A retrospective analysis of "real-world" data on pericarditis patients

Pericarditis in a Swiss regional hospital

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Summary

BACKGROUND: Pericarditis is a probably underestimated differential diagnosis of acute chest pain. Pericarditis outcome is favourable, but no real-world data for Swiss hospitals are available as yet. Therefore, a retrospective single-centre analysis on a prospective cohort of patients with pericarditis was conducted in a regional hospital with specialised tertiary care in Switzerland.

METHODS: Between January 2011 and December 2016, a total of 44 patients with pericarditis were prospectively registered at the emergency department of the GZO Zurich Regional Health Centre and followed up for 7–79 months. Based on this database, a retrospective analysis was performed. Analysis included presumed aetiology, symptoms at enrolment, ECG changes, echocardiographic and laboratory findings, comorbidities, therapy, recurrence rate and complications.

RESULTS: Of the 44 registered patients, 33 had a first episode of pericarditis and 11 were classified as recurrences. Male to female ratio was 5.7:1 for patients below 45 years, and 1.2:1 above the age of 45. In 35 cases pericarditis was classified as idiopathic and in 9 cases it was due to postcardiotomy injury syndrome (Dressler syndrome). Nearly two thirds of patients reported either influenza-like symptoms or infections 2–4 weeks prior to the hospitalisation. Thirty-nine patients (89%) presented with chest pain; 36 (82%) patients showed ECG changes and 31 (71%) had a pericardial effusion. Pleural effusions were detected in 30% of the cases (13 patients). A pericardial friction rub was reported in 6 patients (14%) only. Ninety-one percent of patients had elevated C-reactive protein levels at enrolment. Troponin elevations were reported for 23 patients (52%). Five patients (11%) were treated with aspirin, and 31 patients (70%) received another NSAID. Colchicine was administered to 33 patients (75%) corticosteroids to 8 patients (18%) and mycophenolate to 2 patients (5%). On follow-up, 30 patients with a first diagnosis of pericarditis and 8 patients with a recurrence remained free from further recurrences. Three recurrences affected patients with a first episode of pericarditis and three further recurrences were observed in patients who were enrolled after pericarditis recurrence.

CONCLUSIONS: In patients with pericarditis, males predominate, but the male to female ratio shifts towards a higher proportion of women in patients above 45 years of age. Chest pain and ECG changes are the most common clinical findings in the emergency department and outcome is generally favourable with low recurrence rates.

Key words: pericarditis; myopericarditis; age; gender; treatment; recurrence

Introduction

Pericarditis is a probably underestimated differential diagnosis of acute chest pain. It accounts for 5% of all chest pain emergency referrals [1].

Approximately 80% of pericarditis cases are either idiopathic or postviral [1, 2]. Accordingly, many patients report respiratory or intestinal infections several weeks before disease onset [2, 3]. In addition, postcardiac injury syndrome (PCIS), which comprises postinterventional, postsurgery and posttraumatic pericarditis, accounts for a relevant number of cases [2, 4]. PCIS most likely reflects autoimmune responses against cardiac and pericardial self-antigens released during heart injury [4]. PCIS typically appears after a latent period of a few weeks [5]. Men have a higher risk of developing an acute episode of pericarditis than women [6].

Acute pericarditis is defined by the following criteria: chest pain, pericardial friction rub, pericardial effusion or typical electrocardiogram (ECG) changes [2, 5, 7]. Two of these four criteria are required for diagnosis [2, 5, 7, 8]. Patients commonly show elevation of C-reactive protein (CRP) levels and other markers of inflammation [5, 7]. Several studies suggested that increased CRP levels are required for a pericarditis diagnosis [2, 9, 10]. Troponin elevations are also common in pericarditis and reflect myocardial involvement, as well as damage to cardiomyocytes extending from the root of the pulmonary artery to the pericardium [2, 5].

The 2015 European Society for Cardiology (ESC) Guidelines recommendation for first-line treatment of acute pericarditis consists of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) combined with colchicine [5]. Colchicine prevents recurrences and expedites

List of abbreviations used

ESC	=	European Society for Cardiology
PCIS	=	postcardiac injury syndrome
ECG	=	electrocardiogram
CRP	=	C-reactive protein
CT	=	computed tomography
MRI	=	magnetic resonance imaging

healing [8, 11, 12]. Corticosteroids are rather discouraged in idiopathic or viral pericarditis because of a higher recurrence risk [12]. Nevertheless, corticosteroids are still required in pericarditis associated with systemic autoimmune diseases or in patients refractory to NSAIDs, aspirin and colchicine [7, 12]. Postviral and idiopathic pericarditis are usually self limiting and have, despite a remarkable risk of recurrences, an excellent prognosis [7]. Predictors of poorer outcome are major risk factors such as fever >38°C, a subacute disease course, cardiac tamponade, pericardial effusions larger than 20 mm and failure to respond to NSAIDs or aspirin [13]. Complications of pericarditis are cardiac tamponade, constriction and recurrences [13]. The most frequent complication is recurrence [7].

