Sudden Cardiac Death in Swedish Orienteers

BY

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ABSTRACT


An accumulation of sudden unexpected cardiac deaths (SUCD) occurred in young Swedish orienteers, most of whom were elite athletes. From 1979 to 1992 the incidence in 18 to 34 year old male elite orienteers ranked on the national level the same year as death was calculated to 30 (per 100,000), which represents a 20 to 40 fold increase from the expected rate. From 1989 to 1992, the incidence was 50. There were, however, no indications on any similar clusters of SUCD in other sports. A special program to alter behavior in orienteers was implemented in 1992-1993, after which there have been no further cases of SUCD in orienteers below 35 years of age. A histopathological re-evaluation of 16 cases of SUCD revealed myocarditis in 75% of these cases. In parallel, four of those cases also had changes mimicking arrhythmogenic right ventricular cardiomyopathy (ARVC). The combination of an increased incidence and myocarditis suggested that infection may be a pathogenetic factor. A broad search for different microorganisms in archival sera from five cases and tissues from the autopsies in two of those cases revealed the only common finding that all had antibodies to *Chlamydia pneumoniae*. DNA from *C. pneumoniae* was detected in the lung and heart in one of two cases. The intimate contact with nature of orienteers suggested possible zoonotic/vectorborne pathogens. Bartonella is such a pathogen and known to cross-react with *C. pneumoniae*. The use of PCR to test for DNA from the *gltA* gene of *Bartonella* in the two formerly mentioned cases of SUCD, and in three additional cases, gave positive bands from the hearts in four cases and the lung in a fifth case. The PCR products were sequenced and found to be identical to *B. henselae* in three cases and almost identical to *B. quintana* in the remaining two cases. Four of the five cases had antibodies to *Bartonella* when using a micro immunofluorescence test with the antigens *B. henselae*, *B. quintana*, and *B. elizabethae*. The total prevalence of antibodies to *Bartonella* was 31% in 1,136 elite orienteers vs. 6.8% in 322 healthy blood donors (p<0.001), suggesting widespread exposure in the elite. It is hypothesized that subacute or reactivated *Bartonella* infection has a pathogenetic role in SUCD in orienteers, and may be involved in the development of ARVC-like diseases.

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This thesis is based on the following articles, which are referred to in the text by their Roman numerals:


INTRODUCTION AND BACKGROUND

Sudden unexpected death (SUD)
SUD can be defined as unexpected death occurring as a result of natural causes in which loss of all functions occurred instantaneously or within 6 hours of the onset of symptoms or collapse and of a previously witnessed usual state of normal health (41).

Sudden infant death plays a major role for mortality in the first year of life. The incidence is 50-250 per 100,000 born alive in the Nordic countries. Several risk factors have been identified, including sleeping in a prone position or parental smoking. Information campaigns to the public about the risk factors have led to a significant decrease in the incidence in the Nordic countries (61). Thus, a fatal disease can be confronted even though the causes remain obscure.

After the first year, the incidence of sudden unexpected cardiac death (SUCD) remains at a low rate at 0.4 - 2.4 per 100,000 person years until 30-35 years of age (50, 112, 113, 134, 135, 137, 143, 179) after which ischemic heart disease starts to take a heavier toll causing a significant rise in the incidence rate and eventually compromises 90% of SUCD cases. The highest incidence of 2.4 was noted in all male personnel below 35 years of age in the British Army from 1978 to 1982 and also includes cases with no further data available (113) The male to female ratio in SUD shows a clear preponderance for men (179).

In the south of Sweden the incidence of SUCD in persons in the age range 1 to 20 years, with previous known or unknown cardiac disease, was measured at 0.4 per 100,000 person years between 1974 and 1979. Infectious diseases such as sepsis, pneumonia, epiglottitis or peritonitis caused the majority of noncardiac SUD cases. In addition, there were asthma, epilepsy, and Addison's disease. The overall rate of sudden death from natural causes with symptoms starting within 10 days was 1.1 per 100,000 (129). In Denmark, the incidence of SUD in 15 to 30 year-old persons was 1 per 100,000 during a 10-year period (84). In Sweden, there has been no national surveillance of SUD in sports or otherwise except for information that can be extracted from the annual report of Causes of Death from the National Central Bureau of Statistics.

Diagnoses of sudden unexpected cardiac death (SUCD) victims
In clinical routine, there are usually no problems in attributing a death to cardiac causes. However, the different forms of cardiomyopathies reflect syndromes that, by definition, are of unknown etiology (3) and where the appearance in histology may be hard to interpret even among specialists of heart pathology. This may partly account for the different percentages reported for such disorders as hypertrophic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy. The World Health Organization recently proposed a somewhat modified definition of the cardiomyopathies (2) because increased understanding of etiology and pathogenesis has made the difference between cardiomyopathy and specific heart muscle disease indistinct. The classification is based on the dominant pathophysiology or, if possible, by etiological/pathogenetic factors.

Hypertrophic cardiomyopathy (HCM) is characterized by disproportionate hypertrophy of the left ventricle, which typically involves the septum more than the free wall but sometimes is concentric (3). This occurs in the absence of a recognizable stimulus to hypertrophy. Typical morphological changes include myocyte hypertrophy and disarray.
surrounding areas of increased loose connective tissue (2). In HCM a significant subaortic stenosis may be precipitated by physical exertion and result in sudden death. Outflow obstruction may become acutely severe as blood flows at an increased velocity through the narrow outflow region and will display a fluid dynamic phenomenon known as the Venturi effect. This can be compared with the sounding of a clarinet. Gentle blowing into the slit between flexible reed and stem meets little resistance and makes no sound. More forceful blowing meets with higher resistance as the Venturi/occlusive cycle comes into play and becomes coupled with oscillations in the air column of the sounding instrument. For HCM patients this may be recorded by Doppler technique as an outflow gradient within normal range at rest but during stress rising to >100 mmHg (89). Sports-related SUCD was significantly elevated for persons dying from HCM implicating exercise to precipitate SUCD (30).

In living persons, HCM is usually considered when the maximal diastolic left ventricular wall thickness is measured to be 15 mm or more by echocardiography. Highly trained athletes with physiologic hypertrophy of the heart may show a wall thickness ranging up to 16 mm, which exceeds the normal upper limit of 12 mm (141). Because of such a broad range as the basis for comparison, this clearly leaves an individual athlete in an inconclusive diagnostic "gray zone." When examining victims of SUCD, the measurements of the ventricular wall from the autopsy cannot be transformed into the reference system derived from echocardiographic measurements without caution, especially if measurements are regarded in retrospect and were not carried out systematically and in a standardized fashion. It has also been proposed that in previously normal individuals HCM may be induced by exercise itself (30).

In a proportion of HCM cases, estimated to be over 15% and that are familial, cardiac troponin T gene mutations are apparently of great pathogenetic importance and implicate a poor prognosis. Disease penetrance in subjects >16 years old was 80% according to both ECG and echocardiographic abnormalities. The cumulative mortality for males was 64% at the age of 28 years (131).

The prevalence of HCM has been estimated to 20-200 per 100,000 and the incidence to 2.5 per 100,000 person years (37, 116). Most published reports regarding the role of HCM in SUCD have come from two referral centers. It has been proposed that selection bias occurs and that the natural history of HCM may be more benign (98, 171). Persons with HCM and symptoms of impaired consciousness and inducible ventricular tachycardia (VT), as well as sustained VT induced at electrophysiological study, especially associated with cardiac arrest or syncope, identify a subgroup at high risk for subsequent cardiac events (57).

Arrhythmogenic right ventricular dysplasia (ARVD) is a term that is no longer in use because it implicates an inborn disease where aplasia or hypoplasia of the right ventricular wall is present. ARVD was recently renamed arrhythmogenic right ventricular cardiomyopathy (ARVC) (2). The syndrome was first described in 1977 (60) and is a heart muscle disease of unknown etiology characterized by cardiac electrical instability because of progressive fibrofatty atrophy of the right ventricular myocardium (2, 126). Segmental right ventricular disease is common, but evolution to more diffuse right ventricular involvement and left ventricular abnormalities with heart failure have been described. The incidence is unknown. It is a familial disease in less than 30% with an autosomal dominant inheritance (133, 145), and there are familial cases without family history of heart disease found in preceding generations (169). It remains unclear whether the genetic background predisposes to a degenerative disease with atrophy and fibrofatty replacement or whether the inflammatory cells seen in 25%
of cases indicate an infectious or in other way triggered immune pathogenesis. Basso et al. have reviewed current opinions on pathogenesis (12). ARVC may be regarded as a chronic myocarditis because of the frequent findings of lymphocyte infiltrates associated with myocyte death. In a case report of a previously healthy 47 year-old man who had fever, arthralgia and subsequently developed ventricular tachycardia, repeated endomyocardial biopsies demonstrated a gradual development of acute to healed myocarditis and fibrofatty replacement. There were also subsequent angiographic findings highly suggestive of ARVC (78).

