Good Prognosis for Pericarditis With and Without Myocardial Involvement:

Results from a Multicenter Prospective Cohort Study

Running title: Imazio et al.; Outcome of myopericarditis/perimyocarditis

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Abstract:

Background—The natural history of myopericarditis/perimyocarditis is poorly known and recently published data have presented contrasting data on their outcomes. The aim of the present article is to assess their prognosis in a multicenter, prospective cohort study.

Methods and Results—A total of 486 patients (median age 39 years, range 18-83, 300 men) with acute pericarditis or a myopericardial inflammatory syndrome (myopericarditis/perimyocarditis) (85% idiopathic, 11% connective tissue disease or inflammatory bowel disease, 5% infective) were prospectively evaluated from January 2007 to December 2011. The diagnosis of acute pericarditis was based on the presence of 2 of 4 clinical criteria (chest pain, pericardial rubs, widespread ST-segment elevation or PR depression, and new or worsening pericardial effusion). Myopericardial inflammatory involvement was suspected with atypical ECG changes for pericarditis, arrhythmias, cardiac troponin elevation and/or new or worsening ventricular dysfunction on echocardiography, and confirmed by cardiac magnetic resonance. After a median follow-up of 36 months normalization of LV function was achieved in >90% of patients with myopericarditis/perimyocarditis. No deaths were recorded, as well as evolution to heart failure or symptomatic LV dysfunction. Recurrences (mainly as recurrent pericarditis) were the most common complication during follow-up and were more frequently recorded in patients with acute pericarditis (32%) than myopericarditis (11%) or perimyocarditis (12%; p<0.001).

Troponin elevation was not associated with an increase of complications.

Conclusions—The outcome of myopericardial inflammatory syndromes is good. Unlike acute coronary syndromes, troponin elevation is not a negative prognostic marker in this setting.

Key words: pericarditis; myopericarditis; perimyocarditis; prognosis.
Myocarditis and pericarditis may share common etiological agents, either infectious (mainly cardiotropic viruses) or non infectious (i.e. immune mediated such as systemic inflammatory diseases, vaccine-related).\(^1\)\(^2\) Thus, in clinical practice a spectrum of myopericardial syndromes can be encountered ranging from pure pericarditis to increasing degrees of inflammatory myocardial involvement (myopericarditis and perimyocarditis) up to pure myocarditis.\(^1\)\(^-\)\(^4\) The term “myopericarditis” has been designated to indicate a primarily “pericarditic syndrome”, while “perimyocarditis” refers to a primarily “myocarditic syndrome”.\(^1\)\(^2\) However, in the literature, these terms are often confused and used interchangeably.

Despite a large amount of data have been published on myopericarditis related to smallpox vaccination, as a consequence of the recent US Federal government vaccination program for military forces,\(^5\)\(^-\)\(^7\) few data are available on the prognosis of sporadic cases not related to vaccination.\(^8\)\(^-\)\(^1\)\(^1\) Moreover published outcome results presented contrasting data and diagnostic evaluation has been heterogeneous (for instance based on simple clinical criteria and troponin elevation) and did not rely on the confirmatory findings of cardiac magnetic resonance (CMR).\(^8\)\(^-\)\(^1\)\(^1\)

The aim of this work is to evaluate the clinical presentation, and outcome of acute myopericarditis/perimyocarditis confirmed by CMR and compare these features with those of simple acute pericarditis in a prospective multicenter study including all consecutive cases of acute inflammatory pericardial syndromes (acute pericarditis, myopericarditis, and perimyocarditis).

**Methods**

**Participants**

Between January 2007 and December 2011, all consecutive cases of pericardial inflammatory
syndromes (acute pericarditis, myopericarditis, and perimyocarditis) were prospectively enrolled in 3 Italian referral centers for pericardial diseases (Torino, Bergamo, and Modena). The protocol was designed prospectively before data collection. Patients with pure acute myocarditis were excluded.

