathic or viral acute pericarditis was reached at the end of the diagnostic assessment, which included chest x-ray, echocardiography, viral serology, and other specific testing according to the initial clinical presentation. Pericardiocentesis was done when a bacterial or neoplastic etiology was suspected or in case of cardiac tamponade or severe pericardial effusion without response to medical therapy after 1 week. Patients with a final diagnosis of viral and idiopathic pericarditis were included in the

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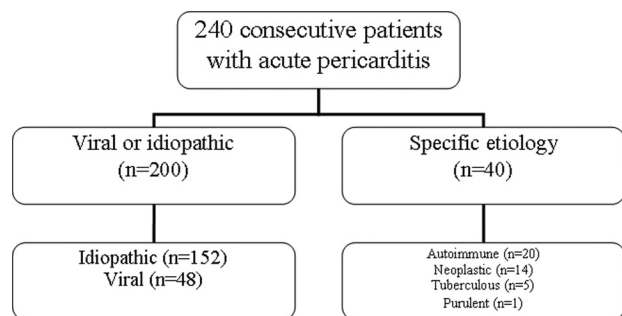


Figure 1. Flow diagram of the studied population with acute pericarditis (autoimmune etiologies included pericardial injury syndromes and connective tissue diseases).

present study. A flow diagram of the screened and included population is shown in Figure 1. The diagnosis of acute pericarditis was done according to available published criteria.^{1–8} Diagnostic criteria included pericarditic typical chest pain, pericardial friction rubs, widespread ST-segment elevation or PR depressions not reported previously, and new or worsening pericardial effusion. A clinical diagnosis of acute pericarditis was made when at least 2 of these criteria were present. Criteria for the diagnosis of recurrence included recurrent pain and 1 or more of the following signs: fever, pericardial friction rub, ECG changes, echocardiographic evidence of pericardial effusion, and an elevation in the white blood cell count, erythrocyte sedimentation rate, or CRP.^{4–9} During follow-up, the presence or absence of the aforementioned criteria for recurrence was adopted for the definition of recurrence-free survival.

Hs-CRP Assessment

Hs-CRP was determined with the use of an enhanced turbidimetric immunoassay technique (Siemens Healthcare Diagnostics). Testing was done at presentation and then every week until normalization. In healthy young adult volunteer blood donors, the median concentration of CRP is 0.8 mg/L, the 90th centile is 3.0 mg/L, and the 99th centile is 10 mg/L. In unselected general populations of ostensibly healthy subjects, the median CRP value is slightly higher than among blood donors and tends to increase with age, presumably reflecting the increasing incidence of subclinical pathologies. Hs-CRP was considered elevated at a hs-CRP concentration >3.0 mg/L, according to the reference interval for the test employed. De novo hepatic synthesis starts very rapidly after a single stimulus, with serum concentrations rising to >3.0 to 5.0 mg/L by ≈6 hours and peaking at ≈48 hours, and therefore it is possible that an early presentation might influence the observed values of CRP.¹⁰

Medical Therapy

Empirical anti-inflammatory therapy was prescribed to all patients with an attack dose for 7 days (favoring the use of aspirin or a nonsteroidal anti-inflammatory drug over corticosteroids) and then tapering within 3 to 4 weeks.

Specific anti-inflammatory attack doses were as follows: aspirin 750 to 1000 mg every 8 hours, ibuprofen 600 mg every 8 hours, or indomethacin 50 mg every 8 hours. Colchicine was added according to the treating physician's discretion at the dose of 0.5 mg twice daily for patients weighing ≥70 kg for 3 months (0.5 mg once daily for patients weighing <70 kg). Prednisone was used at the attack dose of 0.2 to 0.5 mg/kg per day and then followed by gradual tapering over months.

Follow-Up

Persistence of symptoms at 1 week of therapy, recurrences, cardiac tamponade, and constrictive pericarditis were considered adverse events during follow-up.

