Pericardial Disease

Clinical Profile and Influences on Outcomes in Patients Hospitalized for Acute Pericarditis

Ville Kytö, MD, PhD, MSocSc; Jussi Sipilä, MD; Päivi Rautava, MD, PhD

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

Methods and Results—We studied all patients aged ≥16 years admitted to the hospital because of acute pericarditis (postpericardiotomy and myocardial infarction associated pericarditis were excluded). Data were collected from a Finnish national registry that included data on all cardiovascular admissions (670409) during 9.5 years in 29 hospitals nationwide. During the study period, there were 1361 admissions for acute pericarditis. Pericarditis patients were more likely to be male (64.9% of patients) than female (35.1%), with an age-adjusted likelihood ratio of 1.85 (95% confidence interval [CI], 1.65–2.06; \( P < 0.0001 \)) for male sex. The standardized incidence rate of hospitalizations for acute pericarditis was 3.32 per 100,000 person-years. Men 16 to 65 years of age were at higher risk for pericarditis (relative risk, 2.02; 95% CI, 1.81–2.26; \( P < 0.0001 \)) than women in the general admitted population, with the highest risk difference among young adults. Acute pericarditis caused 0.20% (95% CI, 0.19%–0.22%) of all cardiovascular admissions. The proportion of pericarditis-caused admissions declined by an estimated 51% per 10-year increase in age. The in-hospital mortality rate for acute pericarditis was 1.1% (95% CI, 0.6%–1.8%). Mortality increased with age (hazard ratio, 3.26; 95% CI, 1.78–5.95 per 10-year increase in age; \( P = 0.0001 \)) and severe coinfection (pneumonia or septicemia; hazard ratio, 13.46; 95% 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 male. Increasing age and severe coinfection are associated with greater in-hospital mortality in hospitalized acute pericarditis patients. (Circulation. 2014;130:1601-1606.)

Key Words: aging ■ epidemiology ■ pericarditis ■ sex

Acute pericarditis is an inflammatory disease of the pericardium commonly triggered by viral infections in developed countries, whereas tuberculosis is the most common cause in developing countries.\(^1,2\) Experimental studies have found males to be at higher risk for acute viral heart disease,\(^3,4\) but clinical studies have reported conflicting results on sex distribution of acute pericarditis patients.\(^5,7\) It is commonly thought that there is no specific sex predisposition to pericarditis.\(^8\) Murine studies have also found the susceptibility for viral heart disease to be significantly age dependent, with the highest sensitivity at adolescence or young adulthood.\(^9\) The mean age of patients with acute pericarditis in clinical series has ranged from 41 to 60 years,\(^5,10–12\) but sex-associated differences in age have not been reported. The prognosis for viral/idiopathic pericarditis is good,\(^12\) but purulent and tuberculosis pericarditis have high mortality.\(^13\) Female sex has been associated with complications after acute pericarditis,\(^14\) 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.

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Methods

Study Patients and Data Collection

Patients aged ≥16 years admitted to the hospital because of acute pericarditis during a 9.5-year period were studied. Postpericardiotomy syndromes and postinfarction pericarditis were excluded. Data concerning all cardiovascular hospital admissions (n=670409) between May 1, 2000, and October 31, 2009, in 29 hospitals were retrospectively collected from the Finnish Hospital Discharge Register, a nationwide database maintained by the Finnish National Institute for Health and Welfare that contains hospital discharge data for all hospital admissions in Finland. Patients aged ≥16 years with acute pericarditis as the primary cause of admission (International Classification of Diseases, 10th Revision codes I01.0 and I30) were identified. Comorbidities and potential causes were detected from hospital discharge diagnoses. The study population was mainly white. Differences in incidence rate were estimated with age- and sex-matched population data from Finland from the study period (39523746 person-years) obtained from Statistics Finland.