All patients provide informed consent. Moreover the investigation conforms to the principles outlined in the Declaration of Helsinki, and with the local legal requirements.

**Diagnostic criteria**

A diagnosis of acute pericarditis was performed with at least two of the following clinical criteria: pericarditis chest pain, pericardial friction rub, widespread ST-segment elevation or PR depression on the electrocardiogram (ECG), and new or worsening pericardial effusion. A clinical diagnosis of myopericarditis was performed in patients with a definite diagnosis of acute pericarditis and elevation of cardiac markers of injury (Troponin I or T, creatine kinase-CK-MB fraction) without new onset of focal or diffuse depressed left ventricular function by echocardiography or CMR. Perimyocarditis was diagnosed in patients with clinical criteria for acute pericarditis, elevation of cardiac markers of injury, and evidence of new onset of focal or diffuse depressed left ventricular function by echocardiography or CMR. The rationale for these diagnostic criteria is that pure pericardial or predominant pericardial inflammatory involvement is not characterized by significant impairment of myocardial function, and that, on the contrary, focal or diffuse abnormalities of ventricular wall motion or function imply a substantial myocardial inflammatory involvement.

Myocardial inflammatory involvement was clinically suspected in case of atypical ECG changes for pericarditis (i.e. localized ECG changes, abnormal ST segment or T waves changes or evolution, new Q waves), arrhythmias, cardiac troponin elevation and/or new or worsening
ventricular dysfunction on echocardiography and was confirmed by CMR.\textsuperscript{14,15} CMR imaging included T2-weighted imaging for assessment of edema, T1-weighted imaging before and after contrast administration for evaluation of hyperemia, and assessment of late gadolinium enhancement. CMR results were considered to be consistent with the diagnosis of myocardial inflammatory involvement if 2 of 3 CMR techniques were positive.\textsuperscript{14,15}

**Diagnostic work-up.**

Each patient was assessed by clinical evaluation, routine blood chemistry (including blood count, markers of inflammation and myocardial lesion, creatinine, transaminases) and additional tests aimed at the identification of the etiology based on the presentation features. All patients were submitted to echocardiography at presentation. CMR was performed within 2 weeks from symptoms onset when myocardial inflammatory involvement was suspected. Pericardial effusion was assessed in a semiquantitative way by two-dimensional echocardiography as mild (echo-free space of <10 mm during diastole), moderate (10-20 mm), and large (>20 mm). To facilitate correct definition of the effusion size and to allow follow-up studies, the largest size as well as the site and view were recorded.\textsuperscript{12}

Cardiac tamponade was diagnosed by the combination of clinical features (pulsus paradoxus, elevated jugular venous pressure, and tachycardia) and echocardiographic data (pericardial effusion with echocardiographic signs of tamponade).

Coronary artery disease was excluded in cases with coronary risk factors or dubious presentation with need for a differential diagnosis with acute coronary syndromes by means of coronary angiography at initial presentation. Subsequent CMR was also used to rule out possible cases with acute myocardial infarction necrosis but without significant coronary artery disease.\textsuperscript{16}

Histopathological confirmation of the presence of concomitant inflammatory myocardial
involvement requires an endomyocardial biopsy (EMB), but this is usually not performed in patients with no or mild left ventricular systolic dysfunction and no symptoms of heart failure according to the indications for endomyocardial biopsy that have been issued by a scientific statement from the American Heart Association/American College of Cardiology, and European Society of Cardiology. In this study the following indications were considered for EMB: subacute or acute symptoms of heart failure refractory to standard management, substantial worsening of the ejection fraction (EF) despite optimized pharmacological treatment, development of haemodynamically significant arrhythmias, heart failure with concurrent rash, fever or peripheral eosinophilia, history of collagen vascular disease, suspicion of possible giant cell myocarditis (young age, new subacute heart failure or progressive arrhythmias without apparent etiology).

