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The incidence and epidemiology of myocarditis

See page 1020 for the article to which this Editorial refers

Inflammatory cardiomyopathy, i.e. myocarditis in association with cardiac dysfunction[1], in adolescents and adults may have disparate clinical presentations, including (a) acute onset of symptoms mimicking those of myocardial infarction[2–3]; (b) cardiac insufficiency of acute or insidious onset that may develop into dilated cardiomyopathy[4]; and (c) sudden unexpected cardiac death[5]. Arrhythmia may be a feature in (a) and (b) and is the usual cause of (c). The severity of symptoms is highly variable and subclinical myocarditis is common.

Although several non-infectious causes are known, the majority of myocarditis instances are considered to have an infectious origin[6–7]. There is solid evidence to suggest that the microbial pathogenesis may be complex[8]. One very recent contribution to this intriguing field of research is the finding of a link between *Chlamydia* spp. and heart disease through antigenic mimicry[9]. It is commonly recognised that myocarditis may develop as a complication of an infection elsewhere, most often an upper respiratory tract or gastrointestinal infection, where general symptoms such as fever and myalgia predominate for some microorganisms. In such cases, several days or even weeks may elapse until cardiac involvement occurs, which may or may not be linked to clinical symptoms[6–7]. One study encompassing 12 747 unselected routine autopsies performed over a 10-year period in a defined geographical area in Sweden showed a frequency of histopathological myocarditis fulfilling the Dallas criteria of 1·06%[10]. However, the true incidence of myocarditis, whether clinical or subclinical, across various age segments of the general population remains unknown.

To carry out prospective clinical studies to establish the incidence and epidemiology of myocarditis associated with cardiac symptoms and of its various aetiologies in a defined population is a formidable undertaking for sundry reasons. For instance, the relative infrequency of the disease requires a large study population and, in acute myocarditis, the patient will have to be examined during the early course of the disease so that a reasonably certain clinical diagnosis is feasible[11–12]. Furthermore, to establish a microbial aetiology, an early blood sample is required for comparison with subsequently obtained samples in serological tests. This is because 'paired sera' is mandatory for organisms for which specific IgM methods are not available.

The article by Karjalainen and Heikkilä in this issue[13] represents a solid contribution to the field of myocarditis epidemiology. One merit of this publication is that it is an extremely large-scale study that included 672 672 Finnish military conscripts with a mean age of 20 years. The sample is representative of healthy, young Finnish men, of whom 85% eventually serve in the Armed Forces. A second merit is that, at the beginning of the study, special effort within the Finnish Armed Forces health care system was

initiated and reportedly sustained throughout the study period. The primary objective of this care system, as defined by the authors, was to create a high level of vigilance among military doctors at different regiments throughout the country in order to detect acute cardiac disease in the recruits seeking their medical advice. All cases with suspected heart disease were referred to the Central Military Hospital in Helsinki for evaluation by Karjalainen and Heikkilä and to establish a final diagnosis. To make a diagnosis of myocarditis in patients with chest symptoms, changes in serial ECGs in combination with the detection of markers of myocardial injury in serum were required; in patients presenting dilated cardiomyopathy of recent onset, an endomyocardial biopsy was carried out, and in conscripts succumbing to sudden unexpected death, an autopsy was performed. The reported numbers would ideally carry a high level of validity as to the true incidence of myocarditis, in which symptoms were severe enough to prompt the draftee to attend a doctor and typical enough to make the doctor suspect possible heart involvement. However, it would seem reasonable that the host of military doctors involved during the extended study period of 20 years would make variability inevitable with respect to the criteria used in referring patients to the Central Military Hospital. The authors do not report the number of referred patients over the years in cases in which myocarditis could not be confirmed.

'Minor (or major) chest pain or other symptoms suggesting possible heart involvement'[13] were required for inclusion. It is noteworthy that in a previous study using ECG screening of conscripts suffering various infectious diseases the same authors found subclinical myocarditis to be common, especially in conscripts suffering from adenovirus and influenza A infection[14]. Consequently, subclinical myocarditis cases are not included in the current study.