Hospital organization in Finland consists of 3 main levels: Five university hospitals represent the highest level of hierarchy, followed by 16 central hospitals with coronary angiography laboratory and intensive care units, and smaller regional hospitals. Treatment of acute cardiovascular patients occurs mainly in university and central hospitals. The present study included data from all university and central hospitals and 8 large regional hospitals located across the

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From the Heart Center, (V.K.), Clinical Neurosciences, Neurology (J.S.), and Clinical Research Center (P.R.), Turku University Hospital, and PET Center (V.K.), Neurology (J.S.), and Public Health (P.R.), University of Turku, Turku, Finland.

Correspondence to Ville Kytö, MD, PhD, Heart Center, Turku University Hospital, POB 52, FI-20521 Turku, Finland. E-mail ville.kytö@utu.fi

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country. The study was conducted according to the National Institute for Health and Welfare permission (THL/1576/5.05.00/2010).

Statistical Analysis
Data were 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 use of modified Poisson regression with robust error variances. In-hospital mortality during admission for acute pericarditis was studied with a Cox regression model stratified by study year with an exact method for failure time ties. The 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 sex and age were considered as potential predictors of in-hospital mortality. Scale variables are presented as means±SD or median with interquartile range as appropriate. Total incidence rates were standardized with US 2000 standard population by a direct method. Categorical variables are presented as counts, percentages, or relative risks with 95% confidence intervals (CIs) as appropriate. CIs were calculated by Poisson distribution. P values <0.05 were considered statistically significant. The SAS system version 9.3 (SAS Institute Inc, Cary, NC) was used for statistical analyses.

Results
Frequency
The study period included 1361 hospital admissions with acute pericarditis as the primary diagnosis. Pericarditis patients were more likely to be male (64.9% of patients; 95% CI, 60.7%–69.3%) than female (35.1%; 95% CI, 32.0%–38.4%), with an age-adjusted likelihood ratio of 1.85 (95% CI, 60.7%–69.3%) than female (35.1%; 95% CI, 32.0%–38.4%), with an age-adjusted likelihood ratio of 1.85 (95% CI, 60.7%–69.3%) than female (35.1%; 95% CI, 32.0%–38.4%), with an age-adjusted likelihood ratio of 1.85 (95% CI, 60.7%–69.3%) than female (35.1%; 95% CI, 32.0%–38.4%).

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

Incidence Rate
The overall incidence rate of acute pericarditis was similar in the population aged 16 to 49 years but increased in the older population (Figure 3A). The incidence rate among men was 4.52 (95% CI, 4.22–4.83) per 100000 person-years, with a declining trend between 16 to 45 years followed by an increase in older population segments (Figure 3B). Among patients was most commonly 50 to 59 years old, with a median age of 52 years (range, 16–93 years; interquartile range, 35–63 years; Figure 1A). Male patients were significantly younger than female patients (mean 45.9±18.3 versus 56.2±17.3 years; P<0.0001). Age distribution varied significantly by sex, because the proportion of male patients was notably higher in patients aged 16 to 65 years (Figure 1B). Median duration of admission for acute pericarditis was 5 days (interquartile range, 3–8 days). Women were treated longer than men (7.5±6.9 versus 6.1±5.1 days; age-adjusted P<0.0001). Admission lengthened by an estimated 10% per 10-year increase in age (relative risk, 1.10; 95% CI, 1.09–1.12; P<0.0001).

Table 1. Patient Characteristics and Sex Differences

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Total (n=1361)</th>
<th>Women (n=478)</th>
<th>Men (n=883)</th>
<th>RR (95% CI)</th>
<th>P Value</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 mellitus</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 origin†</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>

CI indicates confidence interval; and RR, relative risk.
*Previous admission caused by acute pericarditis during the study period.
†Excluding mycobacterium.
women, the standardized incidence rate of acute pericarditis was 2.11 (95% CI, 1.91–2.32) per 100,000. Incidence was lowest among young women, followed by a gradual increase with age, with a peak in the population aged 65 to 74 years. Young men (16–35 years old) had the highest incidence of acute pericarditis compared with young women (incidence rate ratio 4.65; 95% CI, 3.52–6.14; \( P < 0.0001 \)). The sex difference in incidence rate was reduced with increasing age, and in the population aged \( \geq 66 \) years, the rate for acute pericarditis was similar in both sexes (Figure 4). The total standardized incidence rate of acute pericarditis was 3.32 (95% CI, 3.14–3.50) per 100,000 person-years. The incidence rate of acute pericarditis was 2.02 (95% CI, 1.81–2.26; \( P < 0.0001 \)) times higher among men than among women in the total population (Figure 4).