**Treatment**

Aspirin or a non-steroidal anti-inflammatory drug (NSAID), generally ibuprofen, was considered the mainstay of treatment in patients with an established diagnosis of acute pericarditis or myopericarditis/perimyocarditis. Aspirin was the first-choice drug and was given at the dose of 750 to 1000 mg orally every 6 or 8 hours for 7–10 days with gradual tapering over 2–3 weeks. Ibuprofen was prescribed at the attack dose of 600 mg three times a day, and then tapered in 2 to 3 weeks. In animal models of myocarditis, NSAIDs are not effective and may actually enhance the myocarditic process and increase mortality. On this basis reduction of the dosage of aspirin to 500 mg every 8 to 12 hours was considered for patients with myopericarditis/perimyocarditis. Corticosteroids were considered as the second choice for patients with contraindications or intolerance to aspirin and NSAIDs. In every case gastroprotection with a proton pump inhibitor was prescribed. Colchicine use (0.5 mg twice daily
for 3 months, or 0.5 mg once daily in patients <70Kg) was optional for patients with pure acute pericarditis and was limited in patients with myopericarditis and perimyocarditis, because of the lack of clinical trials or studies to support this indication.20

Clinical measures and follow-up

The relative frequency of myopericarditis/perimyocarditis was assessed among patients with acute pericardial inflammatory syndromes. Main clinical characteristics and treatments were recorded for all cases. During follow-up, clinical evaluation, ECG and routine blood chemistry was performed at 1 month, 6 months, and 12 months, and then every year, if the course was uncomplicated. Treadmill testing was performed at 6 months for patients with myopericarditis/perimyocarditis. All adverse events were recorded, including recurrent pain, relapses (either of pericarditis or other inflammatory myopericardial syndrome), cardiac tamponade, constrictive pericarditis, residual left ventricular dysfunction, heart failure, and overall and cardiovascular mortality.

Statistical analysis

Continuous data are reported as means ± SD. Patients groups are compared by using t-test for continuous variables and a chi-square analysis for categorical variables. Time to event distributions were estimated by using Kaplan-Meier method and compared by using the log-rank test. A probability value of <0.05 was considered to show statistical significance. Analyses were performed with SPSS, version 13.0 (SPSS, Chicago, Illinois). 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

In the study period 486 cases of inflammatory myopericardial syndromes were recorded (346
cases of acute pericarditis, 114 cases of myopericarditis, and 26 cases of perimyocarditis) (Figure 1).

Clinical presentation and baseline features

Detailed baseline features are reported in Table 1. Patients with inflammatory myocardial involvement were younger and more frequently male than those with acute pericarditis (p<0.001). Moreover the following features were more commonly associated with acute pericarditis: pericardial rubs on physical examination, and pericardial effusion on echocardiography (for all, p<0.01). On the contrary heart failure signs and symptoms and cardiac arrhythmias were recorded with increasing frequency in patients with myocardial inflammatory involvement (myopericarditis/perimyocarditis). Left ventricular ejection fraction was only mildly reduced in patients with perimyocarditis (44±9%). White blood cells and C-reactive protein elevations were more common in acute pericarditis than in myopericarditis and perimyocarditis (p<0.001), while markers of myocardial lesions (cTnI and CK-MB) were overlapping in patients with myopericarditis and perimyocarditis. CMR was performed in 255 cases: all patients with troponin elevation (n=140) and additional patients with a clinical suspicion of inflammatory myocardial involvement on the basis of clinical presentation (atypical ECG changes for pericarditis, arrhythmias, cardiac troponin elevation and/or new or worsening ventricular dysfunction on echocardiography). CMR data on myocardial involvement included respectively: edema (T2-weighted imaging)/hyperemia in 93.0% of patients with myopericarditis, and 92.3% of patients with perimyocarditis, late gadolinium enhancement was detected in all cases. In patients with a final diagnosis of pericarditis who performed CMR for a clinical suspicion of myocardial involvement (n=115), pericardial abnormal T2-weighted imaging (edema and hyperemia) and late gadolinium enhancement were recorded in 104 of 115 patients (90.4%).
The initial presentation mimicked a ST-segment elevation myocardial infarction in 87 of 114 (76.3%) cases of myopericarditis and 20 of 26 (76.9%) cases of perimyocarditis and only 8 of 346 cases (2.3%; p<0.001) of simple acute pericarditis. All these patients underwent coronary angiography that excluded the presence of significant coronary artery disease. Acute myocardial infarction in the absence of significant coronary artery disease was also excluded by CMR. The etiology (Table 2) was similar in different myopericardial subgroups (idiopathic in 84-85%, infectious in 4-5%, and connective tissue disease or inflammatory bowel disease in 10-12% of cases).