Most clinical, epidemiological and outcome data on pericarditis were collected from research teams in Northern Italy, Israel and, to a minor extent, in the United States of America.

The aim of the present study was to provide real-world data on patients referred to a regional hospital in the greater Zurich area in Switzerland.

Methods

Study design and setting

A retrospective analysis of a prospectively generated database of patients with the diagnosis pericarditis was performed. All patients with an acute, incessant ("persistent pericarditis or with a symptom free interval of less than 6 weeks"), chronic (>3 months) or recurrent ("defined by a first episode, a symptom free interval of 4–6 weeks or longer and detection of subsequent recurrent pericarditis") pericarditis who were admitted to the emergency department of the GZO Zurich Regional Health Centre between January 2011 and December 2016 were registered and followed up [5]. All patients were evaluated and treated according to in house standard operating procedure guidelines. The retrospective analysis was approved by the Ethics Committee and informed consent was obtained from all patients.

Study population and diagnostic criteria

Pericarditis was diagnosed with two of the following four criteria as reported in the ESC Guidelines 2015, based on several key papers [2, 5, 7]: pericardial chest pain, pericardial friction rub, pericardial effusion and electrocardiogram changes. Typical ECG changes were defined as widespread concave ST elevations in all areas, and/or PR depressions in leads I–III, avF, V1–V6 or PR elevation in avR. Pericardial effusion was detected with echocardiography or computed tomography (CT).

Patients with an ejection fraction <45% at enrolment were excluded. Patients with an elevation of myocardial injury markers were included as myopericarditis, if they fulfilled diagnostic criteria for pericarditis and showed wall motion abnormalities in echocardiography [7]. One enrolled patient refused consent to evaluate his data.

Follow-up

Two to four weeks after diagnosis and initiation of therapy, as well as after 3, 6 and 12 months, a clinical visit including routine laboratory test and ECG was carried out. Echocardiography was performed at enrolment and after 12 months in all uncomplicated cases, or at the discretion of the attending physician in charge of the patient. Magnetic resonance imaging or CT scans were ordered if indicated.

Study parameters

Study parameters included demography (age, gender, residence, aetiology), first episode or recurrence at enrolment, diagnostic criteria and symptoms at presentation, presence or absence of flu-like symptoms or infections 2–4 weeks prior hospitalisation, comorbidities (coronary heart disease, cancer history, renal disease, hypothyroidism, autoimmune disease), major risk factors (fever >38°C, failure to respond to NSAIDs within 7 days, subacute course, large effusion >20 mm, cardiac tamponade), minor risk factors (myopericarditis, immunosuppression, trauma, oral anticoagulant therapy), pleural effusion, classification of pericardial effusion (mild <10 mm, moderate 10–20 mm, large >20 mm), previous cardiac surgery or cardiac interventional procedure, PCIS, number of cardiovascular risk factors (family history, hypertension, dyslipidaemia, diabetes, smoking), drugs, outcome (death, constrictive pericarditis, tamponade, recurrence on follow-up), ejection fraction, diastolic dysfunction, clinical findings (blood pressure, heart rate, body core temperature), laboratory findings (creatinine, electrolytes, troponin I and T levels, liver enzymes, CRP-levels, haemoglobin, leucocytes, thyroid hormones, antinuclear antibodies, anti-DNA-antibodies, rheumatoid factor, serum electrophoresis, urine analysis) as well as therapy (NSAIDs without aspirin, aspirin, colchicine, corticosteroids, mycophenolate, intravenous immunoglobulin [IVIG], interleukin-1 receptor antagonists, azathioprine).

Statistical analysis

Data from 44 patients were available. In PivotTables, the sum and percentages of the study parameters mentioned above were computed and compared between

men and women, idiopathic/viral pericarditis versus PCIS and the group of patients with a first episode versus those enrolled with a recurrence of pericarditis. Fisher's exact test was performed on categorical data. A p-value <0.05 was considered significant.