An incomplete response to therapy was considered the persistence of symptoms with evidence of disease activity (fever without alternative causes, pericardial rubs, new or worsening ECG changes, elevated hs-CRP, and appearance or worsening of pericardial effusion) without a free interval, whereas recurrence was considered a situation in which a new attack occurred after a period of complete disappearance of symptoms and CRP normalization if previously elevated.^{6,7,9}

Follow-up data were collected after clinical visits and after ECGs and echocardiograms were performed.

Statistical Analysis

Continuous data were reported as mean±SD and compared with the Mann-Whitney test. Categorical variables were expressed as proportions or percentages and compared with the χ^2 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 recurrences. A stepwise selection procedure was adopted. A *P* value of <0.05 was considered to show statistical significance and was adopted as the significance level for variable entry and stay for stepwise selection. Statistical analysis was performed with the use of SPSS 13.0 software (Chicago, IL).

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

Results

Baseline Features

A total of 200 patients aged 18 to 90 years (mean age, 53±15.5 years; 103 men) were included in the study period. Hs-CRP was normal in 44 cases (22%) and elevated in 156 of 200 study patients (78%) at presentation. Identified causes of initial negative results were as follows: (1) early assessment in 15 of 44 cases (34%) because hs-CRP became positive at a second determination within 24 to 48 hours and (2) use of previous empirical anti-inflammatory therapy in 22 of 44 cases (50%). Therefore, only 7 of 200 patients (3.5%) had a persistently normal hs-CRP with no previous treatment. Baseline data including diagnostic criteria for acute pericarditis in patients with or without hs-CRP elevation are reported in Table 1.

Elevated hs-CRP was recorded in 31 of 40 patients (77.5%) with a specific etiology (Figure 2).

Follow-Up Data

A nonelevated hs-CRP was found in 120 of 200 patients (60%) at week 1, 170 of 200 patients (85%) at week 2, 190 of 200 patients (95%) at week 3, and all cases (100%) at week 4 (Figure 3). Normalization was achieved within 2 weeks in most cases, and normalization was achieved at 1 month in all cases. Patients with persistent elevation of hs-CRP after 1 week of therapy had a shorter recurrence-free survival (Figure 4). All patients were analyzed for outcomes, and no patient was lost at follow-up.

After a mean follow-up of 24 months, the following adverse events were noted: persistence of symptoms and incomplete response to anti-inflammatory therapy at week 1 were recorded in 66 cases (33%), recurrences in 70 cases (35%), and cardiac tamponade in 4 cases (2%). No cases of constrictive pericarditis were recorded.

In multivariable analysis (including age, gender, pericardial effusion, elevated hs-CRP at presentation, cortico-

Table 1. Comparison of Baseline Clinical Characteristics of Patients With or Without High-Sensitivity C-Reactive Protein Elevation at Presentation

Characteristic	High-Sensitivity C-Reactive Protein		P
	(≤3.0 mg/L) (n = 44)	(>3.0 mg/L) (n = 156)	
Mean age, y	52±16	53±14	0.686
Female gender (n=97)	22 (50.0)	75 (48.1)	0.959
Pericarditic chest pain (n=200)	44 (100.0)	156 (100.0)	0.999
Pericardial rub (n=66)	14 (31.8)	52 (33.3)	0.996
Diagnostic ECG changes* (n=170)	37 (84.1)	133 (85.3)	0.966
New or worsening pericardial effusion (n=90)	19 (43.2)	71 (45.5)	0.921
Fulfilled diagnostic criteria			
2 of 4	44 (100.0)	156 (100.0)	0.999
3 of 4	36 (81.8)	130 (83.3)	0.993
4 of 4	20 (45.5)	72 (46.2)	0.929
Aspirin or NSAID (n=170)	37 (84.1)	133 (85.3)	0.966
Corticosteroid therapy (n=30)	7 (15.9)	23 (14.7)	0.966
Colchicine (n=100)	21 (47.7)	79 (50.6)	0.866

Values in parentheses are percentages. NSAID indicates nonsteroidal anti-inflammatory drug.