**Patient management**

Aspirin or ibuprofen were prescribed as anti-inflammatory therapy in 95% of patients with acute pericarditis, 89% of those with myopericarditis, and 18% of patients with perimyocarditis. Corticosteroids were prescribed in 6% of patients with acute pericarditis, and 4 to 6% of patients with myopericarditis/perimyocarditis. Colchicine was added to anti-inflammatory therapies in 55% of patients with acute pericarditis, 18% of patients with myopericarditis, and 15% of cases with perimyocarditis. In patients with myocardial inflammatory involvement a beta-blocker (bisoprolol 1.25 mg then increased to reach a heart rate of 55 to 60 bpm at rest) was prescribed in 49 to 77% of cases, and an ACE-inhibitor (ramipril 1.25 mg as starting dose then uptitrated as tolerated) in 25 to 58% of cases of myopericarditis/perimyocarditis with evidence of left ventricular dysfunction (Table 2). Patients with a clinical diagnosis of myopericardial inflammatory syndromes were temporarily excluded from competitive and amateur-leisure time sport activity. This recommendation was independent of age, gender, symptoms degree, or concurrent medical therapy. After resolution of the clinical picture (at least 3 months after the onset of the disease for simple acute pericarditis and 6 months for those with
myopericarditis/perimyocarditis), clinical reassessment was performed prior re-entering physical activity beyond sedentary life and competitive sport lifestyle.\textsuperscript{21-23}

**Outcome and follow-up data**

After a median follow-up of 36 months (range 6-66) no cases of deaths or heart failure were recorded (Table 3). A residual mild left ventricular (LV) dysfunction was recorded in 8% of cases of myopericarditis and 15% of cases of perimyocarditis (p<0.001). An increase of mean LVEF was recorded in all subgroups at 12 months (Figure 2).

Recurrences were more common in acute pericarditis (31.8%) than myopericarditis (10.5%) or perimyocarditis (11.5%; p<0.001). In more than 95%, recurrences of pericarditis and myopericarditis/perimyocarditis were manifested as relapses of pericarditis and only rarely as myopericarditis or perimyocarditis either in patients with previous simple pericarditis or myopericarditis/perimyocarditis. Recurrence-free survival was similar in patients with myopericarditis and perimyocarditis (Figure 3). No cases of cardiac tamponade were recorded in patients with myopericarditis and perimyocarditis and one case of constrictive pericarditis was recorded in patients with myopericarditis. Troponin elevation was not associated with an increase of complications during follow-up.

**Discussion**

**Relative frequency of myopericarditis/perimyocarditis**

For the first time, this prospective cohort study provides evidence of the relative frequency of myopericardial inflammatory syndromes in adults. Myocardial involvement is relatively frequent and was recorded in one third of patients with acute pericardial inflammatory syndromes. Myopericarditis is more frequent than perimyocarditis (respectively 23.5\% vs. 5.4\% of all patients with acute pericardial inflammatory syndromes; p<0.001).
Peculiar features of myopericarditis/perimyocarditis

Patients with myocardial involvement are younger than those with simple acute pericarditis, moreover male gender is commoner in patients with myopericarditis/perimyocarditis, as already reported in previous reports,\(^4^9 10^\) and this suggests the possibility that hormonal factors may play a role in the etiopathogenesis of myopericardial inflammatory syndromes.