Results

Patient characteristics and comorbidities

The study cohort consisted of 44 patients aged 15 to 84 years (mean age 44.45 years). There were more male (n = 28, 64%) than female (n = 16, 36%) patients. Interestingly, almost all patients younger than 45 years were male (male to female ratio 5.7:1). In contrast, the gender distribution was nearly balanced in the patients aged >45 years (male to female 1.2:1) (fig. 1). The difference in male to female ratios between patients <45 versus patients >45 were significant (p = 0.011). All patients were Swiss residents and all except five were of Caucasian origin. Cardiovascular risk factors were present in 29 patients (smoking in 17, hypertension in 14, diabetes in 9, dyslipidaemia in 13, family history for coronary arterial disease in 10). Coronary heart disease affected nine patients (21%, four women, five men). Eleven patients had undergone cardiac surgery or a cardiac interventional procedure during the year prior to the pericarditis diagnosis. Eight patients were immunosuppressed on admission and four received anticoagulant therapy. Hypothyroidism, history of cancer, renal or pre-existing autoimmune diseases were rare (table 1). On the basis of elevated cardiac enzymes, myopericarditis was diagnosed in 23 (52%) of patients.

Pericarditis was considered idiopathic in 35 patients and autoimmune in 9 cases. All of these nine patients fulfilled PCIS criteria. Patients with PCIS had a previous cardiac interventional procedure or cardiac surgery and suffered more frequently from coronary heart disease. All PCIS patients had one or more cardiovascular risk factors.

Table 1: Comorbidities.

Comorbidity	Number of patients (n = 44)
Cardiovascular risk factors	29 (66%)
Family history	10 (23%)
Hypertension	14 (32%)
Dyslipidaemia	13 (30%)
Diabetes	9 (21%)
Smoking	17 (39%)
Coronary heart disease	9 (21%)
Hypothyroidism	3 (7%)
Renal disease	7 (16%)
Pre-existing autoimmune disease	4 (9%)
History of cancer	5 (11%)
Influenza-like symptoms / infection	27 (61%)
Alcohol	13 (30%)

Diagnostic criteria, and clinical, laboratory and echocardiographic findings

Of the total cohort, 39 patients (89%) had chest pain on admission, 36 (82%) showed ECG changes and in 31 (71%) pericardial effusions were detected. Pericardial effusions were classified as mild (n = 22, 50%), moderate (n = 5, 11%) or large (n = 4, 9%). Pericardial friction rub occurred less frequently (n = 6, 14%). In three cases only, all four diagnostic criteria were met. Eighteen patients showed three, and 23 only two diagnostic criteria. In addition, further clinical findings were noted: fever (n = 4, 9%), tachycardia (n = 8, 18%) and hypertension (n = 9, 20%).

In six patients a reduced ejection fraction of <55% and in seven diastolic dysfunction was detected. In addition, pleural effusions were found in 30% of cases (n = 13). Pleural effusions were more common in patients with PCIS; however ECG changes, chest pain and elevated CRP levels occurred more frequently in patients with idiopathic pericarditis. Twenty-six of the cases with idiopathic pericarditis and one patient with PCIS reported either influenza-like symptoms or infections 2–4 weeks prior to the hospitalisation.

CRP levels >5 mg/l were present in 40 patients (91%). Troponin-T elevations >0.014 µg/l were detected in 23 cases (52%) (table 2). All patients with a troponin increase also had CRP elevations. Leukocytosis was present in 55% (n = 24) and lymphopenia in 30% (n = 13) of patients.
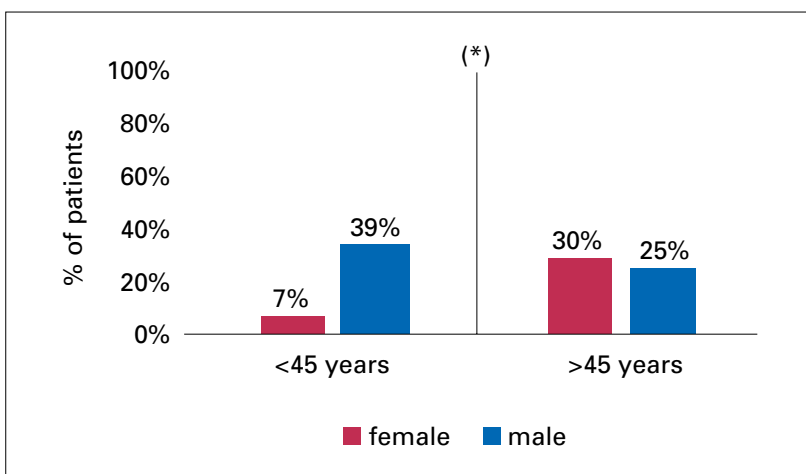

Figure 1: Age distribution in patients with pericarditis; p = 0.011 male to female in patients <45 years vs patients >45 years.