ARVC is a well-recognized cause of SUCD (174, 190) and the SUCD risk is particularly high in those subgroups of ARVC patients where myocardial inflammatory infiltrates coexist or where the fibrofatty replacement engages even the left ventricle (12, 59). Thirty-two athletes diagnosed as having ARVC were followed during a period of about 7 years and findings indicated that 50% developed severe symptoms during sports activity (64). Attempts are made to alter the prognosis in some cases by surgical treatment using cryoablation, myocardial excision, and in cases with involvement of the left ventricle, also by implantable cardioverter or cardiac transplantation (128).

Conduction system abnormalities. The Wolff-Parkinson-White syndrome is characterized by the appearance of a delta wave on ECG representing accessory conduction pathways and a tendency for a variety of arrhythmias. In asymptomatic individuals, the incidence of SUCD is proposed to be less than 1 per 1,000 years of patient follow-up (93). There is at present no consensus whether catheter ablation is indicated. Thus far, results from about 700 patients, mostly symptomatic, have been reported. Successful ablation of the accessory pathway occurred in 86-99% removing the risk of syncope or cardiac arrest (55).

Mitral valve prolapse is diagnosed when there is increased thickness, floppiness, and a redundancy of the leaflets, intercordal hooding, and billowing of the leaflet toward the left atrium (36). It is a common disorder affecting 5% of the population and generally has a favorable prognosis. It has, however, been implicated to play a major role for some cases of SUCD (36, 82, 177), especially in victims above 30 years of age.

Myocarditis was first recognized in 1812 (42, 163) when it was postulated that Corynebacterium diphtheriae, an infectious agent, might elicit an inflammatory response that culminates in subacute-to-chronic myocardial disease. The definitions of this condition have ever since been imprecise. In 1983, the cardiac pathologist E.C.J. Olsen defined myocarditis as the presence of inflammatory cells in the myocardium with evidence of fraying or necrosis of adjacent fibers but without concomitant sequential fiber necrosis (139). He and eight other cardiac pathologists, referred to as "the Dallas panel," proposed identical criteria for the diagnosis of myocarditis in 1984 (8); these criteria have since been used as the golden standard. However, in clinical practice, they are very difficult to satisfy, because they require consecutive endomyocardial biopsies and immunohistochemically proven inflammatory infiltrates. Furthermore, this is merely a histopathological classification, and it is not possible to make a judgment of etiology without additional information, such as microbiological test results. Since the 1995 WHO classification (2), myocarditis has been a subgroup of the specific cardiomyopathies in cases where impairment of cardiac function can be demonstrated as well. It is then named inflammatory cardiomyopathy.
In comparison, the clinical definition of myocarditis is broader and less distinct. The designation *perimyocarditis* is often used based on the occurrence of chest symptoms often mimicking those of myocardial infarction with or without prior concomitant catarrhal symptoms, ECG alterations and elevations of cardiac serum markers of myocardial lesion, such as aminotransferases, MB fraction of creatine kinase, or cardiac troponins.

When using the Dallas criteria in a large clinical trial of immunosuppressive treatment of myocarditis where endomyocardial biopsies were used systematically, only 10% of patients fitting clinical criteria also had myocarditis according to the local pathologist. Of 2,000 patients included on clinical grounds, only 111 could be evaluated (118, 125). Consequently, the usefulness and distinguishing capacity of results obtained this way has consequently been questioned.

In a 10-year review of 13,000 autopsies performed until 1984 in Malmö, Sweden, myocarditis was found in 1% of the cases examined (69). The mean age of male patients was 72 years (range 44-94 years). The study reflects the situation in an elderly population who died in hospital and is not representative for the problems discussed here. It was, however, concluded that the low rate of subendocardial inflammatory infiltrates found in those having myocarditis emphasizes the limited sensitivity of endomyocardial biopsies when used for diagnosing myocarditis.

Patients diagnosed with myocarditis fall into different subsets depending on which case definition that was used. The pathogenesis is not necessarily the same in those having myocarditis on histopathological grounds compared with those diagnosed by other clinical criteria.

Myocarditis is infrequent in most previously published studies of SUCD, usually below 10% but ranging from 0 to 38% of reported cases (41, 87, 106, 117, 179). The highest figure was presented in a report on US Air Force recruits during a 20-year period (ending in 1985) in which myocarditis was the most common diagnosis, found in 38% of the cases with a total incidence of 0.14 per 100,000 (143).

*Coronary artery disease* increases with advanced age, comprising more than 90% of SUCD cases after 35 years of age. This reflects the great impact of this disease on society. However, a certain overrepresentation of coronary artery disease as a SUCD cause probably exists, because there may be cases of moderate arteriosclerosis in which the pathologist attributes a death to coronary artery disease even if acute infarction or a coronary thrombus/embolus cannot be demonstrated at the autopsy, and if there is no better explanation.

In persons 15 to 35 years of age the distribution of SUCD diagnosed in published studies are mainly as follows: HCM 5-46%, ischemic heart disease/obstructive coronary arteriosclerosis, or coronary anomalies 2-24%, ARVC 3-22 %, conduction system abnormalities 10%, and mitral valve prolapse 2-24% (40, 117, 177). Myocarditis 0-38% (41, 51, 72, 87, 104, 106, 115, 143, 179) is typically infrequent and usually below 10%. Even less frequent diagnostics are Marfan's syndrome, aortic stenosis, sarcoidosis, and coronary vasculitis.

*Intoxication* by cardioactive illegal or legal drugs, such as cocaine, amphetamine, anabolic androgenic steroids (111, 114) diuretics (155), or tricyclic agents are never reported among other heart-related deaths, but are also found in some cases of SUD in
athletes. Some investigators focus on SUD rather than SUCD, reporting additional diagnoses, including subarachnoidal hemorrhage, pulmonary embolism, bronchial asthma, epilepsy, heat stroke, septicemia, or other systemic infections (51). This difference must be kept in mind, especially when comparing incidence. Anorexia nervosa is also associated with SUD because of imbalance in electrolytes, extreme bradycardia, and a prolonged QT interval (80).

**Athlete's heart**
In 1884, Bergmann first observed that wild animals had larger hearts than their domesticated counterparts (15). In 1935, Kirsh reported findings in 35 athletes who died from SUD. He postulated that the hearts were healthy and had become hypertrophied as a result of exercise (90). During the succeeding decades, there have been different views on whether the phenomenon is physiologic or pathologic. There are two basic forms of exercise, namely isotonic (dynamic) exercise and isometric (static) exercise. Distance running is typically isotonic and requires a change in muscle length against a small change in tension. There is increased venous return, resulting in cardiovascular volume load. In weight lifting, on the other hand, the development of high tension is decisive and the muscle contraction is thus primarily isometric with often small changes in muscle length. This results in dramatic increase in systemic blood pressure and a cardiovascular pressure load is observed.

The cardiovascular system adapts to isotonic training by increasing ventricular stroke volume, left end-diastolic volume, left ventricular end-diastolic diameter, oxygen consumption at peak exercise, skeletal muscle respiratory enzyme concentrations and capillary muscle density. The left ventricular mass increases as a result of isometric training (188). The electrocardiogram (ECG) of athletes may differ from that of sedentary controls. The majority of aberrations are a response to increased vagal/reduced sympathetic tone and physiologic hypertrophy (195).