This study also underlines specific peculiarities of the clinical presentation. The presence of pericardial rubs and pericardial effusion are usually associated with less myocardial involvement, while the presence of ST and PR abnormalities suggest an increased likelihood of myocardial involvement.

ST-segment elevation or PR depression, usually considered hallmark of acute pericarditis, can be recorded in only 50 to 60% of patients with simple acute pericarditis. These ECG changes reflect the extent of subepicardial involvement, since the pericardium is electrically silent, and are especially suggestive of concomitant myocardial inflammatory involvement rather than simple acute pericarditis. Myocardial involvement is often associated with ST-segment elevation (>75% of cases), with an initial presentation that may simulate an acute coronary syndrome in a substantial number of cases (about 75%). Also arrhythmias are peculiar of myocardial inflammatory involvement and should alert the clinician when are recorded in a patient with presumed "acute pericarditis".

Another significant issue is that related to biomarkers expression in different types of inflammatory myopericardial syndromes. Elevation of C-reactive protein is recorded in all subgroups but higher levels are found in patients with simple pericarditis compared with those with myopericarditis/perimyocarditis. Cardiac troponin elevation is roughly related to the extent of myocardial involvement (respectively median 9.4, range 1.0-44.0 ng/ml in perimyocarditis.
and median 7.2, range 1.0-34.7 ng/ml in myopericarditis) and was largely overlapping in the two
syndromes.

**Etiology and therapeutic issues**

The etiology is similar in different subgroups, regardless of the entity of myocardial
inflammatory involvement. Most cases still remain idiopathic with a conventional diagnostic
approach and these results are consistent with already published data.4,10,11

Empirical anti-inflammatory therapies with aspirin or a NSAID were mainly adopted for
patients with prevalent pericardial involvement (>85% of cases) while reduced doses were
considered in patients with perimyocarditis because of the fear of possible negative effects of
these therapies with myocarditis. Also in this setting, corticosteroids should probably not be used
as first line therapy, while we have limited data on the use of colchicine, since patients with
myocardial involvement have been excluded in previous clinical trials for treatment and
prevention of pericarditis.20

**Prognostic issues**

Unlike acute coronary syndrome cardiac troponin elevation was not a negative prognostic marker
in myopericarditis/perimyocarditis; and the degree of troponin elevation did not correlate with
the likelihood of subsequent recovery. Most of these patients had a normal or nearly normal left
ventricular function at presentation and generally improved during a 12-month follow-up with
normalization of LV function in >90% of cases for myopericarditis, and >80% of cases with
perimyocarditis. No deaths correlated to pericardial or myocardial involvement were recorded
during follow-up. These data are reassuring and confirm preliminary findings in pediatric
populations and adults (Table 4).4,10,11 Recurrences were more common with prevalent
pericardial involvement and generally occurred as recurrent pericarditis.
Clinical implications