**Table 2:** Diagnostic criteria of pericarditis.

Diagnostic criteria	Number of patients (n = 44)
Chest pain	39 (89%)
ECG changes	36 (82%)
Pericardial friction rub	6 (14%)
Pericardial effusion	31 (71%)
CRP >5 mg/l	40 (91%)
hsTroponin >0.014 µg/l	23 (52%)

Gender differences

Pleural effusions were significantly more common in women (n = 9, 56%) than men (n = 4, 14%; p = 0.0058). Likewise, pericardial effusions were present in all female and in more than half of male patients (57%) (fig. 2). Smoking was the most common cardiovascular risk factor in men. On the other hand, hypertension, diabetes and dyslipidaemia were more frequently found in female patients. These differences, however, were not statistically relevant. Almost every man and nearly two thirds of the women showed typical ECG changes. Elevation of troponin I and T was more frequent in men than women, but not significant for the numbers of patients in our study (fig. 3). CRP levels were balanced in both genders and no other relevant differences in laboratory findings were evident.

Therapy

NSAIDs without aspirin were prescribed for 31 (70%) patients, aspirin was given to 5 (11%) and a combination of NSAIDs and aspirin to 4 patients (9%). NSAIDs were prescribed most frequently, followed by colchicine (n = 36, 82%), corticosteroids (n = 8, 18%) and mycophenolate (n = 2, 5%). Most patients received aspirin or NSAIDs
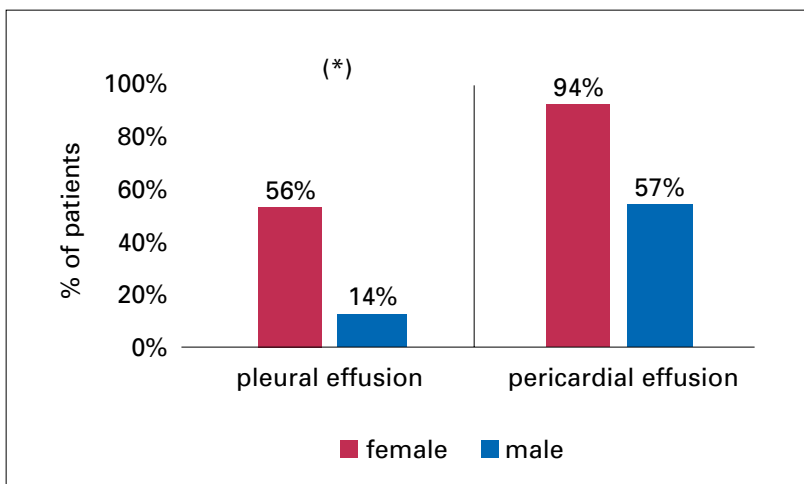
Figure 2: Gender-dependent pleural and pericardial effusions in patients with pericarditis; p = 0.0058 male vs female for pleural effusion.
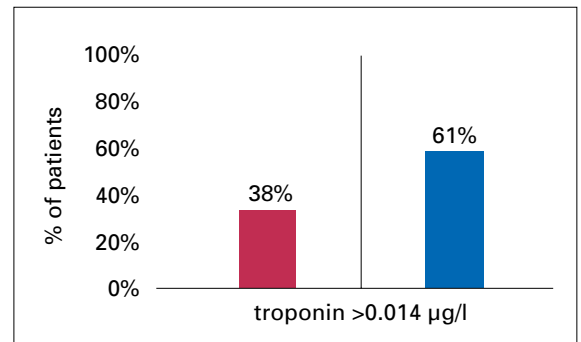
Figure 3: Gender-Dependent Troponin Elevations in Patients with Pericarditis; p = 0.211 male vs female for troponin >0.014 µg/l.

Table 3: Outcomes of pericarditis.

Outcome	Number of patients (n = 44)
Recurrences in all patients enrolled	6 (14%)
Recurrences in patients enrolled after a first episode	3 (9%)
Tamponade	0 (0%)
Constrictive pericarditis	0 (0%)
Cancer diagnosis on follow-up	0 (0%)

combined with colchicine (n = 33, 75%). Out of these patients, two were additionally treated with corticosteroids and another two with corticosteroids/mycophenolate. Furthermore, seven patients obtained solely anti-inflammatory and one patient solely corticosteroid therapy. Corticosteroids and colchicine were combined in three patients.

