Clinical Profile and Influences on Outcomes in Patients Hospitalized for

Acute Pericarditis

Running title: Kytö et al.; Clinical Profile and Acute Pericarditis

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Abstract

Background—The clinical profile with regard to gender and the influences on outcomes in patients who have been hospitalized for acute pericarditis are largely uncharacterized.

Methods and Results—We studied all patients aged ≥16 years admitted to hospital due to acute pericarditis (post-pericardiotomy and myocardial infarction associated pericarditis were excluded). Data were collected from a Finnish national registry including data on all cardiovascular admissions (670,409) during 9.5 years in 29 hospitals nationwide. During the study period there were 1,361 admissions for acute pericarditis. Pericarditis patients were more likely to be male (64.9% of patients) than female (35.1%) with age-adjusted likelihood ratio of 1.85 (95% confidence interval (CI) 1.65-2.06, p<0.0001) for male sex. Standardized incidence rate of hospitalizations for acute pericarditis was 3.32 per 100,000 person-years. Men aged 16-65 were at higher risk for pericarditis (relative risk (RR) 2.02; CI 1.81-2.26; p<0.0001) than women in general admitted population with highest risk-difference among young adults. Acute pericarditis caused 0.20% (CI 0.19-0.22%) of all cardiovascular admissions. Proportion of caused admissions declined by estimated 51% per 10-year increase in age. In-hospital mortality rate for acute pericarditis was 1.1% (CI 0.6-1.8%). Mortality increased with age (HR 3.26; CI 1.78-5.95; per 10-year increase in age; p=0.0001) and severe co-infection (pneumonia or septicemia) (HR 13.46; CI 2.26-80.01; p<0.005) but was not associated with sex in multivariate analysis.

Conclusions—Patients hospitalized for acute pericarditis are more commonly men. Increasing age and severe co-infection are associated with greater in-hospital mortality in hospitalized acute pericarditis patients.

Key words: pericardial disease, pericarditis, sex, aging, epidemiology
Acute pericarditis is an inflammatory disease of pericardium triggered commonly by viral infections in developed countries, while tuberculosis is the most common cause in developing countries. Experimental studies have found males to be at higher risk for acute viral heart disease, but clinical studies have reported conflicting results on sex distribution of acute pericarditis patients. It is commonly thought that there is no specific sex predisposition to pericarditis. Murine studies have also found the susceptibility for viral heart disease to be significantly age-dependent with highest sensitivity at adolescence or young adulthood. Mean age of acute pericarditis patients in clinical series has ranged from 41 to 60 years, but sex associated differences in age have not been reported. Prognosis of viral/idiopathic pericarditis is good, but purulent and tuberculosis pericarditis have high mortality. Female sex has been associated with complications after acute pericarditis, but this little is known about the effect of age. We studied the associations of age- and sex- with occurrence of acute pericarditis in all-comer adult patients using a multihospital, nationwide setting.

Methods

Study patients and data collection

Patients aged ≥ 16 years admitted to hospital due to acute pericarditis during a 9.5 year period were studied. Postpericardiotomy syndromes and post infarction pericarditis were excluded. Data of all cardiovascular hospital admissions (n=670,409) between May 1st, 2000 and October 31st, 2009 in 29 hospitals were retrospectively collected from the Finnish Hospital Discharge Register (FHDR), a nationwide maintained by the Finnish National Institute for Health and Welfare database containing hospital discharge data of all hospital admissions in Finland. Patients aged ≥ 16 years with acute pericarditis as the primary cause of admission (ICD-10 codes I01.0 and I30)
were identified. Co-morbidities and potential etiologies were detected from hospital discharge diagnoses. Study population was mainly Caucasians. Differences in incidence rate were estimated using age- and sex-matched population data of Finland from the study period (39,523,746 person-years) obtained from Statistics Finland.

Hospital organization in Finland consists of three main levels: 5 university hospitals represent the highest level of hierarchy, followed by 16 central hospitals with coronary angiolaboratory and intensive care units, and smaller regional hospitals. Treatment of acute cardiovascular patients occurs mainly in university and central hospitals. This study included data from all university and central hospitals and 8 large regional hospitals located across the country. The study was conducted according to the National Institute for Health and Welfare permission (THL/1576/5.05.00/2010).