Some involvement of the myocardium should be suspected in any young patient with chest pain, ST-segment elevation at presentation, and cardiac arrhythmia (sustained or not, either supraventricular or ventricular) (Table 1), while rubs and pericardial effusion are more suggestive of isolated pericardial involvement. In the setting of myopericarditis/perimyocarditis the differential diagnosis should especially include acute coronary syndromes, and up to 3 of 4 of these patients may have a presentation that may simulate an acute coronary syndrome. Coronary angiography is necessary to rule out and promptly treat acute myocardial infarction with ST-segment elevation. For those without evidence of coronary artery disease or a pseudo-infarctual presentation, CMR is an useful non-invasive diagnostic tool for the clinical diagnosis of myopericardial inflammatory syndromes and to rule out acute myocardial infarction with normal coronary arteries.\textsuperscript{16,24-28} In these cases, the diagnostic utility of EMB is clearly reduced for clinicians. Although EMB may establish a definite diagnosis, it is difficult to justify its clinical utility in patients with myopericarditis/perimyocarditis in the absence of major cardiac arrhythmias, heart failure or failure of conventional therapies, since treatment and management are not affected by the results of EMB and the prognosis seems benign. Moreover recently published data have compared the diagnostic performance of CMR imaging with EMB.\textsuperscript{29} In 132 patients with suspected acute myocarditis (≤14 days) or chronic myocarditis (defined as symptoms>14 days) the overall diagnostic sensitivity, specificity, and accuracy of CMR was respectively 76%, 54%, and 68% and was better in the setting of acute cases (respectively 81%, 71%, and 79%). Thus, in clinical practice, CMR is useful for non-invasive diagnosis of myocardial inflammatory involvement, especially in patients with recent symptoms onset (< 2 weeks) as patients included in the present study.
This cohort study is reassuring about the prognosis of myopericardial inflammatory syndromes. Patient with acute pericarditis and myopericarditis have a very good prognosis without worsening of LV function, and no recorded deaths. During follow-up recurrences are the only significant complications and are generally manifested as recurrent pericarditis either following acute pericarditis or myopericarditis and perimyocarditis.

**Study limitations**

At present this is the first study to include patients with myopericarditis and perimyocarditis and to emphasize the clinical spectrum of myopericardial inflammatory syndromes. A first limitation of the study is that the diagnosis was based on clinical criteria and not confirmed by EMB, since no patients fulfilled indications for endomyocardial biopsy according to AHA/ACC/ESC guidelines. However there is now good and growing evidence to support the use of CMR as non-invasive diagnostic tool for the clinicians, especially when additional invasive tools do not affect the subsequent therapy and management of patients. A second and third limitations are related to the length of our follow-up and the subgroup sample size. Longer follow-up are needed to confirm the benign outcome as well as larger populations, although, at present, this study includes the largest published group of patients with inflammatory myopericardial syndromes.

In conclusion, myopericardial inflammatory syndromes (myopericarditis/perimyocarditis) are benign clinical syndromes that can be frequently encountered in patients with an initial suspicion of pericarditis. The main differential diagnosis is with ST-segment elevation myocardial infarction and coronary angiography may be required. CMR is an useful diagnostic tool for the non-invasive diagnosis of concomitant myopericardial inflammatory involvement and may help to distinguish these syndromes from myocardial infarction.
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Conflict of Interest Disclosures: None.

References:


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Table 1. Demographic features and clinical presentation of patients with inflammatory myopericardial syndromes.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Pericarditis (n=346)</th>
<th>Myopericarditis (n=114)</th>
<th>Perimyocarditis (n=26)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>41.0 (22.0)</td>
<td>29.0 (14.5)</td>
<td>24.0 (17.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>189 (54.6%)</td>
<td>89 (78.1%)</td>
<td>22 (84.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recent febrile syndrome</td>
<td>237 (68.5%)</td>
<td>69 (60.5%)</td>
<td>18 (69.2%)</td>
<td>0.212</td>
</tr>
<tr>
<td>Chest pain</td>
<td>336 (97.1%)</td>
<td>112 (98.2%)</td>
<td>23 (88.5%)</td>
<td>0.909</td>
</tr>
<tr>
<td>Pericardial rub</td>
<td>83 (24.0%)</td>
<td>15 (13.2%)</td>
<td>2 (7.7%)</td>
<td>0.005</td>
</tr>
<tr>
<td>ECG changes</td>
<td>190 (55.0%)</td>
<td>100 (88.2%)</td>
<td>20 (76.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Supraventricular arrhythmias</td>
<td>20 (5.8%)</td>
<td>10 (8.8%)</td>
<td>5 (19.2%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>1 (0.3%)</td>
<td>5 (4.4%)</td>
<td>2 (7.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>254 (73.4%)</td>
<td>30 (26.3%)</td>
<td>10 (38.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AV-block</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>HF symptoms/signs</td>
<td>0 (0.0%)</td>
<td>4 (3.5%)</td>
<td>3 (11.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EF, mean (SD)</td>
<td>58.9±3.6</td>
<td>58.1±4.2</td>
<td>44.0±9.0</td>
<td>by definition</td>
</tr>
<tr>
<td>WBC elevation</td>
<td>249 (72.0%)</td>
<td>31 (27.1%)</td>
<td>6 (23.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>7.7±4.7</td>
<td>5.3±4.6</td>
<td>3.2±2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>cTnI (ng/ml)†</td>
<td>0.0 (0.0-0.0)</td>
<td>7.2 (0.5-34.7)</td>
<td>9.4 (0.5-44.0)</td>
<td>by definition</td>
</tr>
<tr>
<td>CK-MB (ng/ml)‡</td>
<td>0.0 (0.0-0.0)</td>
<td>24.0 (12-52)</td>
<td>34.2 (17-83)</td>
<td>by definition</td>
</tr>
</tbody>
</table>