**In-Hospital Mortality**

The in-hospital mortality rate for acute pericarditis was 1.10% (95% CI, 0.61%–1.82%). Female sex was associated with increased mortality in univariate analysis but was not an independent predictor of death in the multivariate model (Table 2). Mortality increased significantly with age in both univariate and multivariate analysis (Table 2). The strongest predictor of in-hospital mortality in acute pericarditis was severe coinfection (pneumonia or septicemia). Comorbidities listed in Table 1 but not in Table 2 were not associated with in-hospital mortality in univariate analysis.

**Discussion**

This nationwide multihospital study describes the age- and sex-associated occurrence of acute pericarditis at the population level. Previous studies have reported conflicting results on the effect of sex on the risk of pericarditis.\(^5,7\) A recent randomized trial of 240 patients with acute pericarditis found 60% were male,\(^6\) whereas previous studies have reported higher male prominence\(^5\) but also female prominence.\(^7\) We found 65% of 1361 patients to be male, and the age-adjusted likelihood of an acute pericarditis patient being male was 1.9. Furthermore, the incidence rate of acute pericarditis in the general adult population was 2-fold among men compared with women.

The cause of acute pericarditis is idiopathic in the majority of cases but includes an immune-mediated process that is probably triggered by a viral infection in many cases.\(^16,17\) Reasons for 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 the
development of myocarditis, because exogenous testosterone increases viral replication and inflammation in the heart and gonadectomy inhibits cardiac inflammation in experimental viral myocarditis.\(^\text{19,20}\) Mechanisms of testosterone action include inhibition of anti-inflammatory cells,\(^\text{19}\) commitment to a Th1-type immune response,\(^\text{21}\) and increasing viral binding to myocytes.\(^\text{20}\) In accordance with a testosterone effect, we found the risk for pericarditis to be significantly higher among young men than among women. Although the occurrence of acute pericarditis in men declined with age after the teenage years, there was an increase in occurrence after 45 years of age. This may suggest that the interaction of testosterone with a susceptibility to pericarditis may not be linear or that an unrecognized cause of pericarditis varies by age.

Female sex hormones also affect the risk for cardiac inflammation. Progesterone aggravates cardiac inflammation,\(^\text{22}\) whereas estrogen has inhibitory effects by favoring the inhibition of proinflammatory T cells,\(^\text{23}\) stimulating inhibitory T cells,\(^\text{24}\) and favoring a Th2-type immune response.\(^\text{21}\) Accordingly, we found the incidence of pericarditis in women to be highest during the postmenopausal period, when estrogen levels are low. In addition to viral infections, systemic connective tissue diseases are potential causes of acute pericarditis.\(^\text{25}\) In line with previous studies,\(^\text{6,7}\) connective tissue disease was diagnosed in 2% of the patients in the present study. Women have a higher tendency to develop connective tissue diseases associated with pericarditis (eg, systemic lupus erythematosus and rheumatoid arthritis),\(^\text{26}\) but we found no sex difference in prevalence among acute pericarditis patients. Systemic autoimmune diseases are, however, a diagnostic challenge,\(^\text{27}\) and autoimmune processes begin earlier than classic clinical symptoms are diagnosed.\(^\text{28}\)

Few studies have reported on the epidemiology of pericarditis. Pericarditis is found in 4.4% of patients who present to an emergency department with chest pain\(^\text{29}\) and in 1.7% of patients with ST-segment elevation\(^\text{30}\) in whom myocardial infarction has been 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 for men in younger age groups but for women at ages 46 to 75 years. Overall, pericarditis caused 0.2% of hospital admissions, which is comparable to previous estimate of acute pericarditis causing 0.1% of all hospital admissions.\(^\text{1}\) A Swedish registry study found an incidence rate of 18.0 per 100,000 for pericarditis in the general population,\(^\text{31}\) whereas a clinical study conducted in an Italian