**Statistical analysis**

Data was analyzed with Poisson regression models. In the Poisson model of incidence rate, the logarithm of population was used as an offset and in the model for the proportion of cardiovascular admissions, the logarithm of total cardiovascular admissions was used as an offset. Sex-differences in dichotomous variables were estimated by modified Poisson regression with robust error variances\(^{15}\). In-hospital mortality during admission for acute pericarditis was studied using Cox-regression model stratified by study year with exact method for failure times. Multivariate mortality model included patient characteristics associated with mortality at the level of p<0.1 in univariate analysis. Variables displayed in Table 1 in addition to gender and age were considered as potential predictors of in-hospital mortality. Scale variables are presented as mean±standard deviation or median with interquartile range (IQR) as appropriate. Total incidence rates were standardized with US 2000 standard population by using a direct method.
Categorical variables are presented as counts, percentages or relative risks (RR) with 95% confidence intervals (CI) as appropriate. Confidence intervals were calculated using Poisson distribution. P-values <.05 were considered statistically significant. The SAS system version 9.3 (SAS Institute Inc, Cary, NC, USA) was used for statistical analyses.

Results

Frequency

The study period included 1361 hospital admissions with acute pericarditis as primary diagnosis. Pericarditis patient was more likely to be male (64.9% of patients; CI 60.7-69.3%) than female (35.1%; CI 32.0-38.4%) with age-adjusted likelihood ratio of 1.85 (CI 1.65-2.06, p<0.0001) for male sex. Prevalence of potential etiological co-morbidities was similar between men and women, but previous acute pericarditis was more common among women (Table 1). In addition, bacterial etiology was confirmed more commonly in women. Acute pericarditis patient was most commonly aged 50-59 years with median age of 52 years (range 16-93, IQR 35-63 years) (Figure 1A). Male patients were significantly younger than female patients (mean 45.9±18.3 vs. 56.2±17.3 years, p<0.0001). Age distribution varied significantly by sex, as proportion of male patients was notably higher in patients aged 16-65 years (Figure 1B). Median duration of admission for acute pericarditis was 5 days (IQR 3-8). Women were treated longer than men (7.5±6.9 vs. 6.1±5.1 days, age-adjusted p<0.0001). Admission lengthened by estimated 10% per 10-year increase in age (RR 1.10; CI 1.09-1.12, p<0.0001).

Acute pericarditis as cause of hospital admission

Acute pericarditis caused 4% of all cardiovascular admissions among adults aged 16-20 years, but the proportion decreased by estimated 51% (RR 0.49; 95% 0.48-0.51, p<0.0001) per 10-year
increase in age to 0.02% in patients aged 85 years or older (Figure 2). Overall, 0.20% (CI 0.19-0.22%) of cardiovascular admissions were caused by acute pericarditis. In men, pericarditis caused 0.24% (CI 0.22-0.25%) of admissions while this proportion was 0.16% (CI 0.15-0.18%) in women. Men aged 16-35 were more likely to have acute pericarditis as the cause of admission than women, while opposite was true for patients aged 46-75 (Figure 2B).

**Incidence rate**

Overall incidence rate of acute pericarditis was similar in population aged 16-49 years, but increased in older population (Figure 3A). Incidence rate among men was 4.52 (CI 4.22-4.83) per 100,000 person-years, with declining trend between 16-45 years followed by re-increase in older population segments (Figure 3B). Among women, standardized incidence rate of acute pericarditis was 2.11 (CI 1.91-2.32) per 100,000. Incidence was lowest among young women, followed by gradual increase with age with peak in population aged 65-74 years. Young (16-35 year old) men had highest incidence of acute pericarditis compared to young women (incidence rate ratio 4.65; CI 3.52-6.14, p<0.0001). Sex-difference in incidence rate was reduced with increasing age, and in population aged ≥66 years rate for acute pericarditis was similar in both sexes (Figure 4). Total standardized incidence rate of acute pericarditis was 3.32 (CI 3.14-3.50) / 100,000 person-years. Incidence rate of acute pericarditis was 2.02 (CI 1.81-2.26; p<0.0001) times higher among men compared to women in total population (Figure 4).