**SUD in athletes**
SUCD is second only to trauma in fatalities among athletes. American football is the most widely practiced sport in the USA. Records of deaths have been systematically kept for decades. In the 55 years between 1931 and 1986 there were 289 deaths caused by systemic failure, cardiovascular collapse being one among several causes. There were 591 deaths from trauma during the same period (33). In 1996, the population of the USA (265 million) was about 30 times larger than that of Sweden (9 million). Since 1982, the National Center for Catastrophic Sports Injury Research in the USA has compiled data on non-traumatic fatalities in high school and college athletes. From 1982 to 1993, the incidence for SUD per 100,000 athletes per year in high school was 0.75 for men and 0.13 for women. In college athletes the incidence was 1.5 for men and 0.66 for women. Heart-related death was most common, representing 74% in men and 50% in women (179). These data correspond to an incidence of male athletic SUCD of 0.55 in high school and 1.1 in college. The overall incidence of non-traumatic SUD for cross-country skiers was calculated to 0.40 in an earlier report (33). Among young runners in the state of Rhode Island, annual death incidence during recreational exercise has been calculated to 0.4 (144).

During the period between 1979 and 1996 in the Veneto region of Italy, SUCD in athletes was calculated to 1.6 per 100,000, the relative risk being 2.1 ($p<0.001$) in comparison with the whole population below the age of 35 years (41).
In Sweden, there is no national surveillance of SUD in sports or otherwise, except from what can be extracted from the annual report on causes of death from the National Central Bureau of Statistics in which all deaths in Swedish residents are classified.

Heat stroke was formerly deemed a significant factor in athletes but nowadays the necessity of keeping an adequate fluid balance is stressed and heat stroke accounts for only a minor part of SUCD. In the USA, between 1979 and 1992 the incidence of death from heat stroke was <0.05 per 100,000 among persons 15 to 34 years old (1). Hyperthermia and dehydration-related SUD still occurs in wrestlers trying to achieve rapid weight loss to qualify for competition by restricted food and fluid intake, wearing vapor-impermeable suits and exercising vigorously in hot environments (155).

Male Finnish top athletes participating in the national teams from 1920 to 1965 have an increased life expectancy compared with controls, matched for age and area of residence, mainly because of decreased cardiovascular mortality (164). The risk of having a myocardial infarction was lower for 269 Finnish male orienteers compared with 188 male non-smoking controls during an 11-year follow-up starting in 1985. Two (0.7%) of the orienteers and 10 (5.3%) of the controls suffered myocardial infarction ($p=0.0059$). The age-adjusted odds ratio was 0.15 (95% confidence interval 0.03-0.67). The mean age at baseline was 49 years for orienteers versus 50 years for controls (105).

**Accumulation of SUD**

The occurrence of a moderate number of additional SUD cases because of a specific reason is noticeable only in the young because death is so uncommon during youth. For persons above 35 years of age, however, the overall SUD incidence rises quickly, and an additional moderate rise will most likely remain undetected. If such an increased death rate appears in a well-defined and organized group of young people such as in the present case of about 2,000 ranked male orienteers, it is likely to be recognized.

Apart from reports in infants, accumulation of SUD has been reported in young healthy Thai men living in different parts of the world (68, 191). These men die in their sleep without any premonitory signs. The phenomenon was discovered in the early 1980s as large numbers of people from Southeast Asia immigrated to the USA and a subset of young males died suddenly and unexpectedly. Autopsies failed to reveal a cause of death. The case definition used by the Centers for Disease Control and Prevention (CDC) in the USA since 1984 has been extended and now includes persons born in or having at least one parent born in Vietnam, Cambodia, Laos, Thailand, the Philippines or some other South-east Asian country (140). In Japan, the phenomenon was reported as early as 1959 (173). The incidence has ranged from 40 to 574 deaths per 100,000. The causes of these deaths remain uncertain but are not connected with exercise or distinct morphological changes of the heart.

Incidence of SUCD was 19 to 24 per 100,000 player-years among young Aboriginal football players in the Northern Territory of Australia from 1982 to 1996. This figure can be compared with 0.54 per 100,000 player-years among footballers of similar ages in Victoria (193). This is, to the best of my knowledge, the only example of an increased rate of SUCD in a defined subgroup of inhabitants in a country. These deaths were caused by ischemic heart disease as judged from the results of the autopsies.

In late 1994, the Centers for Disease Control and Prevention in the USA funded four programs for surveillance of unexplained deaths due to possible infectious causes for
the purpose of early detection of new infectious diseases. The first report was presented in 1996 (142) based on ICD-9 coded multiple cause-of-death data for the USA for 1992 from the National Center for Health Statistics. The overall incidence, in the age group 15 to 34 years, was 5 per 100,000 for the 77 different diagnoses likely to represent unexplained deaths due to possible infectious causes. The selection included diagnoses such as myocarditis, pericarditis, endocarditis, primary and secondary cardiomyopathies, unknown cause of sudden death, instantaneous death, death occurring in less than 24 hours from the onset of symptoms and not otherwise explained, unattended death, and other ill-defined and unknown causes of mortality. In addition, there was a broad range of other diagnoses. The fourth most common cause of death, as well as the most common heart-associated diagnosis, was "425.4 other primary cardiomyopathy," accounting for 7% of the total deaths.

Orienteering in Sweden

In orienteering, the task is to find the fastest track through forested or open terrain between defined checkpoints by means of map and compass. The origin is found in military training, but for decades orienteering has been a popular sport in Sweden. At present, a broad spectrum of some 160,000 people, corresponding to 2% of the entire population, pursues this sport. Of these, about 60,000 persons take part in competition each year. A top segment of 3,000 are ranked, of whom 70% are men, which closely reflects the male-to-female ratio within the sport. About 200 compete at the international elite level.

Events are based both on individual and team performance. All kinds of terrain are used nationally and internationally. In a typical male elite race the winners have been running a self-decided track for 90 minutes, often right through dense vegetation and with significant changes in altitude. Events are run both in daylight and at night using flashlights mounted on the head for guidance. In the winter a number of orienteers take part in orienteering using cross-country ski equipment.

Performance in competitive orienteering is affected by physiological and mental capacity as well as the ability to understand and translate details from a map to navigation in terrain.

During the past two decades, the competitive demands have increased with longer and tougher courses and an increased number of qualified competitors on the international elite level. In parallel, the Swedish Orienteering Federation (SOFT) introduced new classes of competition in 1991 featuring short 15-minute sprint-courses for spectator reasons. They became popular with both competitors and organizers and now account for about 50% of all competitive events. Elite ranking is not mandatory for participation because of the short course, which has resulted in a steady decreasing number of annual rankings. The World Championships in 1999 was a great disappointment for the Swedish national team. To meet the standards of international competitors it was then decided to focus on longer, tougher courses again, and in 2000 to introduce a special upper elite class (the elite series) having prize money. Compared with other elite endurance sports, elite orienteers show aerobic work capacities comparable to cross-country skiers, cyclists, and long distance runners. The members of the Swedish male national team have an oxygen uptake of 75-81 ml/kg/min, with a training background of 5-15 years at international top level (159). Running velocity varies from 3 to 10 min per kilometer. During an event, the heart rate is close to 90% of maximal and the blood lactate level is high (49). By increasing the technical demand in the courses, running speed becomes slower and the heart rates are lowered significantly (18). Other factors
necessary for good performance is an excellent running economy and the ability to run fast in extremely rough terrain where it is necessary to jump over obstacles often on a steep up- or downhill course (81).

**Previous disease related to orienteering**

During the late 1950s it became evident that an epidemic of jaundice was taking place in Swedish orienteers. As epidemic hepatitis was a reportable disease, this contributed significantly to a correct epidemiological approach. There were widespread speculations of what could be the cause with a special diagnosis being introduced i.e. *hepatitis silvatica*. Many favored a toxic explanation because the liver was affected. Pesticides or insecticides were implicated as causative. However, the epidemiologists checking procedures during the events began to suspect a contagious disease spread by blood-to-blood contact because of poor hygienic facilities when washing after races. Small bowls, often with unchanged water, common soap and towels were used, which enabled extensive exposition to blood. At that time competitors ran barelegged and bare-armed in the heat of the summer. This meant that during the event many competitors would become notoriously scratched from vegetation. The hepatitis cases occurred 3 to 6 months after the competitive season ended. The epidemiologists tried to impose different regulations to avoid further spread but these efforts were without noticeable effects. It was only when all competition was completely halted for one season in the spring of 1962 that the problem declined dramatically. A smaller epidemic re-emerged 1965 when all regulations were abandoned, but this time it was easier to convince everybody to abide to hygienic precautions. Because of the epidemic, special mobile installations for sanitation and showering had been developed to fulfill acceptable hygienic standards.