*Widespread ST-segment elevation or PR depressions.

steroid use, incomplete response to therapy at week 1, and elevated hs-CRP at week 1), incomplete response to empirical anti-inflammatory therapy at week 1 (hazard ratio, 2.98; 95% confidence interval, 1.80 to 4.94;

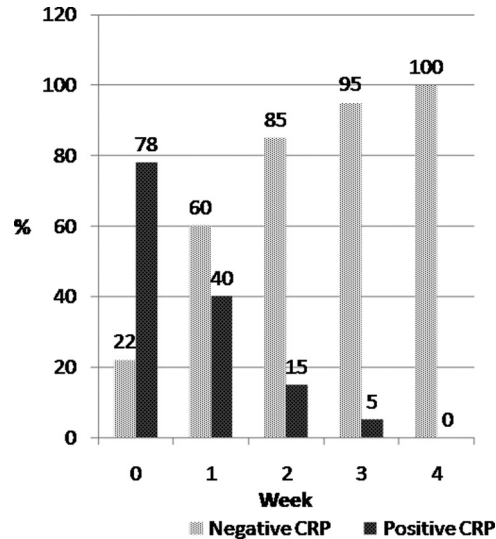


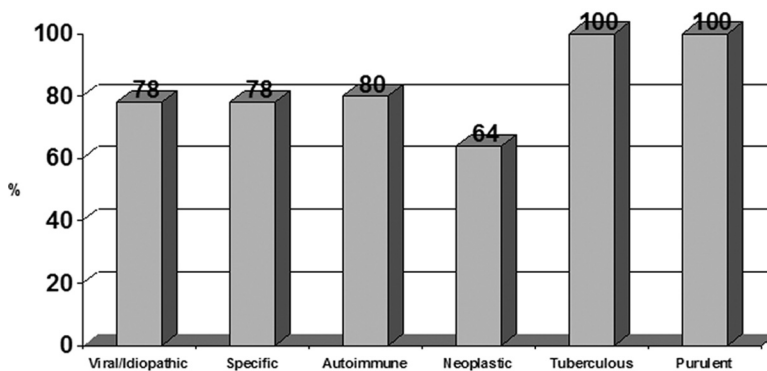
Figure 3. High-sensitivity C-reactive protein (CRP) elevation at presentation and its time course of normalization in patients with idiopathic or viral acute pericarditis (weekly assessment).

$P<0.001$), corticosteroid therapy (hazard ratio, 2.80; 95% confidence interval, 1.59 to 4.95; $P<0.001$), and the presence of elevated hs-CRP at week 1 (hazard ratio, 2.36; 95% confidence interval, 1.32 to 4.21; $P=0.004$) were independent risk factors for recurrences considered as major adverse events during follow-up (Table 2).

Discussion

The use of elevated markers of inflammation has been recommended for diagnostic purposes by the 2004 Euro-

Hs-CRP elevation



Etiology	hs-CRP elevation (%)
Idiopathic/viral (n=200)	156/200 (78.0%)
Specific etiologies (n=40)	31/40 (77.5%)
Autoimmune (n=20)	16/20 (80.0%)
Neoplastic (n=14)	9/14 (64.3%)
Tuberculous (n=5)	5/5 (100.0%)
Purulent (n=1)	1/1 (100.0%)

Figure 2. High-sensitivity C-reactive protein (hs-CRP) elevation at presentation in patients with acute pericarditis and a nonviral, nonidiopathic etiology.