**In-hospital mortality**

In-hospital mortality rate for acute pericarditis was 1.10% (CI 0.61-1.82). Female sex was associated with increased mortality in univariate analysis, but was not an independent predictor of death in multivariate model (Table 2). Mortality increased significantly with age in both univariate and multivariate analysis (Table 2). Strongest predictor of in-hospital mortality in
acute pericarditis was severe co-infection (pneumonia or septicemia). Co-morbidities listed in Table 1, but not in Table 2 were not associated with in-hospital mortality in univariate analysis.

Discussion

This nationwide multi-hospital study describes age- and sex- associated occurrence of acute pericarditis at the population level. Previous studies have reported conflicting results on effect of sex on risk of pericarditis 5-7. Recent randomized trial of 240 acute pericarditis patients found 60% of patients to be male6, while previous studies have reported higher male prominence7, but also female prominence5. We found 65% of 1361 patients to be male and the age-adjusted likelihood of acute pericarditis patient to be a male was 1.9. Furthermore, the incidence rate of acute pericarditis in general adult population was two-fold among men compared to women.

Etiology of acute pericarditis is idiopathic in majority of cases but with an immune-mediated process probably triggered by a viral infection in many cases16, 17. Reasons of sex differences in pericardial inflammation are unknown, but experimental viral studies of myocardial inflammation have suggested that although genetic differences have some effect, sex hormones are major contributors for sex predisposition 3, 18. Testosterone appears to play a major role in development of myocarditis, as exogenous testosterone increases viral replication and inflammation in the heart and gonadectomy inhibits cardiac inflammation in experimental viral myocarditis 19, 20. Mechanisms of testosterone action include inhibition of anti-inflammatory cells 19, commitment to Th1 type immune response 21, and increasing viral binding to myocytes 20. In accordance with testosterone-effect, we found the risk for pericarditis to be significantly higher among young men compared to women. Although occurrence of acute pericarditis in men declined with age after teenage years, there was a re-increase in occurrence
after 45 years of age. This may suggest that interaction of testosterone with susceptibility to pericarditis may not be linear or that unrecognized etiology of pericarditis varies by age.

Female sex hormones also affect the risk for cardiac inflammation. Progesterone aggravates cardiac inflammation while oestrogen has inhibitory effects by favouring inhibiting pro-inflammatory T-cells, stimulating inhibitory T cells and favouring Th2 type immune response. Accordingly, we found the incidence of pericarditis in women to be highest at postmenopausal period when estrogenic levels are low. In addition to viral infections, systemic connective tissue diseases are potential causes of acute pericarditis. In line with previous studies, connective tissue disease was diagnosed in 2% of our patients. Women have a general higher tendency for connective tissue diseases associated with pericarditis, e.g., systemic lupus erythematosus and rheumatoid arthritis, but we found no sex difference in prevalence among acute pericarditis patients. Systemic autoimmune diseases are however a diagnostic challenge and autoimmune processes begin earlier than classical clinical symptoms are diagnosed.

Few studies have reported on epidemiology of pericarditis. Pericarditis is found in 4.4% of emergency room chest-pain patients and in 1.7% of patients with ST-segment elevation of whom myocardial infarction is ruled out. We found acute pericarditis to be a significant cause of cardiovascular admissions among young adults, but with increasing general morbidity the proportion deceased logarithmically with aging. Pericarditis was a more likely cause of admission to men at younger age-groups, but to women at ages of 46-75. Overall, pericarditis caused 0.2% of hospital admissions, which compares to previous estimate of acute pericarditis causing 0.1% of all hospital admissions. Swedish registry study found incidence rate of 18.0 per 100,000 for pericarditis in general population while clinical study conducted in Italian
urban metropoly area reported incidence rate of 27.7 per 100,000\textsuperscript{11}. In retired US military personnel, the incidence rate of pericarditis is 7.4 / 100,000\textsuperscript{32}. We found an incidence rate of 3.3 per 100,000, reflecting the fact that we included only patients with acute pericarditis admitted to hospital and excluded pericardiotomy and myocardial infarction caused disease. Since overdiagnosis of pericarditis is common\textsuperscript{14}, we maximized the accuracy of real-life diagnosis by including patients that had been examined and diagnosed at the hospital ward. This, in addition to the fact that our data collection did not cover all of the smallest regional hospitals that treat cardiac patients, may result in underestimation of the absolute incidence rate of acute pericarditis.