When tests for hepatitis B became available about 10 years later, it was possible to test sera that had been collected from 1961 to 1962 and had been stored frozen for many years. It was shown that 45 of 91 were positive for HBsAg (158). The negative sera were taken late in the course of the disease. In total, 564 cases of hepatitis were reported. There were about 10,000 orienteers active at that time. Only 40 % of hepatitis B cases develop jaundice. If 80% of jaundiced cases were also reported, this would implicate that at least 15-20 % of the orienteers taking part in events were infected. It is probable that many cases in the beginning of the epidemic were not reported. There were also cases in Norway though these were not given much public attention. Many parallels can be drawn from these historic events to the handling and development of the present study.

**SUCD in orienteers**

In the fall of 1991, the medical staff of the SOFT was troubled after the occurrence of SUCD in three young orienteers during the past 8 months. All three were men and representative of a small but high performing elite within the sport. The Department of Infectious Diseases at Uppsala University Hospital was asked by the SOFT to evaluate whether this was to be regarded as an unacceptable accumulation of cases.

**Infections in orienteers**

The members of the Danish national team in orienteering have recorded infections that prevented them from training. These were mainly respiratory tract infections. There was a significant training increase within the last week before the onset of disease. Infections were most numerous in autumn and spring. Men had, on average, 2.3 and women 1.1 such incidents per year (85), which is lower than the population average of 4.9 and 5.9, respectively, per year in Denmark (148). The mean duration was 7.9 days
for the orienteers, which indicates that minor infections not affecting training were not registered and the figures may therefore not be comparable. The training load was 9 to 15 hours per week.

**Infections caused by *Bartonella***

Hematophagous arthropods, including fleas, lice, and flies are often involved in the transmission of bartonellosis. These bacteria have the ability to induce angiogenic tumors in humans, and bacteriemia may persist long after disappearance of clinical signs of disease. Detection in conventional automated blood culture systems remains difficult as the organisms produce little or no carbon dioxide and yield little visible growth. It usually takes several weeks before growth may be detected by acridine orange dye staining. Information regarding new species and pathogenicity for humans and animals is accumulating at a fast rate. More than 90% of the reports on *Bartonella* spp. that are indexed in Medline were published after 1993, including reviews (4, 6, 7, 83, 120, 150).

*B. bacilliformis* causes a biphasic disease consisting of an acute feverish hemolytic anemia with high mortality (Oroya fever) and a chronic form ( verruga peruana) that presents with vascular proliferative skin lesions (6, 157, 166). The disease is limited to certain areas of South America and is spread by the sand fly (*Lutzomyia verrucarum*). No other reservoir than humans has been demonstrated. Archeological evidence from the remains of pre-Columbian cultures suggests that the disease was present at least 1,000 years before the arrival of the Europeans, and one of the first reports on bacteria seen in the blood is from 1909 (11).

*B. quintana* (formerly *Rickettsia quintana, R. volhynica, R. weigli, Rickettsia rochalimae, Rochalimea quintana*) caused the clinical entity "trench fever" (127) that was responsible for great morbidity among troops during World War I and II. It was characterized by relapsing fever, accompanied by severe pain in the shins and prolonged disability. A few presumed contemporary cases in Sweden were published (16). *B. quintana* is spread by the human body louse (*Pediculus humanus corporis*) when feeding or from louse excrement carrying the bacteria and entering the circulation trough abrasions from scratching or bites. The head louse (*Pediculus humanus capitis*) can transmit the disease in experimental infection (182), but has never been implicated otherwise. Already in 1916 it was suggested that large numbers of voles infesting the trenches could be involved in the outbreaks of trench fever (162), but the only proven reservoir thus far is humans. After 1945, the medical interest for *B. quintana* diminished until other manifestations of this infection re-emerged in immunocompromized persons. In 1983, a syndrome in AIDS patients was described, including multiple cutaneous skin lesions (172), which were assumed to be of infectious origin because these lesions contained bacilli that stained with the Warthin-Starry stain and resolved on antibiotic treatment. The condition was named bacillary angiomatosis, and later also included deep-tissue engagement. In 1990, it was possible to amplify PCR products from biopsies of such lesions using primers that hybridized to the 16S rRNA gene of most bacteria. The base sequences derived from four patients (of which one was a heart transplant recipient) indicated the presence of a bacterium closely related to *B. quintana* (154). The organism was subsequently cultured and named *B. henselae*, and surprisingly, *B. quintana* was also cultured from skin lesions confirming that both are etiological agents of the bacillary angiomatosis (96, 151, 153, 168, 185). In recent years, infection with *B. quintana* has re-emerged in persons characterized by homelessness, alcoholism and exposure to lice and manifestations such as bacillary angiomatosis, severe leg pain and headaches and having chronic
bacteriemias, with or without fever or endocarditis (27, 28, 48, 170). Outbreaks in 1993 were reported occurring simultaneously in San Francisco (97) and Seattle (170). B. henselae (formerly Rochalimea henselae) causes cat-scratch disease (43, 46, 83, 152), which is the most common zoonosis in the USA with more than 40 000 cases reported each year. The reservoir is the domestic cat and transmission between cats is facilitated by cat-flea (Ctenocephalides felis) infestation. Bacteria are present in feces from the fleas and contaminate the fur, the claws, and cat saliva explaining the role of cat scratches or cat bites in the transmission. Cat-scratch disease is characterized by prolonged lymphadenopathy, low-grade fever and papules at the inoculation site. It is usually a benign and self-limiting disease of the young, but occasionally presenting with complications. In immunocompromized persons the course may be different, which may also necessitate antibiotic treatment.

B. elizabethae has only been retrieved once from humans. It was found in the blood of a 31 year-old man suffering from aortic valve endocarditis living in the USA but born in Puerto Rico (44). There are indications that one reservoir may be sewer rats (Rattus norwegicus) (20) that also harbors other Bartonella spp., (e.g. B.tribocorum) which are closely related genetically to B. elizabethae (13, 54).

A number of other Bartonella species have recently been described of which some have also proved to cause disease in humans (Table I). Some Bartonella spp. are not fully characterized yet from roe deer (Capreolus capreolus) and their ticks in the Netherlands (165), from wild and domestic ruminants in North America (34) from rodents in the Southeastern USA (103), and from different animals in a region endemic for human bartonellosis in Peru (20).

Bartonella spp. may cause endocarditis in humans (44, 48, 73, 146, 161, 170) as well as in dogs (24, 26). Chronic experimental infection in cats has been associated with myocarditis (101). Bartonella has recently been detected in dogs having cardiac arrhythmias and myocarditis, some of whom succumbed to sudden death (24). In this study, evidence is presented suggesting that a subacute or reactivated Bartonella infection in the myocardium is an important etiologic factor in the SUCD cases in Swedish orienteers.

Bartonella spp. has recently been cultured from Swedish cats at the Swedish National Veterinary Institute (personal communication Dr. Eva Olsson). Cat flea infestation is mostly found in the southern parts of Sweden having a warmer and more humidified climate. In other parts of the country, cats and dogs contract more transient flea infestations with other flea species related to wildlife. In Sweden, Bartonella has also recently been cultured from wild ruminants and small mammals (unpublished data).

**Associations between Bartonella and Chlamydia**

Bartonella and Chlamydia are not phylogenetically related but the genomes show similarities, and antibodies to one of the species may cross-react with antigens from the other. Both are intracellular bacteria facing the same milieu. Moreover, the adaptation processes for survival of both bacteria have come up with similar solutions.

In 1950, an agent of the psittacosis-lymphogranuloma venerum (LGV) group, nowadays commonly known as Chlamydiae, was suggested to be the etiology of cat-scratch disease (CSD) (130). The association was based upon clinical similarities of lymphoid hyperplasia, observations of bodies resembling the elementary bodies of the LGV agent in stained sections of infected human and monkey lymph nodes and the finding of complement fixation (CF) antibody to the chlamydial group antigen in approximately 50% of patients convalescent from CSD. The chlamydial link to the etiology of CSD was never proved conclusively but it remained suggestive for more
that 30 years (181). During the last eight years, *B. henselae* has been characterized (151) and shown to be the etiology in most cases of CSD (150) though the role for other related agents, such as *Afipia felis*, remains possible in some cases of CSD or related syndromes.