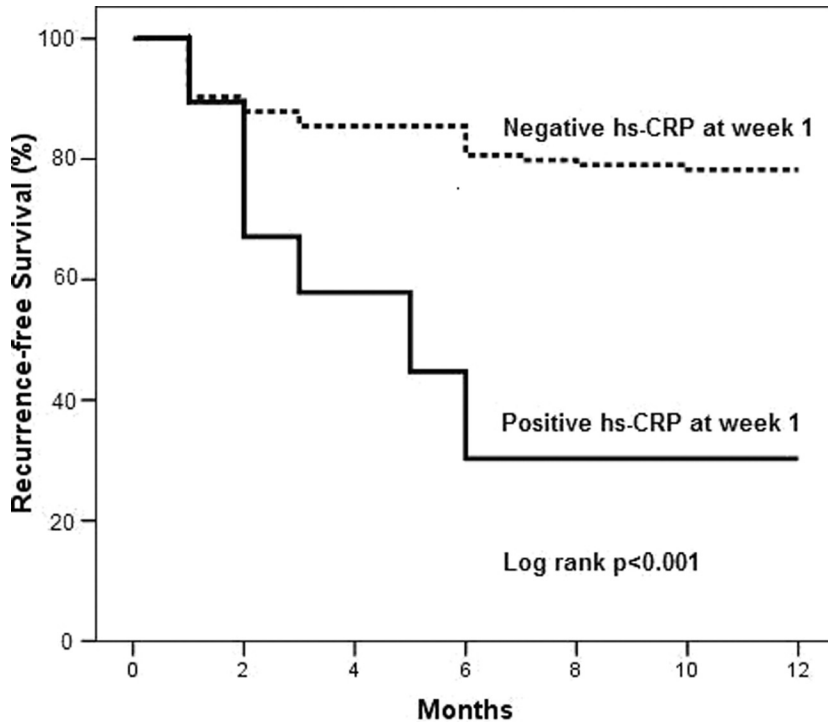


Figure 4. Recurrence-free survival in patients with (dotted line) or without (thick line) high-sensitivity C-reactive protein (hs-CRP) elevation at week 1. Differences of event-free survivals are evident after 2 months and increase in the first 12 months.

Patients at risk:

	0	2	4	6	8	10	12
Negative hs-CRP at week 1:	120	112	106	106	99	98	83
Positive hs-CRP at week 1:	80	68	44	34	23	23	22

pean guidelines on the management of pericardial diseases.¹¹ However, the role of elevated markers of inflammation (ie, CRP) is not well defined. Currently adopted diagnostic criteria are mainly clinical and are based on symptoms (pericarditic chest pain), signs (pericardial rubs), or instrumental findings (widespread ST-segment elevation, pericardial effusion) and do not include markers of inflammation. Nevertheless, pericarditis is generally an intense inflammatory disease, and elevation of such markers could be useful to confirm the diagnosis. Moreover, the treatment of pericarditis is empirical for either the choice of drugs or length of therapy and is expected to extinguish the inflammation. CRP could be used as a diagnostic marker and also to monitor the disease activity and the appropriate length of therapy.^{5,12}

CRP is one of the “acute phase” proteins, the serum or plasma levels of which rise during a general, unspecific response to infectious and noninfectious inflammatory processes. Because elevated CRP values are always associated with pathological changes, the CRP assay may provide useful information for the diagnosis, therapy, and monitoring of inflammatory processes such as acute pericarditis.

Plasma CRP is produced only by hepatocytes, predominantly under transcriptional control by the cytokine interleukin-6. De novo hepatic synthesis starts very rapidly after a single stimulus, with serum concentrations rising to >5 mg/L by ≈6 hours and peaking at ≈48 hours. The plasma half-life of CRP is ≈19 hours and is constant under all conditions of health and disease, so that the sole determinant of circulating CRP concentration is the synthesis rate, which thus directly reflects the intensity of the pathological processes stimulating CRP production. When the stimulus for increased production ceases completely, the circulating CRP concentration falls rapidly, at almost the rate of plasma CRP clearance.¹⁰

At present, the frequency of hs-CRP elevation is unknown in pericarditis as well as the time course of its normalization and the possible prognostic significance.

In this prospective study, we demonstrated an elevation of hs-CRP in 3 of 4 cases at presentation; thus, hs-CRP

Table 2. Hazard Ratios for Recurrence in the Cox Proportional Hazards Model

Risk Factor	Hazard Ratio	95% Confidence Interval	P
Incomplete response to therapy at week 1	2.98	1.80–4.94	<0.001
Corticosteroid therapy	2.80	1.59–4.95	<0.001
Elevated hs-CRP at week 1	2.36	1.32–4.21	0.004

hs-CRP indicates high-sensitivity C-reactive protein.