*= comparison of acute pericarditis vs. myopericarditis and perimyocarditis.

IQR= interquartile range; ECG changes= ST-segment elevation or PR depression, HF= heart failure, EF= ejection fraction. CRP= C-reactive protein. †= data are expressed as median with range.

Table 2. Etiology and treatments in different inflammatory myopericardial syndromes.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Pericarditis (n=346)</th>
<th>Myopericarditis (n=114)</th>
<th>Perimyocarditis (n=26)</th>
<th>All (n=486)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic*</td>
<td>294 (85.0%)</td>
<td>96 (84.2%)</td>
<td>22 (84.6%)</td>
<td>412 (84.8%)</td>
</tr>
<tr>
<td>Infectious†</td>
<td>16 (4.6%)</td>
<td>5 (4.4%)</td>
<td>1 (3.9%)</td>
<td>22 (4.5%)</td>
</tr>
<tr>
<td>Connective tissue disease/Inflammatory bowel disease</td>
<td>36 (10.4%)</td>
<td>13 (11.4%)</td>
<td>3 (11.5%)</td>
<td>52 (10.7%)</td>
</tr>
<tr>
<td>Aspirin/NSAID</td>
<td>327 (94.5%)</td>
<td>101 (88.6%)</td>
<td>5 (17.6%)</td>
<td>433 (89.1%)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>19 (5.5%)</td>
<td>7 (6.1%)</td>
<td>1 (3.8%)</td>
<td>27 (5.6%)</td>
</tr>
<tr>
<td>Colchicine</td>
<td>191 (55.2%)</td>
<td>21 (18.4%)</td>
<td>4 (15.4%)</td>
<td>216 (44.4%)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>2 (0.6%)</td>
<td>56 (49.1%)</td>
<td>20 (76.9%)</td>
<td>78 (16.1%)</td>
</tr>
<tr>
<td>ACE-inhibitor</td>
<td>2 (0.6%)</td>
<td>28 (24.6%)</td>
<td>15 (57.7%)</td>
<td>45 (9.3%)</td>
</tr>
</tbody>
</table>

