Incidence of three presentations of acute myocarditis in young men in military service

A 20-year experience

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Aims The incidence of myocarditis is uncertain as diagnostic criteria have been vague. We evaluated the incidence of myocarditis presenting in three well defined forms (mimicking myocardial infarction, presenting as dilated cardiomyopathy, and as a cause of sudden death) in young men in military service over a 20-year period.

Methods and Results The study population consisted of 672,672 Finnish men at a mean age of 20 years conscripted from 1977–1996. All those suspected of having myocardial disease were studied prospectively in the same institution. A clinical diagnosis of myocarditis mimicking myocardial infarction required ECG signs (ST-segment elevation followed by T-wave inversion) and a simultaneous detection of serum markers of acute myocardial injury (CK-MB and/or troponin T) in an infectious patient with chest pain. This form of myocarditis was diagnosed in 98 men, the incidence being 0·17 (95% CI 0·14–0·21) · 1000 man-years

Causative microbes were those commonly infecting the conscripts, but Coxsackievirus aetiology could be confirmed in only 4% of the cases. Nine patients presented with dilated cardiomyopathy of recent origin (incidence 0·02 · 1000 man-years

None had histopathological evidence of myocarditis. Myocarditis caused one of the 10 sudden unexpected deaths (incidence 0·002 · 1000 man-years

Conclusions The usual presentation of acute myocarditis in young men mimicks alterations evoked by myocardial infarction but not those of dilated cardiomyopathy.

Key Words: Myocarditis, dilated cardiomyopathy, sudden death, incidence, military medicine.

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Introduction

The incidence of acute myocarditis is uncertain. Earlier clinical studies based the diagnosis of myocarditis on equivocal electrocardiographic changes in connection with infectious diseases but without other evidence of myocardial involvement[1,2]. This caused an obvious over-diagnosis of possible myocarditis, because as many as one third of patients hospitalized for Mycoplasma pneumoniae or viral infections displayed such non-specific ECG changes[3]. More recent studies have used endomyocardial biopsy to diagnose myocarditis[4–6]. However, as these studies are from cardiac referral centres, the selection bias of the patients and the well known uncertainties in the biopsy diagnosis of myocarditis make incidence evaluation at the population level unreliable.

Acute myocarditis presents in many ways and distinct clinical forms of the disease have been established[7,8]. One presentation is acute or insidious heart failure without other obvious causes. This is the characteristic indication for endomyocardial biopsy in the search for myocarditis. However, when rigorous histological criteria are used, myocarditis is seldom diagnosed in patients with a clinical picture of dilated cardiomyopathy[6,9,10]. Another presentation of myocarditis more or less mimicks acute myocardial infarction[11–14]. In patients with this form, chest pain is the leading symptom, electrocardiography displays ST-segment elevations and markers of myocardial injury are found in the blood. These patients may be treated mistakenly with thrombolysis[15]. A third presentation of myocarditis is sudden unexpected death. Such unfortunate cases, for example among athletes, have generated great publicity[16,17].
We had the opportunity to study all cases of suspected acute myocarditis in a defined population of healthy young men in compulsory military service. Using the same strict clinical criteria throughout for the diagnosis of acute myocarditis, we were able to estimate its occurrence over a 20-year period in this population, which consisted of most young Finnish men. We also investigated whether myocarditis explained any of the sudden unexpected deaths in the study population.

**Subjects and methods**

Finnish army conscripts from 1977–1996 formed the study population. Eighty-five percent of all men in Finland (total population 5 million) are conscripted at a mean age of 20 years (range 17–29) and for 8–11 months duration. During the study period 672 672 conscripts served a total of 495 283 man-years.

When myocarditis was perceived as an important cause of sudden unexpected death in conscripts\[^{[18]}\], a special effort was made from 1977 to diagnose this condition among conscripts in Finnish Defence Forces. Emphasis was put on primary care military physicians to study ECGs even in cases of minor chest pain or other symptoms suggestive of possible heart involvement, and in particular in infectious patients. All cases of suspected heart disease were referred and studied in the same institution, the Central Military Hospital, and all patients in this series were studied by at least one of the two authors. Conscripts admitted to local civil hospitals with acute heart symptoms were also transferred to the Central Military Hospital for evaluation after their condition had stabilized.