### Table 2. Predictors of In-Hospital Mortality

<table>
<thead>
<tr>
<th></th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Female sex</td>
<td>3.66 (1.11–12.05)</td>
<td>0.03</td>
</tr>
<tr>
<td>Age per 10-y increase</td>
<td>3.61 (1.94–6.72)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Septicemia or pneumonia</td>
<td>8.53 (2.27–32.06)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Heart failure or cardiomyopathy</td>
<td>4.54 (0.88–23.15)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

This Table represents the results of both univariate and multivariate Cox analysis. See Methods for details. CI indicates confidence interval; and HR, hazard ratio.

![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.](http://circ.ahajournals.org/)

![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.](http://circ.ahajournals.org/)
urban metropolitan area reported an incidence rate of 27.7 per 100,000. In retired US military personnel, the incidence rate of pericarditis is 7.4 per 100,000. We found an incidence rate of 3.3 per 100,000, which reflects the fact that we included only patients with acute pericarditis admitted to a hospital and excluded pericardiomyopathy- and myocardial infection–caused disease. Because overdiagnosis of pericarditis is common, we maximized the accuracy of real-life diagnosis by including patients who had been examined and diagnosed in 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 classic symptoms of cardiac tamponade. A prodromal syndrome of fever, myalgia, and malaise is common. Main findings include ST-level changes in the ECG, the elevation of circulating inflammatory markers, friction rub in cardiac auscultation, fever, and pericardial effusion in echocardiography. In clinical practice, and in the present study, diagnosis is based on clinical judgment, fever, and pericardial effusion in echocardiography. In the present study, diagnosis is based on a combination of these findings, the exclusion of acute coronary syndromes when appropriate, and clinical judgment. However, diagnosis of even life-threatening pericarditis is a challenging task, as demonstrated by study of the unrecognized causes of death in an intensive care unit.

The present study has some limitations. Its 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 the accuracy of comorbidity data. In addition, because we included only hospitalized patients, our results may underrepresent patients with low-risk features who may have been treated without being admitted to the hospital. Although we report on potential causative comorbidities, the nature of the present data does not allow a description of detailed etiologic studies. Also, because the prevalence of tuberculosis in northern Europe is very low, the present results may not be applicable worldwide.

The prognosis for 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 approximately 40% even when treated. Purulent pericarditis is commonly a complication of intra-thoracic infection or as a consequence of hematologic bacterial spread. Accordingly, we found pneumonia and septicemia to be strong predictors of in-hospital mortality. Female sex has been associated with complications in acute pericarditis. We found female sex to be associated with mortality in univariate analysis but not in multivariate analysis. Increasing age, however, was an independent predictor of death.

In conclusion, men have a 2-fold higher incidence rate of acute pericarditis than women, with the highest difference occurring among young adults. Increasing age and severe coinfection predict in-hospital mortality in acute pericarditis, but sex does not appear to be an independent risk factor for death.

Sources of Funding
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Disclosures
None.

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**CLINICAL PERSPECTIVE**

Acute pericarditis is an inflammatory disease of the pericardial sac commonly triggered by a viral infection. The epidemiology of acute pericarditis and the clinical profiles of patients with regard to sex are largely uncharacterized. We evaluated occurrence, clinical profiles, and in-hospital mortality of 1361 consecutive adult patients hospitalized for acute pericarditis during 9.5 years at the population level in Finland. Men were found to have a 2-fold higher incidence rate of acute pericarditis admissions compared with women. Acute pericarditis was a significant cause of cardiovascular admissions among young adults, but with increasing general morbidity, the proportion decreased logarithmically with aging. Increasing age and severe confection predicted in-hospital mortality for acute pericarditis in multivariate analysis. Our results describe the occurrence of acute pericarditis in a general adult population and emphasize the sex bias in the likelihood of acute pericarditis.