*= without a known specific etiology after diagnostic work-up
†= including known viral and bacterial (tuberculosis) etiologies. Detailed infectious etiologies included: a) pericarditis: Coxackievirus in 4 cases (25.0%), Epstein-Barr virus (EBV) in 3 cases (18.75%), Parovirus in 3 cases (18.75%), Adenovirus in 3 cases (18.75%), CMV in 2 cases (12.5%), and Influenza in 1 case (6.25%); b) myopericarditis: Coxackievirus in 3 cases (60.0%) and Parovirus in 2 cases (40.0%); c) perimyocarditis: Parovirus in 1 case (100%). Percentages are reported according to diagnosed infectious cases in each group: acute pericarditis, myopericarditis, and perimyocarditis.
Table 3. Follow-up data.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Pericarditis (n=346)</th>
<th>Myopericarditis (n=114)</th>
<th>Permyocarditis (n=26)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>110 (31.8%)</td>
<td>12 (10.5%)</td>
<td>3 (11.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac Tamponade</td>
<td>8 (2.3%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Constrictive pericarditis</td>
<td>2 (0.6%)</td>
<td>1 (0.9%)</td>
<td>0 (0.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>LV dysfunction (EF&lt;55%) at 12 months</td>
<td>4 (1.1%)</td>
<td>9 (7.9%)</td>
<td>4 (15.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All cause death</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*= comparison of acute pericarditis vs. myopericarditis and perimyocarditis.
Median follow-up of 36 months (range 6 to 88 months). Recurrences were manifested as recurrent pericarditis in >90% of cases.

Table 4. Major clinical studies on the outcome of myopericarditis and perimyocarditis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Setting</th>
<th>Troponin (peak)</th>
<th>Follow-up</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imazio M et al.</td>
<td>2008</td>
<td>Myopericarditis/Adult</td>
<td>TnI 7.7 ± 6.7 ug/l (1.5-22.5)</td>
<td>12 months</td>
<td>0% Normalization of parameters in 97.5%</td>
</tr>
<tr>
<td>Machado S et al.</td>
<td>2010</td>
<td>Myopericarditis/Adult</td>
<td>TnI 7.3 ug/l (4.4-10.2)</td>
<td>20 months</td>
<td>21.4%</td>
</tr>
<tr>
<td>Kobayashi D et al.</td>
<td>2012</td>
<td>Myopericarditis/Pediatric</td>
<td>TnI 4.75 ug/l (1.35-9.72) (2 weeks to 3 years)</td>
<td>2 months</td>
<td>0% Normal LVEF and function</td>
</tr>
<tr>
<td>Buiatti A et al.</td>
<td>2012</td>
<td>Perimyocarditis/Adult</td>
<td>TnI 10.5 ± 17.0 ug/l</td>
<td>4.5 ± 0.8 years</td>
<td>0% Normalization of echo features in 100%</td>
</tr>
</tbody>
</table>

Figure Legends:

Figure 1. Study population of pericardial inflammatory syndromes.

Figure 2. Evolution of mean values of left ventricular ejection fraction (LVEF) in study subgroups from baseline to 12 months. Mean values ± SD.
Figure 3. Recurrence-free survival in different sub-groups of inflammatory myopericardial syndromes.
Overall cohort with Inflammatory Pericardial Syndromes (n=486)

- Troponin Elevation?
  - yes
    - n=140
    - New onset of focal or diffuse depressed LV function?
      - yes
        - n=26 PERIMYOCARDITIS
      - no
        - n=114 MYOPERICARDITIS
  - no
    - n=346 PERICARDITIS
Recurrence-free Survival

Log rank p = 0.001

Time (months)

Patients at risk:
Pericarditis:
346 306 234 169 143 110 98 81 75 36 22
Myopericarditis:
114 109 94 78 65 59 50 36 21 16 12
Perimyocarditis:
26 26 24 20 18 14 7 5 3 2 2
Good Prognosis for Pericarditis With and Without Myocardial Involvement: Results from a Multicenter Prospective Cohort Study
Massimo Imazio, Antonio Brucato, Andrea Barbieri, Francesca Ferroni, Silvia Maestrini, Guido Ligabue, Alessandra Chinaglia, Davide Cumetti, Giovanni Della Casa, Federica Bonomi, Francesca Mantovani, Paola Di Corato, Roberta Lugli, Riccardo Faletti, Stefano Leuzzi, Rodolfo Bonamini, Maria Grazia Modena and Riccardo Belli

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