Cross-reactions in serology between *Chlamydiae* and European *Bartonella* strains have been reported in human cases where *Bartonella* infection is believed to be a major factor in pathogenesis. In 1992, 10 cases of endocarditis from *Chlamydia* was reported (56); however, further testing of these and additional cases revealed *Bartonella* to be the causative agent (146). In a case report, a 41 year-old alcoholic, homeless man having prolonged history of contact with cats and enduring multiple lice bites was reported to suffer from endocarditis caused by *Coxiella burneti* and *C.pneumoniae* simultaneously. However, in light of current knowledge the etiology was probably *Bartonella* (189). Recently, disease caused by *Chlamydia* was misdiagnosed as being caused by *Bartonella* (121).

**Table I. Different Bartonella spp. and the associated reservoirs, diseases and vectors.**

<table>
<thead>
<tr>
<th>Bartonella sp.</th>
<th>Reservoir</th>
<th>Clinical disease in humans</th>
<th>Vector</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>B. bacilliformis</em></td>
<td>Humans</td>
<td>Oroya fever, verruga peruana, internal vascular proliferative lesions</td>
<td>Sand fly</td>
<td>6, 157, 166</td>
</tr>
<tr>
<td><em>B. quintana</em></td>
<td>Humans</td>
<td>Trench fever, bacillary angiomatosis, endocarditis, fever and bacteriemia, lytic bone lesions, CNS manifestations</td>
<td>Human body louse</td>
<td>120, 138</td>
</tr>
<tr>
<td><em>B. henselae</em></td>
<td>Domestic cat, wild felids?</td>
<td>Cat-scratch disease, bacillary angiomatosis, peliosis of liver and spleen, endocarditis, fever and bacteriemia, CNS manifestations</td>
<td>Cat, cat flea, tick?</td>
<td>83, 160</td>
</tr>
<tr>
<td><em>B. claridgeiae</em></td>
<td>Domestic cat</td>
<td>Skin papules, febrile lymphadenopathy</td>
<td>Cat</td>
<td>102</td>
</tr>
<tr>
<td><em>B. elizabethae</em></td>
<td><em>Rattus norvegicus</em>?</td>
<td>Endocarditis</td>
<td>?</td>
<td>44, 54</td>
</tr>
<tr>
<td><em>B. tribocorum</em></td>
<td><em>Rattus norvegicus</em>?</td>
<td>?</td>
<td>?</td>
<td>76</td>
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<tr>
<td><em>B. vinsonii</em></td>
<td>subsp. berkoffi</td>
<td>Wild canides</td>
<td>Coyote, dog tick?, flea??</td>
<td>35, 100, 16</td>
</tr>
<tr>
<td><em>B. vinsonii</em></td>
<td>subsp. arupensis</td>
<td>Rodents?</td>
<td>?</td>
<td>184</td>
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<tr>
<td><em>B. grahamii</em></td>
<td>Rodents</td>
<td>Neuroretinitis</td>
<td>?</td>
<td>19, 54, 88</td>
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<tr>
<td><em>B. talpae</em></td>
<td>Rodents, moles, moles</td>
<td>Unknown, type strains lost</td>
<td>?</td>
<td>19</td>
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<tr>
<td><em>B. peromysci</em></td>
<td>Rodents</td>
<td>Unknown, type strains lost</td>
<td>?</td>
<td>19</td>
</tr>
<tr>
<td><em>B. taylorii</em></td>
<td>Rodents</td>
<td>?</td>
<td>?</td>
<td>19</td>
</tr>
<tr>
<td><em>B. doshiae</em></td>
<td>Rodents</td>
<td>?</td>
<td>?</td>
<td>19</td>
</tr>
<tr>
<td><em>B. wessii</em></td>
<td>Ruminants?, cats??</td>
<td>?</td>
<td>Tick?</td>
<td>25, 34</td>
</tr>
<tr>
<td><em>B. koehlerae</em></td>
<td>Cats?</td>
<td>?</td>
<td>Cat flea??</td>
<td>52</td>
</tr>
<tr>
<td><em>B. alsatica</em></td>
<td>Rabbits?</td>
<td>?</td>
<td>?</td>
<td>75</td>
</tr>
</tbody>
</table>
Parallels to SUD, heart disease, and *Bartonella* infection in animals

There are many examples of a periodically increased incidence of sudden deaths in different wild or domesticated animals for different reasons, including infectious myocarditis (149). These observations are for the most part not comparable to SUD in humans, but some observations may be mentioned because of similarities to athletes. Primary heart disease with similarities to human HCM occurs spontaneously in domestic cats (63, 107) and dogs (108, 175). The cases have demonstrable outflow obstruction, asymmetric hypertrophy, myocardial fiber disarray, abnormal intramural coronary arteries and myocardial fibrosis. In a study comparing 38 humans, 51 cats and 10 dogs it was concluded that substantial structural similarities exist between the animal and human cases (109). In addition, other variants similar to human congestive cardiomyopathy have been reported (176). Sudden death in young dogs has occurred from myocarditis caused by parvovirus (74). ARVC has been documented repeatedly in dogs (124, 132, 167) and recently in cats (62). The parallel to SUCD in orienteers is of particular interest because cats are the only demonstrated reservoir of *B. henselae* infection. *Bartonella* has been detected in the hearts of cats having chronic infections with *B. henselae* or *B. clarridgeae* (101). The intensified interest of *Bartonella* infections during recent years is mainly provided by the knowledge gained from HIV infected humans. In cats, *B. henselae* infection occurs as a common prolonged or chronic bacteremia without apparent disease. However, co-infection of *B. henselae* and feline immunodeficiency virus (FIV) has been reported to be associated with lymph node swelling and gingivitis (178).

SUD has been observed in "canine athletes," i.e. hard working sled dogs (180). They had changes in the hearts described as fibrosis and fat infiltration (17), raising suspicions of ARVC. There are recent reports on *Bartonella* infection in dogs (99, 100) and other canines (35). In one study, *Bartonella* infection was associated with dogs having cardiac arrhythmias, endocarditis or myocarditis. Some of the dogs succumbed to SUD, collapsed or experienced syncope (24). SUCD occurs in dogs having HCM (175).

Racehorses may die unexpectedly during competition. Severe spontaneous hemorrhage, particularly from epistaxis and in the thorax, is often noticed in such cases, and post-mortem examinations have not always included histopathological evaluation of the hearts. However, sometimes only cardiovascular lesions suspected of causing arrhythmias are observed (29, 66, 70, 91). In one report, the agonal hemorrhage in five cases was attributed secondary to acute cardiac failure and severe hypoxemia. Instead, focus was put on arrhythmias from myocardial fibrosis, sometimes accompanied by adipose tissue and extensive loss of heart muscle fibers (91).
AIMS OF THE PRESENT STUDY

The aims of the study were as follows:

• investigate if an increased death rate from SUCD existed in Swedish orienteers,
• evaluate if microbes or other factors were involved in the pathogenesis, and
• determine if there was evidence of widespread subacute subclinical heart disease in
  elite orienteers, and to set a scale useful for medical evaluation of orienteers admitted
  for possible cardiac disease.

In addition, the present study sought to:

• create an inventory of all cases of sudden death that occurred before 1992 in
  orienteers less than 35 years of age or having achieved a national ranking in 1979 or
  later;
• identify all new cases of sudden death in orienteers of the same category, preferably
  within 24 hours of death;
• characterize the circumstances in the individual cases of SUCD in orienteers and to
  find factors in common;
• possibly intervene such that the risk of sudden cardiac death in young orienteers is
  comparable to that for other persons of the same age;
• create a biological bank holding sera or other specimens from orienteers intended for
  future reference purposes; and
• create a database of all orienteers taking part in events each year in order to survey
  mortality in the group.
MATERIALS AND METHODS

Different populations of orienteers (studies I and V)
An orienteer was defined as a person having registered as a member of the Swedish Orienteering Federation (SOFT) or taking part in events arranged by organizations within the SOFT. About 40% of registered orienteers take part in events arranged by the SOFT. Orienteers were considered elite if having achieved a national ranking at least once in the past five years or when attending a school for especially talented orienteers. Both ranking and high school for talented orienteers starts at the age of 16 to 17. Therefore, only a small number of those students are not ranked at the age of 18. Orienteers having achieved ranking longer than five years ago were designated as former elite.