Of the 99 diagnosed myocarditis cases, all but one suffered acute onset symptoms mimicking those in myocardial infarction, establishing that that particular clinical presentation was almost exclusive in myocarditis in this age group. Cardiac symptoms occurred in connection with an acute respiratory infection in most of the cases and, in 10 cases, myocarditis emerged as a complication of inoculation of vaccinia virus before that practice was discontinued. Vaccinia inoculation is a recognised cause of myocarditis[15]. In only two cases could it be shown that myocarditis was connected with non-infectious causes. Simultaneous pericarditis, as diagnosed by auscultation of a friction rub or by demonstration of a pericardial effusion on echocardiography, appeared in 19% of the cases.

The mean incidence of acute myocarditis was $0{\cdot}17 \cdot 1000$ man-years^{-1} (vaccinia myocarditis cases excluded) with no significant yearly variation. As speculated by the authors, the myocarditis incidence might be higher among military recruits than among non-enlisted men of the same age. This is because under military conditions, in comparison to civilian life, there is a more intense transmission of respiratory pathogens. Moreover, there is exposure to heavy exercise, which is a potentially aggravating factor in myocarditis. Although this notion is theoretically in line with the fact that respiratory pathogens, such as the adenoviruses, *Mycoplasma pneumoniae*, beta-haemolytic streptococci of group A, Epstein–Barr virus and influenza A, were the predominating microbial aetiologies among those cases in which a specific aetiology could be confirmed, under-diagnosis of enteroviral infection may have been a more important determinant of the low percentage of established enteroviral myocarditis of 5% in the present study (coxsackievirus in 4%).

This low percentage of enteroviral myocarditis is one of the most conspicuous features of the present study since in most myocarditis studies the enteroviruses are the predominant aetiologies (except for studies during epidemics of other infectious diseases)[6,7,16–20]. The primary focus of this study was not on microbial diagnostics, and so several routine diagnostic methods were employed during the course of the study. Perhaps for this reason the authors do not state their sensitivity and specificity values. Because of the large number of existent enterovirus strains, an optimal sensitivity of such tests is often hard to achieve. In 44% of cases in the Karjalainen and Heikkilä study[13] no aetiology could be confirmed.

The authors found nine patients presenting with dilated cardiomyopathy of recent onset, corresponding to an incidence of $0{\cdot}02 \cdot 1000$ man-years^{-1}. This is an incidence rate similar to that in previous European studies: Torp recorded $0{\cdot}03 \cdot 1000$ persons^{-1} in Sweden[21] and Rakar *et al.* registered $0{\cdot}025 \cdot 1000$ persons^{-1} in Italy[22]. In not one of the present patients could myocarditis be diagnosed histologically by endomyocardial biopsy. Citing the Myocarditis Treatment Trial, in which definite myocarditis was found in only a low percentage of the enrolled patients[23,24], the authors conclude that definite myocarditis as a cause of heart failure of recent origin is uncommon. A negative biopsy, however, does not rule out a prior inflammatory process that has fallen into a state of quiet. The limited sensitivity of the endomyocardial biopsy technique for diagnosing myocarditis histologically is well recognised, of which sampling error is one factor.

Interestingly, in a recent study it was found that immunohistological analysis of the biopsies substantially increased the sensitivity. In that way, evidence of myocarditis was found in a majority of patients with clinically suspected myocarditis, whereas histological analysis established a myocarditis diagnosis in only a small number of the patients[25]. In addition, subgroups of patients may represent situations quite different from that of unselected patients. One such example is HIV-infected patients. Barbaro *et al.*[26] recently found histological signs of myocarditis in 83% of cases with an echocardiographic diagnosis of dilated cardiomyopathy. Nucleic acid of HIV, as well as of coxsackievirus, was found in the myocytes in several of these biopsies, and of cytomegalovirus and Epstein–Barr virus in a few. Furthermore, even several myocarditis-negative biopsies were virus-positive. In another cardiomyopathy study it could be shown that patients with enterovirus-positive biopsies had a more unfavourable prognosis than patients in the biopsies of whom no enterovirus-RNA could be detected[27].