elevation at presentation is common but not present in all cases. In some patients, hs-CRP was initially normal but increased later. A diagnosis of pericarditis should rely on clinical criteria and not only on CRP elevation, although it may support the clinical suspicion. In patients with pericarditis, common causes of normal hs-CRP at presentation may include previous empirical anti-inflammatory therapy (50% of cases) and an early assessment without serial testing of hs-CRP (approximately one third of the initially negative cases). On this basis, if pericarditis is suspected, repeated testing for hs-CRP is indicated with an initial negative finding, and the possible role of recent empirical anti-inflammatory drugs should also be considered. An alternative cause to be considered is also the presence of myocardial involvement because hs-CRP may be normal in myocarditis.^{13,14} Overall, we found only 7 of 200 patients (3.5%) with a persistently negative hs-CRP in the absence of previous anti-inflammatory treatments. This finding is important in the clinical setting because an initial negative hs-CRP does not rule out pericarditis.

Data from the overall group of patients with acute pericarditis (Figures 1 through 3) show that elevation of hs-CRP at presentation is equally distributed in patients with or without a specific etiology, although elevation of hs-CRP is more common in patients without a neoplastic cause (Figure 2).

Hs-CRP elevation, when available, is especially valuable to guide the length of therapy. Most cases of pericarditis show a normalization of hs-CRP within 2 weeks, but persistent elevation of hs-CRP at week 1 may indicate ongoing inflammation and requires prolonged therapies. Common recommended therapeutic dosing includes 1 to 2 weeks of empirical therapy. However, at the end of the first week, only 60% of patients had a normal hs-CRP test, and thus the attack dose of anti-inflammatory therapy should be continued until the end of the second week in \approx 40% of cases and for an even longer time if hs-CRP is still elevated at week 2, as occurred in 15% of cases in this study. Dosing and serial monitoring of CRP until normalization seem warranted to prevent the early withdrawal of the attack dose. On this basis, appropriate weekly monitoring of CRP may be useful to follow the disease activity and guide the appropriate length of therapy, with continuation of the attack doses until CRP normalization, at which time tapering may be considered. Persistent elevation of CRP should be considered a risk factor for recurrence, as well as other recognized factors such as corticosteroids^{15–19} and incomplete response to medical therapy.^{19,20}

The main conclusions of the study are as follows: (1) hs-CRP is elevated at the initial presentation in \approx 3 of 4 cases of acute pericarditis, and thus a normal value of hs-CRP at presentation does not exclude the diagnosis but may confirm the clinical suspicion; (2) persistently elevated hs-CRP may identify patients at higher risk of recurrence; (3) for patients with elevated hs-CRP, the attack dose of anti-inflammatory therapy should be continued until hs-CRP normalization instead of an empirical therapy length; and (4) in some

patients, hs-CRP, although normal at presentation, may increase within the first week, and thus appropriate serial testing for hs-CRP should be planned for patients with an initial negative result.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Pericarditis is an inflammatory disease, and evidence of elevated markers of inflammation could support the diagnosis. Unfortunately, the appropriate length of therapy is unknown, and drugs are administered empirically. Nevertheless, markers of inflammation (ie, C-reactive protein [CRP]) may be a useful guide for treatment because it can be assumed that anti-inflammatory therapy should be continued until the inflammation is extinguished. On this basis, persistent elevation of inflammatory markers, as evidence of disease activity, could be associated with a worse prognosis. No prospective study has evaluated the prevalence and clinical meaning of CRP for diagnosis, therapy, and prognosis in acute pericarditis. The main conclusions of the study are as follows: (1) high-sensitivity CRP (hs-CRP) is elevated at the initial presentation in ≈ 3 of 4 cases of acute pericarditis, and thus a normal value of hs-CRP at presentation does not exclude the diagnosis but may confirm the clinical suspicion; (2) persistently elevated hs-CRP may identify patients at higher risk of recurrence; (3) for patients with elevated hs-CRP, the attack dose of anti-inflammatory therapy should be continued until hs-CRP normalization instead of an empirical therapy length, as is commonly done in clinical practice; and (4) in some patients, hs-CRP is normal at presentation but may increase within the first week, and thus appropriate serial testing for hs-CRP should be planned for patients with an initial negative result. Hs-CRP is elevated at the initial presentation in ≈ 3 of 4 cases of acute pericarditis, identifies patients at higher risk of recurrence, and could be used to monitor disease activity and select appropriate therapy length.