Calculation of death incidence (study V)
The incidence of SUCD in male elite orienteers was calculated from the ranking records, introduced in 1979, and maintained by the SOFT. The incidence of death for cardiac reasons in 20 to 34 year-old Swedish men was calculated from the 1987 to 1996 causes-of-death statistics in Sweden.

Finding and analysis of fatal cases (studies I, II, III, and V)
The cases were found by alert pathologists, clinicians, relatives or friends of the deceased, notices in the media or by the SOFT. The autopsy reports were re-evaluated and the remaining tissue materials that had been routinely processed using formaline fixation and paraffin embedding were prepared using different staining techniques. Individual data were collected from the patients before death, relatives or friends of the deceased, training diaries, and hospital or military records. Prospectively, autopsies were performed in four cases of orienteers dying suddenly from non-ischemic cardiac causes and tissues were received from a fifth case. Precautions were taken to prevent contamination and enable microbiological testing. Three cases of previously ranked orienteers and one case of another orienteer dying suddenly came to our attention too late to influence procedures at the autopsies.

Collection of data for epidemiology and sera for biological banking and serology (studies I and IV)
All orienteers ranked in 1992 and 1993 were sent a questionnaire and concurrently asked to provide a serum sample to be available for future reference purposes. In addition, ranked orienteers sent us sera on their own initiative on other occasions. In all, 1,820 sera were collected and stored frozen, of which 1,750 sera (67% male sera) were from persons ranked in 1992. This corresponded to 62% of all orienteers ranked that year. Antibodies to C. pneumoniae (77, 187) were tested in 1,790 sera, and antibodies to B. henselae, B. quintana, and B. elizabethae were tested in 1,136 sera. In the questionnaire, the orienteers were asked to provide information with regard to age, gender, region of training and residence, medical background, personal evaluation of health status, degree of exposure to animals/pets, history of tick bites, and travel abroad.

Histopathology (study II)
Slides were made from paraffin embedded tissue blocks and stained with hematoxylin/eosin, van Gieson, elastin, periodic acid-Schiff (PAS), iron, alcian blue-PAS for visualization of mast cells and picro-Sirius for collagen. Gram and Grocott stainings were made for detecting fungi and bacteria. Immunohistochemistry for
identification of macrophages was accomplished using the antibodies MAC 387 and KPN 1, and the biotin-avidin amplification system. Established criteria for myocarditis (the Dallas criteria) (8), hypertrophic cardiomyopathy (53), and ARVC (12) were applied. An essential goal was to establish similarities, if any, in the morphological pictures. Based on the current histopathological observations, and also taking into account macroscopic descriptions of the original autopsy protocols, cases were classified into three different groups: Group A: Myocarditis in different stages present as the sole morphological change; Group B: Myocarditis and, in addition, ARVC-like alterations present, or reported in the autopsy protocol, in either ventricle; Group C: Cases not fulfilling the criteria adopted for groups A or B, i.e. remaining cases.

Microbiology (studies I, III, and IV)

Cultures. Conventional cultures were made for bacteria using a broad range of different substrates, including those recognized for *Mycoplasma* and *Bartonella*. Tissue cultures using different cell lines (human lung fibroblasts, A-549, green monkey kidney, Vero cells, RD cells) were used for detection of virus and bacteria. Special efforts were directed for detection of enterovirus and *Chlamydiae*. Inoculated cell cultures were tested by PCR for enteroviral genomes, by PCR for the 16S rRNA gene of *Chlamydia*, and by immunofluorescence for *Chlamydia* antigen.

PCR. DNA from *Chlamydia pneumoniae* was detected using primers targeting the 16S rRNA gene (65). PCR products were hybridized using *Chlamydia* specific probes. DNA from *Bartonella* spp. was detected by seminested PCR targeting the *gltA* gene (79). PCR products from *Bartonella* DNA were sequenced. PCR was also adopted using common bacterial 16S rDNA primers.

Serology. Microimmunofluorescence was used for measurement of antibodies to *Chlamydia* spp. (67) and *Bartonella* spp. (152). Other serological tests applied from different laboratories were: enterovirus-IgM-SPRIST, enterovirus-IgM-RIA, Coxsackie B1-5-IgM-RIA; complement fixation tests for influenza virus A and B, adenovirus, respiratory syncytial virus, *Mycoplasma pneumoniae*, parainfluenzavirus 1, 2 and 3, and *Chlamydia* group antigen; ELISA tests (IgG and IgM) for herpes simplex, herpes virus 6, cytomegalovirus, Epstein-Barr virus, Sindbis virus, Puumala virus, *Francisella tularensis*, *Borrelia burgdorferi*, *Coxiella burnetii* phases 1 and 2, *Brucella abortus*, and staphylococcal teichonic acid and alphatoxin; neutralization tests for antistreptolysin O and antistreptococcal DNase B; direct agglutination tests (IgG) and immunofluorescence tests (IgM and IgG) for *Toxoplasma gondii*.

RESULTS AND DISCUSSION

Inventory of cardiac deaths in Swedish orienteers from 1979 to 2000

Twenty-five cases of cardiac death, in Swedish orienteers from 1979 to 2000 are presented in Fig. 1. In most cases there was no preceding history of cardiac disease and death was unexpected. In retrospect, 14 cases of SUCD in orienteers less than 35 years of age were identified from 1991 and back to 1979. The ages ranged from 18 to 32 years at death (cases 1-14). In addition, in 1978 a 24 year-old male orientee was successfully resuscitated from cardiac arrest. This orientee gradually recovered though he did continue to suffer malignant arrhythmias, developed right-sided cardiac failure and died eventually in 1984 (case 25).
Investigated cases of death in 25 Swedish orienteers

- Rank. female
- Non-elite
- Other elite
- Rank.>5 yrs ago
- Rank.<5 yrs ago
- Rank.same year

Cases

Year


Case no.

* denotes positive PCR Bartonella

12, 14, 15, 17, 19*
Prospectively, after November 1991, 7 cases of SUCD have occurred in nationally ranked male orienteers, two of whom were less than 35 years of age (study V). Microbiological investigation was possible in the two SUCD victims succumbing in 1992 (studies I, II and III; cases 15-16) and in the latest victim in 1999 (study III; case 19) because they were brought to our attention very quickly after they died.

Furthermore, information was accumulated in about 30 additional cardiac deaths in orienteers older than 35 years, where cardiac infarction was the cause in the majority of these cases. In three of these cases, coronary sclerosis was only mild or moderate and the cause of death was myocarditis or cardiomyopathy (cases 22-24). Microbiological investigation was possible in two of the cases (study III).

It is possible that there are additional SUCDs in young orienteers from 1979 to 2000 that we are unaware of, and most probably several more SUCDs in the elderly population of still active or retired orienteers.

For professional surveillance of the death rate in orienteers, it was deemed necessary to collect data on the social security numbers of all persons taking part in orienteering events each year and identify those with elite status. The Swedish social security numbers are unique for each individual and include date of birth and gender. Such data on orienteers could readily be coordinated with data from the national cause-of-death statistics and provide exact information on mortality. Thus, over several years informal attempts were undertaken to gain access to the already existing computerized administrative routines used by the SOFT for handling their members, routines that often included social security numbers. We later learned, however, that it was impossible to obtain the information in this way. Therefore, in 1996 a formal letter of request was sent to the board of the SOFT, which eventually turned down our request without providing any reasonable explanation other than the argument that it would be an intrusion into their members' personal integrity. For several years, the situation concerning SUCD in orienteering had put considerable strain on the SOFT board members and the decision may well have been caused by extreme fatigue.

Characteristics of the cases
Sixteen cases of SUCD in orienteers younger than 35 years were investigated in studies I and II. These cases, together with nine additional cases, are listed in table II. Common features among these 16 cases were: orienteering on elite level (88%), male gender (94%), death occurring in association with physical exercise (88%), no impairment of physical performance noted close before death (100%), no heart-related symptoms reported (70%), and inflammatory cardiomyopathy (myocarditis in 75%, Fig. 2), in several cases with fibrofatty replacement mimicking ARVC (Fig. 3) but judged by the cardiac pathologists to represent chronic myocarditis, not fulfilling criteria for ARVC diagnose. In other cases fibrosis of the heart was extensive but did not permit a more detailed description because of autolysis or lack of sufficient tissue samples (Fig. 4). In some cases (19%), there were also pathological changes in the thyroid gland (Fig. 5), but the gland had not been sampled in all cases. There were no changes suggesting ischemic heart disease to be of significance in any of these cases.
Figure 2. Inflammatory cardiomyopathy. Myocarditis with inflammatory infiltrates and adjacent necrotic myocytes. The specimen tested positive for B. quintana DNA.