There was one occurrence of myocarditis among 10 cases of sudden unexpected death in Karjalainen and Heikkilä's study (sudden unexpected death incidence $0{\cdot}02 \,.\, 1000$ man-years^{-1}). Moreover, in this age group, sudden unexpected death typically (80%) had a cardiac cause. This sudden unexpected cardiac death incidence level, together with the low myocarditis incidence in sudden unexpected cardiac death, confirms the results of several previous studies of sudden unexpected cardiac death in the young[5,28]. An intriguing observation is that no case of hypertrophic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy, reported as the single most frequent causes of sudden unexpected cardiac death in the U.S.[28] and Italy[29], respectively, was found in the present study.

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Coronary surgery, ethnic origin, and value in health care

See page 1094 for the article to which this Editorial refers

Selecting patients for costly therapy and providing adequate access can be a major sociological problem within medicine today. Such challenges, highlighted in the report by Goldsmith *et al.*[1] in this issue, concern the in-hospital outcome of coronary surgery in patients of Indo-Asian and white Caucasian background in the United Kingdom. The authors compared results of 194 pairs of patients undergoing surgery between November 1994 and January 1997. The patients were matched for age, sex, and date of procedure in the two groups. They noted more non-elective surgery in the Indo-Asian group, as well as a trend toward higher hospital mortality — 6·7% in Indo-Asians vs 2·6% in white Caucasians. The results of this study were confined to the in-hospital period, raising questions, as the authors note, about long-term outcome, including relief of angina pectoris, other measures of quality of life, survival, and freedom from non-fatal events.

A somewhat parallel concern regards the outcome of coronary surgery in African-Americans vs Caucasians in the United States. This comparison was studied by Gray *et al.*, who noted a similar in-hospital mortality in African-Americans and Caucasians but a higher long-term morality in the former due to more co-morbidity[2].

The results of this study probably cannot be adequately used to judge whether there is a different response to coronary surgery in Indo-Asians, which would necessitate using different criteria for patient selection. When several high-risk subgroups were examined, the differences between the Caucasians and the Asians could in part, be accounted for. Thus, in non-elective cases, the mortality was 9% in Asians and 7% in Caucasians. When the patients were stratified by the Parsonnet score[3], there was considerable overlap in mortality between the ethnic groups in both the low-and high-risk patients. Thus, pending further information to the contrary, patient selection in Indo-Asians can quite reasonably continue to be guided by clinical and angiographic suitability, informed by clinical trial results that have compared coronary surgery to medicine, coronary surgery to angioplasty, and outcome data from major single institutions and cooperative registries.

A major and somewhat troubling question raised by this study concerns patient access to care. While a high rate of emergency care was noted in both groups, 42·8% of the Asian group was considered to have had coronary surgery on a non-elective basis. That surgical outcome is generally worse if performed urgently as an emergency[3,4] raises troubling questions about the ability to provide adequate access if the non-elective rate reaches close to 50% and is higher in one population than another.

Patient access to care is a complicated issue that goes beyond simply having facilities available. It includes proximity of facilities, transportation, cultural barriers, and patient and professional education, just to name a few. The general notion in most industrialized countries is that access to care should be similar for different racial, ethnic and economic groups for critical procedures such as coronary surgery. This study suggests that this may not be so. While there is clearly a societal demand for egalitarian provision of critical services, that does not mean it is a reality. In the United States, Carlisle *et al.*[5] have shown that there were higher rates of revascularization in areas of higher socio-economic status, at least suggesting problems in patient access.

Another problem raised by the high frequency of non-elective care, is a lack of standards. The reader may wonder if the high level of non-elective care would be similarly judged in his/her own institution. There is a very clear need to provide standard definitions to permit more meaningful communication. In this regard, professional societies, especially the European Society of Cardiology, the Society of Thoracic Surgeons, and the American College of