Outcomes

In 35 cases pericarditis was considered idiopathic (80%) and in 9 patients due to PCIS (20%). Of the 44 registered patients, 33 (75%) were enrolled due to a first pericarditis episode, whereas 11 cases (25%) were enrolled owing to a recurrence of pericarditis. Out of the 11 patients with recurrent pericarditis, 6 (14%, 3 enrolled after the first episode and 3 enrolled after a recurrence) experienced another recurrence on follow-up. Thirty-eight patients (86%, n = 30 with a first episode, n = 8 of those with a recurrence) remained healthy. There was no death, cardiac tamponade, constrictive pericarditis or a new cancer diagnosis on follow-up (table 3).

Discussion

Major findings

The present study provides real-world data on patients with pericarditis referred to a regional hospital in the greater Zurich area in Switzerland.

The study population, 33 cases with a first episode and 11 cases with a recurrence of pericarditis, included patients from adolescence to elderly (mean age 44.45 years).

Men, who made up 64% of the study population, were more often affected by pericarditis than women. This is in line with data from previous studies [6, 8]. Our observation that male predominance was much more pronounced in patients younger than 45 years has not been described before. Nevertheless, these data are hypothesis-generating only because of the small numbers of patients in our study. It would be interesting to replicate these findings from larger databases in Switzerland or to analyse the gender difference in data registries of already published cohorts.

The present study showed that idiopathic pericarditis is the most common aetiology of pericardial inflammation in Switzerland [1, 2, 7]. Idiopathic pericarditis is most commonly presumed to be viral [14]. Viral infections are supposed to trigger immune-mediated inflammation [6, 14]. In the present study this hypothesis was supported by the fact that nearly two thirds of the study cohort reported either influenza-like symptoms or infections prior to the hospitalisation.

PCIS after a previous cardiac interventional procedure or cardiac surgery accounted for a remarkable number of cases in the present study. Nevertheless, given the high numbers of post-cardiac surgery patients entering our hospital, we would have expected much more cases of PCIS. The exact incidence rates of PCIS, however, have not been established yet [4]. Nevertheless, an incidence between 10 and 40% for post-pericardiotomy patients has been reported in the literature [4]. We believe that many post-pericardiotomy patients were missed because they were discharged before PCIS onset and PCIS was only mild in most of them.

Myocardial inflammation is common in patients with pericarditis and was observed in half of our patients [3]. Moreover, we found high rates of pleural effusions. The high rate of pleural effusion, although only nine patients presented as PCIS, was conspicuous and probably reflected our institutional policy to perform ultrasound evaluation of the pleural space routinely together with echocardiography. Troponin elevation, and pericardial and pleural effusions were frequent, but particularly obvious in women. Gender-dependent differences in troponin elevation, pericardial and pleural effusions had also not been described before. Compared with the literature, chest pain (89%) and pericardial friction rub (14%) were equally frequent, but ECG changes (82%) and pericardial effusions (71%) were more frequent in our cohort

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[5]. Almost all of our patients (91%) showed increased CRP levels, which is higher than the 78% in a recent study [15]. Normal CRP values on admission can result from previous anti-inflammatory treatment or, more likely, early referral [15].

Overall, 75% of patients were treated according to the 2015 ESC guidelines with aspirin or NSAIDs combined with colchicine. Reasons for non-administration of colchicine were sparse data on the effect of colchicine in children and adolescents, and renal dysfunction in some patients. Nevertheless, our hospital reached high guideline adherence.

Our data showed that 86% of all included patients with an acute or a first recurrent pericarditis episode completely recovered without further recurrences. However, 14% of the total study population, 9% of patients enrolled after the first episode and 27% of patients enrolled after a recurrence of pericarditis, suffered from at least one further episode of recurrence within the follow-up period. Previous studies indicated a recurrence rate of up to 15–30% after a first episode of pericarditis and up to 50% if a first recurrence were treated without colchicine [8, 12]. The COPE trial showed a recurrence rate of 10.7%, which is comparable to the recurrence rate of 9% in our study [12]. Our low recurrence rate and therefore the good prognosis of patients with pericarditis is most likely due to application of colchicine, as well as an adequate guideline.

Limitations and expansion capability

Data were obtained from a single hospital centre on 44 patients only. These low numbers affect the power of the statistical analyses. Moreover, the retrospective study design and the fact that diagnosis was made by different physicians, who were not in the study team, might imply potential biases.

Conclusions

Pericarditis, which is a relevant differential diagnosis of acute chest pain, mainly affects men younger than 45 years. At an age above 45, the disease occurrence is balanced between both sexes. Owing to an adequate guideline and consequent application of colchicine, the recurrence rate is low and outcome is favourable.

References
The full list of references is included in the online version of the article at www.cardiovascmed.ch