Figure 3. ARVC-like inflammatory cardiomyopathy (myocarditis) in the left ventricle. Inflammatory infiltrates, fibrofatty replacement and extensive loss of myocytes. The specimen tested positive for B. henselae DNA.
Figure 4. Example of case with extensive myocardial fibrosis.

Figure 5. a) Hyperplasia of the thyroid gland. The specimen tested positive for B. henselae DNA. b) Lymphocytic thyroiditis in another of the cases.
<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age at death</th>
<th>Ranking 1979 or later</th>
<th>Prior heart symptoms or testing</th>
<th>Duration of disease</th>
<th>Histopathology of the heart, and other organs</th>
<th>Microbiology PCR</th>
<th>Ref. article</th>
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<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>Yes</td>
<td>Altered ECG ≥7 months</td>
<td></td>
<td>Myocarditis HCM?</td>
<td>I, II, V</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>Yes</td>
<td></td>
<td></td>
<td>Myocarditis</td>
<td>I, II, V</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>No/elite</td>
<td>Tachycardia ≥11 years</td>
<td></td>
<td>Fibrosis, fatty infiltration. ARVC? HCM?</td>
<td>I, II, V</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>No/elite</td>
<td>Tachycardia ≥2 years</td>
<td></td>
<td>ARVC-like5</td>
<td>I, II, V</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>28</td>
<td>Yes</td>
<td></td>
<td></td>
<td>ARVC-like5</td>
<td>I, II, V</td>
<td></td>
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<tr>
<td>6</td>
<td>28</td>
<td>No</td>
<td></td>
<td></td>
<td>Fibrosis</td>
<td>I, II, V</td>
<td></td>
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<tr>
<td>7</td>
<td>26</td>
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<td></td>
<td></td>
<td>Myocarditis</td>
<td>I, II, V</td>
<td></td>
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<tr>
<td>8</td>
<td>32</td>
<td>Yes</td>
<td>Tachycardia ≥2 years</td>
<td></td>
<td>ARVC-like5</td>
<td>I, II, V</td>
<td></td>
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<tr>
<td>9</td>
<td>19</td>
<td>Yes</td>
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<td></td>
<td>Myocarditis HCM?</td>
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<tr>
<td>10</td>
<td>29</td>
<td>Yes</td>
<td></td>
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<tr>
<td>11</td>
<td>27</td>
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<td></td>
<td>Myocarditis</td>
<td>I, II, V</td>
<td></td>
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<tr>
<td>12</td>
<td>24</td>
<td>Yes</td>
<td>Chest pain ≥7 years</td>
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<td>I, II, V</td>
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<td>Myocarditis</td>
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<td></td>
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<td>14</td>
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<td>Fibrosis</td>
<td>I, II, V</td>
<td></td>
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<tr>
<td>15</td>
<td>27</td>
<td>Yes</td>
<td>Syncope ≥6 months</td>
<td></td>
<td>Myocarditis, fatty streaks B. quintana C. pneum.</td>
<td>I, II, III, V</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>24</td>
<td>Yes</td>
<td>≥1 month</td>
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<td>ARVC-like5 hyperplasia of thyroid gland B. henselae</td>
<td>I, II, III, V</td>
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<td>17</td>
<td>45</td>
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<td>V</td>
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<td>18</td>
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<td>Yes</td>
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</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>V</td>
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<td></td>
<td>V</td>
<td></td>
</tr>
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<td>59</td>
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<td>Myocarditis B. quintana</td>
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<td>55</td>
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<td>Myocarditis, pericarditis, B. henselae</td>
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<td>Myocarditis</td>
<td>V</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>29</td>
<td>No/elite</td>
<td>Resuscitated ≥6 years</td>
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<td>ARVC-like5</td>
<td>V</td>
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</table>
**Footnotes for Table II.**

1. Duration of disease was estimated from onset of symptoms, other clinical history of relevance or theoretically minimal time for histopathological changes to develop.
2. Cases 1 and 2 lived in the same area, were acquainted with one another, met occasionally, and both died within an interval of 4 months.
3. Cases 8 and 12 were members of the same orienteering club.
4. Case 9 was a female. There were conflicting results in the autopsy protocol vs. the re-evaluation protocol. HCM suggestive but only early healing myocarditis could be verified.
5. ARVC-like denotes extensive fibrofatty replacement of myocardium in both ventricles; however, it does not refer to transmural in the right ventricle. These cases had inflammatory lesions fulfilling criteria for myocarditis.

**Malignant arrhythmias in living elite orienteers**

Two male elite orienteers who survived life-threatening arrhythmias were provided with implanted cardioverters (study III). Both have cardiomyopathy compatible with ARVC; in one case, this was verified by endomyocardial biopsy. Two other cases in nationally ranked males are presently under investigation and where ARVC is suggestive, although not yet confirmed (data not reported).

**Increased death rate**

In the subsequent calculations of death rate, only those having achieved a national ranking in 1979 or later were included. This distinction was applied to allow accurate determination of the population at risk.

In 1992, an increased incidence of SUCD was thought to exist in male Swedish elite orienteers (Fig 6). Between 1979 and 1992, the incidence of SUCD in 18 to 34-year old male orienteers ranked at the national level the same year they died was 30 per 100,000 (8 SUCD cases per 26,944 rankings, 95% confidence interval = 9-50). For the same period, the incidence of SUCD in male orienteers regardless of age and having achieved national ranking at least once since 1979 was 15 (12 SUCD cases per 79,986 person years, 95% confidence interval = 6.5-23). Between 1979 and 2000, the incidence of SUCD in female ranked orienteers was lower than 5 (1 SUCD case per 19,557 rankings).

It may be worth noting that only the increase in the death rate merits statistical evaluation of whether there is a true accumulation or if fluctuations over the years should be attributed to chance. However, in the individual case, SUCD can never be attributed to chance but is always the result of a malfunctioning heart, the cause of which often cannot be established. It is always indicated to make a thorough investigation when a young person succumbs to SUCD, particularly because of the many years lost. The forensic routines of today allow for establishing a correct histopathological diagnosis of a malfunctioning heart in most cases; however, further investigation into pathogenesis or on etiology in cases where an infectious disease seems plausible is only conducted if scientific interest exists.

**Microbiology**

*Chlamydia pneumoniae* (study I). In 1992, sera from five deceased elite orienteers were available for testing. In one case, sera had been collected before death, as well as at
The incidence of SUCD in male elite orienteers compared with other athletes and the incidence of overall death from cardiac causes in Swedish men of the same ages. For Italian athletes see reference 41.

Incidence of death in different populations

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases per 100,000</th>
<th>95% confidence intervals are displayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUCD 18-34 y-old male orienteers ranked the year of death 1979-92</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>SUCD Swedish male orienteers ranked 1979-1992</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>SUCD Swedish male orienteers ranked 1997-1999</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>All cardiac deaths in 20-34 y-old Swedish males 1987-1996</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>SUCD in &lt;36 y-old Italian athletes Veneto region 1979-1996</td>
<td>2</td>
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</tbody>
</table>

autopsy; in the remaining four cases serum was obtained only at autopsy. They were tested for antibodies to numerous microbes. The only common finding was IgG antibodies to *C. pneumoniae*. Titers were $\geq 512$ in 4 of 5 cases. Attempts were therefore made to detect *C. pneumoniae* using PCR in different organs from the two latest cases, which were the only cases in which suitable tissue materials were available. In one case (case 15), 16S rDNA binding to a *C. pneumoniae*-specific probe could be amplified and detected in the heart and lung. It was, however, not possible to culture the organism despite numerous efforts (study I).

Sera collected in 1992-1993 from elite orienteers were tested for antibodies to *C. pneumoniae*. The seroprevalence was 53% (947/1,790 sera) in orienteers and 59% (151/254 sera) in healthy blood donors (study I and (77)).