Presentation of pericarditis varies from chest pain to classical symptoms of cardiac tamponade. Prodromal syndrome of fever, myalgia, and malaise is common\textsuperscript{33}. Main findings include ST-level changes in ECG, elevation of circulating inflammatory markers, friction rub in cardiac auscultation, fever, and pericardial effusion in echocardiography\textsuperscript{2,33,34}. In clinical practice, and in the current study, diagnosis is based on combination of these findings, exclusion of acute coronary syndromes when appropriate, and clinical judgment. Diagnosis of even life-threatening pericarditis is however a challenging task as demonstrated by study on unrecognized causes of death in intensive care unit\textsuperscript{35}.

This study has some limitations. Major limitation is the retrospective nature of observational registry data. Thus, diagnoses were made by treating physicians, which may have affected the included patient population and accuracy of co-morbidity data. In addition, as we included only hospitalized patients our results may underrepresent patients with low-risk features that may be treated without admissions\textsuperscript{14}. Although we report on potential etiological co-morbidities, the nature of our data does not allow describing on detailed etiological studies. Also,
since prevalence of tuberculosis in Northern Europe is very low, our results may not be applicable world-wide.

Prognosis of acute pericarditis is usually good. Although mortality in idiopathic / viral pericarditis is low, purulent pericarditis is always fatal if untreated and carries a mortality of c.a. 40% even when treated\textsuperscript{13,36}. Purulent pericarditis is commonly a complication of intra-thoracic infection or a consequence of haematological bacterial spread\textsuperscript{13}. Accordingly, we found pneumonia and septicaemia to be strong predictors of in-hospital mortality. Female sex has been associated with complications in acute pericarditis\textsuperscript{14}. We found female sex to be associated with mortality in univariate analysis, but not in multivariate analysis. Increasing age was however an independent predictor of death.

In conclusion, men have a two-fold incidence rate of acute pericarditis compared to women with highest difference among young adults. Increasing age and severe co-infection predict in-hospital mortality in acute pericarditis, but sex does not appear to be an independent risk factor for death.

**Funding Sources:** This study was funded by the Clinical Research Foundation of Turku University Hospital.

**Conflict of Interest Disclosures:** None.

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22. Lyden DC and Huber SA. Aggravation of coxsackievirus, group B, type 3-induced myocarditis and increase in cellular immunity to myocyte antigens in pregnant Balb/c mice and animals treated with progesterone. *Cell Immunol.* 1984;87:462-472.


Table 1. Patient characteristics and sex-differences.