The present study focuses on the incidence of the three well recognized forms of myocarditis: (1) acute myocarditis mimicking myocardial infarction, (2) myocarditis presenting as dilated cardiomyopathy of recent origin, and (3) myocarditis as a cause of sudden unexpected death.

Patients with myocarditis mimicking myocardial infarction characteristically presented with acute chest pain associated with an infectious disease. The diagnosis required electrocardiographic signs and the simultaneous detection of serum markers of myocardial injury (Fig. 1). Serial ECGs had initially to display ST-segment elevation in several leads, later replaced by T-wave inversions\[^{[19]}\]. Serum markers of myocardial injury were an elevated creatine kinase-MB level (activity above 5 \(U\cdot l^{-1}\) and 3% of total creatine kinase activity, or quantitatively above 7 \(\mu g\cdot l^{-1}\)) and/or a troponin T serum level of 0.2 \(\mu g\cdot l^{-1}\) or more (Boehringer Mannheim). If, in addition, pericardial involvement was detected by an auscultatory pericardial friction rub and/or an effusion on the echocardiogram the disease was registered as acute myopericarditis (perimyocarditis). Coronary artery disease, unlikely in such a young population, was excluded by an absence both of a history of effort angina and of ischaemic changes on the maximal exercise electrocardiogram soon after recovery. Acute myocardial infarction or coronary spasm were also ruled out by the absence of Q waves and by the distribution of ST-segment changes, which did not follow those of main coronary arteries\[^{[11]}\]. In acute myocarditis ST-segment elevations were always present in leads \(V_4\)–\(V_6\), while reciprocal ST-segment depressions were seen only in leads \(V_1\) and \(aVR\) (and exceptionally in leads \(V_2\), III, and \(aVF\)). Coronary angiograms obtained from only two patients, were found to be normal. An endomyocardial biopsy was not clinically indicated and was therefore not performed in these patients.

Patients with a clinical picture of dilated cardiomyopathy of recent origin were included, if their infection fraction was 45% or less, and if an echocardiogram demonstrated a left ventricular end-diastolic diameter of more than 27 mm \(m^{-2}\). To diagnose possible myocarditis, endomyocardial biopsies were obtained from the right ventricular septal wall and Dallas criteria were used for the histological evaluation\[^{[20]}\].

We calculated the annual incidence and mean annual incidence of acute myocarditis and their 95% confidence intervals (CI) during the study period.

**Results**

A total of 98 men fulfilled our clinical criteria of acute myocarditis mimicking myocardial infarction during the 20-year period. Nineteen (19%) of them also had signs of pericardial involvement. Figure 2 shows that the annual incidence of the disease over the study period changed insignificantly from year to year, when cases induced by smallpox vaccination were excluded. The minimum incidence was 0.08 (95% CI 0–0.18). 1000 man-years\(^{-1}\) and the maximum incidence 0.25 (95% CI 0.03 to 0.47) . 1000 man-years\(^{-1}\). The mean annual incidence of
acute myocarditis was 0.17 (95% CI 0.14 to 0.21). 1000 man-years (vaccinia myocarditis cases excluded).

The prognosis was good in this group: there were no deaths among the conscripts admitted to hospital for myocarditis during the 20-year study period. None of the patients progressed to dilated cardiomyopathy or frank heart failure during a 3–24 month follow-up, although some patients had a transiently lowered ejection fraction (40%–50%) on admission. In one patient with the Epstein–Barr virus an akinetic scar developed in the left ventricular inferior wall. Troponin T measurements were available in the late part of the patient series (n=30) and its mean peak serum concentration was 2.1 ng . ml⁻¹ (range 0.2–7.5 ng . ml⁻¹) (Fig. 1). Serum enzyme and echocardiography findings in the early part of the series has been presented earlier[11,19,22].

Figure 1  A clinical diagnosis of acute myocarditis required both new ECG signs of myocardial injury (ST-segment elevation followed by T-wave inversion) and the simultaneous detection of a serum marker of myocardial injury (CK-MB or troponin T). Representative findings in a patient with Mycoplasma pneumoniae infection are shown.

A specific aetiology was identified in 55% of the cases; Table 1. It is of note that the most common associated infection was febrile exudative pharyngotonsillitis (due to adenovirus, group A streptococcus, or Epstein–Barr virus). In streptococcal disease, characteristically myocarditis emerged during the third day of the disease and one day after starting the antibiotic therapy[23]. In 44% of cases in whom the associated infection usually resembled that of viral upper respiratory tract infection, the aetiology could not be established. In 1977–1979, when conscripts were still vaccinated against smallpox, vacciniavirus was the commonest cause of myocarditis.
Otherwise, the causative microbes were those commonly infecting the conscripts. Coxsackievirus aetiology could be confirmed in only 4%.

During the same study period we diagnosed nine cases of acute dilated cardiomyopathy. None had histopathological features of myocarditis, clinical signs of acute myocardial injury, ST-segment elevation or myocardial enzyme release. The incidence of dilated cardiomyopathy was 0·02 (95% CI 0·006 to 0·03). 1000 man-years$^{-1}$.

Over the study period, 21 conscripts died non-violently, 10 (48%) suddenly and unexpectedly (incidence 0·02. 1000 man-years$^{-1}$). In one (10%) of them acute myocarditis was diagnosed histopathologically (incidence 0·002. 1000 man-years$^{-1}$) (Table 2). This deceased soldier had had mild symptoms of respiratory tract infection before his unexpected death.

### Discussion

**Incidence of acute myocarditis**

During a 20-year period and using strict clinical criteria we observed 98 cases of acute myocarditis among a large population of healthy young men and comprising half a million man-years. The incidence of myocarditis was 0·17. 1000 man-years$^{-1}$. These patients characteristically presented with the triad of acute chest pain, ST-segment elevation on the ECG and markers of myocardial injury in the blood, which thus mimicked acute myocardial infarction. Over the same period among the same population we found no case of myocarditis presenting as heart failure of recent onset. One man died suddenly and unexpectedly because of myocarditis.
The incidence and prevalence of possible sub-clinical myocarditis have been based on non-specific ECG changes in many clinical series, as reviewed by Woodruff[9], and more recently by Friman et al.[2]. In contrast, we evaluated the incidence of unequivocal clinical myocarditis. Our study population represented the majority of young Finnish men in a specific age range. Another strength of our study is that the cases were prospectively collected over a long period. However, because our subjects were in military service, where respiratory tract infections are especially common, the observed incidence figure may be higher than among civilians. Age and gender differences may also affect the incidence at the general population level. Thus, myocarditis presenting as myocardial infarction is very uncommon but not unknown in children[24], while women seem to be less susceptible than men[1]. Soldiers are exposed to vigorous exercise, which may theoretically increase the susceptibility to myocarditis; exercise has been shown to markedly increase myocardial virus replication in experimental murine virus infection[25]. The incidence of dilated cardiomyopathy in the present study agrees well with earlier studies: the annual clinical incidence was 0·025 / 1000 persons\(^{-1}\) in Trieste[26] and 0·03 / 1000 persons\(^{-1}\) in Malmö, Sweden[27].

The present findings say nothing about the incidence of subclinical silent myocarditis, whether acute or chronic. Such entities are controversial but reportedly explain many cases of sudden unexpected death[17,28,29], as fatal arrhythmia may be the first and only symptom of the disease. In our study population, myocarditis caused one of the ten sudden unexpected deaths, an incidence comparable to many earlier studies[18,28,29]. Myocarditis was the most common underlying cause of sudden unexpected exercise-related death among US Air Force recruits[30]. A clinically clear-cut acute myocarditis with high myocardial enzyme levels and unequivocal ECG changes can also present without subjective heart symptoms[31]. Therefore we and others[17] have stressed the importance of avoiding strenuous exercise during acute infections irrespective of possible cardiac symptoms.