<table>
<thead>
<tr>
<th>Co-diagnosis</th>
<th>Total (n=1361)</th>
<th>Women (n=478)</th>
<th>Men (n=883)</th>
<th>RR (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous acute pericarditis*</td>
<td>21.9 (19.5-24.5)</td>
<td>28.2 (23.7-33.4)</td>
<td>18.5 (15.7-21.5)</td>
<td>1.53 (1.25-1.87)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6.54 (5.25-8.05)</td>
<td>8.58 (6.16-11.64)</td>
<td>5.44 (4.01-7.21)</td>
<td>1.58 (1.06-2.36)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.75 (2.79-4.93)</td>
<td>3.14 (1.75-5.18)</td>
<td>3.96 (2.76-5.51)</td>
<td>0.79 (0.44-1.43)</td>
<td>0.44</td>
</tr>
<tr>
<td>Heart failure or cardiomyopathy</td>
<td>3.09 (2.22-4.17)</td>
<td>3.56 (2.07-5.69)</td>
<td>2.83 (1.83-4.18)</td>
<td>1.26 (0.69-2.30)</td>
<td>0.46</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3.75 (2.79-4.93)</td>
<td>5.44 (3.55-7.97)</td>
<td>2.83 (1.83-4.18)</td>
<td>1.92 (1.12-3.29)</td>
<td>0.02</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>2.13 (1.43-3.06)</td>
<td>2.93 (1.60-4.91)</td>
<td>1.70 (0.95-2.80)</td>
<td>1.72 (0.84-3.54)</td>
<td>0.14</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1.54 (0.96-2.36)</td>
<td>2.09 (1.00-3.85)</td>
<td>1.25 (0.62-2.23)</td>
<td>1.68 (0.72-3.93)</td>
<td>0.23</td>
</tr>
<tr>
<td>Previous cardiac surgery</td>
<td>1.25 (0.73-2.00)</td>
<td>1.05 (0.34-2.44)</td>
<td>1.36 (0.70-2.37)</td>
<td>0.77 (0.27-2.17)</td>
<td>0.62</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>1.03 (0.56-1.73)</td>
<td>1.26 (0.46-2.73)</td>
<td>0.91 (0.39-1.79)</td>
<td>1.39 (0.48-3.97)</td>
<td>0.54</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>0.73 (0.35-1.35)</td>
<td>0.21 (0.01-1.17)</td>
<td>1.02 (0.47-1.93)</td>
<td>0.21 (0.03-1.62)</td>
<td>0.13</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>0.44 (0.16-0.96)</td>
<td>0.21 (0.01-1.17)</td>
<td>0.57 (0.18-1.32)</td>
<td>0.37 (0.04-3.15)</td>
<td>0.36</td>
</tr>
<tr>
<td>Pneumonia or septicemia</td>
<td>4.04 (3.04-5.26)</td>
<td>5.23 (3.38-7.72)</td>
<td>3.40 (2.29-4.85)</td>
<td>1.54 (0.92-2.59)</td>
<td>0.10</td>
</tr>
<tr>
<td>Rheumatic fever</td>
<td>1.91 (1.24-2.80)</td>
<td>2.72 (1.45-4.65)</td>
<td>1.47 (0.78-2.52)</td>
<td>1.85 (0.86-3.95)</td>
<td>0.11</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>0.59 (0.25-1.16)</td>
<td>1.05 (0.34-2.44)</td>
<td>0.34 (0.07-0.99)</td>
<td>3.08 (0.74-12.83)</td>
<td>0.12</td>
</tr>
<tr>
<td>Confirmed bacterial etiology†</td>
<td>1.69 (1.07-2.54)</td>
<td>2.93 (1.60-4.91)</td>
<td>1.02 (0.47-1.93)</td>
<td>2.87 (1.25-6.59)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* Previous admission caused by acute pericarditis during the study period. †Excluding mycobacterium.
Table 2. Predictors of in-hospital mortality. Results of both univariate and multivariate Cox-analysis. See methods for details.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate analysis</th>
<th></th>
<th>Multivariate analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95%CI)</td>
<td>p</td>
<td>HR (95%CI)</td>
<td>p</td>
</tr>
<tr>
<td>Female sex</td>
<td>3.66 (1.11 - 12.05)</td>
<td>0.03</td>
<td>1.23 (0.32 - 4.74)</td>
<td>0.76</td>
</tr>
<tr>
<td>Age / 10-year increase</td>
<td>3.61 (1.94 - 6.72)</td>
<td>&lt;0.0001</td>
<td>3.26 (1.78 - 5.95)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Septicemia or pneumonia</td>
<td>8.53 (2.27 - 32.06)</td>
<td>0.0008</td>
<td>13.46 (2.26 - 80.01)</td>
<td>0.003</td>
</tr>
<tr>
<td>Heart failure or cardiomyopathy</td>
<td>4.54 (0.88 - 23.15)</td>
<td>0.07</td>
<td>1.54 (0.22 - 10.61)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Figure Legends:

Figure 1. Frequency of acute pericarditis. Age-distribution of all pericarditis patients (A) and by sex (from total number of patients) (B). Error bars represent upper limits of 95% confidence intervals. *** p<0.0005

Figure 2. Cardiovascular admissions caused by acute pericarditis. Proportion of all cardiovascular admissions (A) and by sex (B). Error bars represent upper limits of 95% confidence intervals. *** p<0.0005, ** p<0.005, *p<0.05. Please note logarithmic y-axis.

Figure 3. Incidence rate of acute pericarditis in general population. Total (A) and sex-specific (B) incidence rates (per 100,000 person-years) by age. Error bars represent upper limits of 95% confidence intervals. *** p<0.0005, ** p<0.005.

Figure 4. Sex-associated incidence rate ratio of acute pericarditis by age in general population. Ratio is calculated as men vs. women and adjusted for study year. Error bars represent 95% confidence intervals.
Figure 1
Figure 2
Figure 3
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