It is of note that we could confirm a Coxsackievirus aetiology in only about 4% of the cases, although commonly enteroviruses have been considered as the most important aetiology of myocarditis. There were no significant enterovirus epidemics among conscripts during the study period. Further, the sensitivity of our serological methods may have been inadequate leading to under-diagnosis of Coxsackievirus infections.

**Characteristic presentation of clinical acute myocarditis**

Our study shows that the usual presentation of definite acute myocarditis in young men mimicks myocardial infarction, but not dilated cardiomyopathy. It may occur similarly in older people. Although Dec and co-workers[14] consider this presentation of myocarditis uncommon, their numbers testify differently. They biopsied 1149 non-transplant patients, 95% with unexplained dilated cardiomyopathy, and diagnosed 50 (4%) cases of myocarditis. However, 34 of the biopsied patients presented as myocardial infarction with normal coronary arteries and 11 (32%) of these had histopathological myocarditis. Thus 22% of their biopsy-proven myocarditis patients presented with a picture of myocardial infarction, although nearly all biopsies were targeted at dilated cardiomyopathy patients. Differentiating acute myocarditis from acute myocardial infarction may be clinically difficult, especially in older patients. The young age of our subjects almost excluded the possibility of myocardial infarction. During the study period we did not clinically diagnose any cases of acute myocardial infarction among conscripts, although two of the sudden unexpected deaths in the late 1970s were associated with coronary artery disease (Table 2).

There is further evidence that definite myocarditis as a cause of heart failure of recent origin is uncommon. In a large international multicentre study, the Myocarditis Treatment Trial[6,31] referral centres collected cases for a 5-year period. Altogether, 2233 patients with suspected myocarditis underwent endomyocardial biopsy, of whom only 111 (5%) could be enrolled in the treatment trial. Moreover, only 51% of these fulfilled the rigid histopathological diagnosis of myocarditis approved by a specialist panel[32]. A biopsy diagnosis of myocarditis in unexplained heart failure is problematic as discussed in detail by Lie[10]. If one accepts that myocarditis can be found histopathologically in 4% of dilated cardiomyopathies[9,14] and that the annual incidence of this form of myocarditis would be no more than about 0·001 / 1000 person-years, this figure is even smaller than the incidence of myocarditis-induced sudden unexpected deaths and fits with the fact that we found no such cases in a population followed for half a million person-years.

However, an overlapping of the different presentations of myocarditis is evident. Although not displaying frank heart failure, some of our patients had a transiently low ejection fraction. Similarly, the ejection fraction improved in the Myocarditis Treatment Trial patients during follow-up, irrespective of possible immunosuppressive treatment. In addition, many patients in that study had elevated troponin I or CK-MB serum levels if they were studied during the first week of the disease[33]. It was not reported whether these patients had chest pain or whether the myocardial release of injury markers was associated with the electrocardiographic signs of myocardial injury. In a recent study of Lauer et al.[34] an elevated troponin T level was detected in all patients with histopathologically acute myocarditis. This was also the case in many patients with a clinical suspicion of myocarditis, although histopathological Dallas criteria for diagnosis were not fulfilled. In our experience, myocardial enzyme release is uncommon without simultaneous ST-segment elevation in suspected
acute myocarditis\cite{19}. Further, myocardial injury markers are usually detectable only for a short time, as in myocardial infarction (Fig. 1), and are easily missed if not examined in the very acute stage of the disease. As myocyte necrosis is an essential histopathological feature of acute myocarditis, it seems logical that clinical signs of myocardial injury should also be evident. Thus, it is understandable that in a patient who presents with dilated cardiomyopathy but without clinical signs of myocardial injury, acute ongoing myocarditis will seldom be found histologically.

In summary, we evaluated prospectively the incidence of three different clinical presentations of acute myocarditis in young men over a 20-year period and for half a million man-years. One case presented as sudden unexpected death and 98 cases mimicked acute myocardial infarction. Myocarditis could not be diagnosed in any of the nine cases presenting as dilated cardiomyopathy of recent origin.

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