During the past several years, it has become apparent that *C. pneumoniae* can infect the cardiovascular system, where the organism is supposed to have a pathogenetic role in the development of ischemic cardiovascular disease (9, 14, 32, 45, 71, 192). However, further efforts to culture this organism and to detect chlamydial DNA in several of the present cases of orienteers succumbing to SUCD were unsuccessful (unpublished data).
The finding of DNA from *C. pneumoniae* in one case may represent endothelial infection of uncertain significance to SUCD. Furthermore, our interpretation was that the seroreactivity to *C. pneumoniae* antigen observed in the deceased might be attributable to previous infection, not necessarily affecting the heart. Antibodies to *C. pneumoniae* are found in high prevalence in orienteers and in the Swedish population at large; hence, these antibodies have low predictive value. Another possibility is that the seroreactivity may implicate infection with other cross-reacting microorganisms (22, 23). In bacteria of the genus *Bartonellaceae*, such cross-reactions are well documented (48, 94, 119, 121, 146).

*Bartonella* (studies III and IV). DNA from the *gltA* (citrate synthase) gene of *Bartonella* was amplified from five cases of orienteers dying of cardiac dysfunction, i.e. four cases of SUCD and one case with cardiomyopathy with arrhythmias since many years (Table II). The positive samples were from the heart in cases 16, 19, 22, and 23, and from the lung in case 15. In addition, the hyperplastic thyroid gland tested positive in case 16. In case 19, the spleen and a mediastinal lymph gland tested positive as well. The amplicons were sequenced. The results were identical to *B. henselae* (Houston-1 isolate, ATCC 49882, Acc. no. L38987) in cases 16, 19, and 23 and close to *B. quintana* (Fuller strain, Acc. no. Z70014) in two cases (cases 15 and 22). In case 22, the amplicons presented deletions in two positions (#174 G replaced by A and #495 G replaced by T). The amplicons in case 15 had the same deletions, as well as two additional (#82 C replaced by T and #560 G replaced by A) deletions. Massive efforts to culture microorganisms from the tissues of the deceased (cases 15, 16, 19, 22 and 23) using available standard techniques for tissue culture and liquid or semisolid media were judged negative. Commensal bacteria could be cultured but were not considered significant. PCR testing with common primers for bacterial 16S rRNA also yielded multiple commensals.

Antibodies to *B. henselae*, *B. quintana*, and *B. elizabethae* were tested in the sera of the deceased (study III), as well as in the sera from the large group of elite orienteers (study IV). In four deceased cases in which *Bartonella* spp. DNA was detected in the tissues, antibodies to that particular *Bartonella* spp. were also noted. However, titers to *B. elizabethae* existed as well, and they were even higher. The seroprevalence of antibodies to *B. henselae*, *B. quintana*, and *B. elizabethae* was 3.0%, 1.4% and 31% respectively, in the 1,136 elite orienteers vs. 1.6%, 0.3%, and 6.8% in the 322 healthy blood donors used as controls. The difference between orienteers and controls in the seroprevalence to *B. elizabethae* was significant (*p*<0.001).

Different serotypes of *B. henselae* exist (47). It may be speculated that the observed precedence of *B. elizabethae* over *B. henselae* in the serology tests of the orienteers reflects antigenic differences between Swedish-European *Bartonella* strains and the American variants, but there are no other data to confirm this contention. *Bartonella* strains cultured from humans or animals in Sweden are urgently needed to shed light on this discrepancy and for use as antigens in future tests, including the present cases.

The orienteers that were tested for antibodies to *Bartonella* were also asked to complete a questionnaire on medical background, self-evaluation of health status, degree of exposure to animals/pets, history of tick bites, and travel abroad. No significant odds ratios were seen for any of the issues raised.
Other factors of possible importance
The deaths were mainly detected in the male elite group, and not in the much larger group of recreational orienteers of the same ages. This findings suggests that there may be one or several additional factors associated with elite orienteers that contribute to a fatal course. One such factor may be the high frequency of heavy, sustained physical training practiced by elite orienteers. Male elite orienteers have no breaks in training and competition during the entire year. Hence, it is quite probable that such extensive training impairs immune function (58, 92, 156). *Bartonella* infections often have a prolonged course (31), a course that might be altered in immunocompromized individuals, whereby latent/silent infections could become symptomatic (95, 96, 122, 154). In cats, co-infection of *B. henselae* and feline immunodeficiency virus is associated with gingivitis and lymphadenopathy (178). Furthermore, other concurrent infections could be involved in altering the course of *Bartonella* infections (194).

Orienteers tend to train and compete even in poor health because they understand that navigating skills of a top performer can compensate for a temporarily impaired physical performance. Finally, because elite orienteers frequently visit other countries, it is probable that they are exposed to organisms not endemic to their country.

Attempts to intervene in the course of events
In 1992, two more prospective cases of SUCD occurred in elite orienteers. The SOFT physicians had identified the first case six months earlier when syncope occurred during jogging. He had no further symptoms. We evaluated the clinical condition in May 1992 as part of an ongoing cardiac investigation when he suddenly died in June 1992. The other orienteer had answered a questionnaire sent to 215 elite orienteers, indicating that he was in good health and suffered no heart-related symptoms. Three months later, he succumbed to SUCD. Because an increased death rate seemed obvious and because the actions taken thus far proved inadequate, a decision was thereafter taken together with the SOFT to intervene more aggressively than was done previously. One of these measures included discontinuing all competition in the elite classes for a 6-month period starting in November 1992. This maneuver was implemented in order to alter the behavior of the elite orienteer, as well as to provide a few months of much needed rest to allow "self-healing" of a possible myocardial process. This measure was seen as exceedingly important in that daily strenuous exercise without adequate resting periods during the year may alter immune responses unfavorable. The same measure proved highly effective in ending an epidemic of jaundice in Swedish orienteers in the 1960s. The etiology of hepatitis B virus was revealed 10 years later when it first became possible to test archival serum specimens for HBsAg (158). Hepatitis B virus spread through scratches from vegetation when the participants washed up together after racing events. A second measure was implemented to help orienteers learn to become more sensitive to symptoms associated with illness. Orienteers tend to train and compete even when having a mild viral infection or feeling sickly. This comes from an old tradition within the sport to "always be there" for the team, in addition to the belief that superior navigation through the terrain may compensate for reduced physical performance. Consequently, a massive campaign was set in motion based on the simple message "listen to the signals from your body and refrain from training and competition when you feel poorly." A third measure undertaken was to advocate treatment of ranked orienteers in 1992-1993 with doxycycline on wide indications. This was implemented by sending personal newsletters to the orienteers and to physicians practicing infectious diseases, cardiology, internal medicine or primary care. Together with the attention given in the media, this resulted in an explicit demand by many orienteers to receive doxycycline treatment. This third measure, in conjunction with the mass media, also
had the effect of increasing doctors' willingness to prescribe this treatment. The rational for this form of care was not only the early results on *Chlamydia pneumoniae* (186, 187), but also a suspicion that vector-borne bacteria belonging to the alpha-proteobacteria could be implicated. In Sweden, tick-borne ehrlichiosis of the granulocytic type has been a known illness in dogs and horses for many years (86). Furthermore, we set out to look for rickettsiae in Swedish ticks and found *R. helvetica* (136); moreover, we later identified a previously unknown alpha-proteobacterium in the blood and pericardial fluid of a male hunter suffering from multiorgan disease, including myopericarditis with arrhythmias (21). Researchers have subsequently detected closely related strains, as well as *Bartonella*, in dogs with cardiac arrhythmias, endocarditis or myocarditis (24). We also considered *Bartonella (Rochalimaea)*, but diagnostic methods were not readily available in 1992-1993. Wide prescription of doxycycline or macrolides might have had an effect comparable to that of mass vaccination in altering the course of disease. Such a course of action could have resulted in at least a temporary halt to the rise in the SUCD rate. Similar mass treatment for infections by another alpha-proteobacterium (i.e. *Rickettsia prowazekii*) using only one dose of doxycycline was implemented in the recent outbreak of louse borne typhus in Burundi (147). A fourth preventive measure that was undertaken is related to the general attention that has been focused on orienteers and SUCD since 1992. Because of the relentless attention of the Swedish Orienteering Federation and media to the SUCD occurrences in 1992-1993, we believe that this general alertness has led to an increase in orienteers seeking medical advice. Moreover, physicians are more inclined to maintain a close observation on patients who are orienteers and give special attention to cardiac symptoms in the young.

**No data to support way of transmission of Bartonella to orienteers**

*Bartonella* infection is a zoonosis associated with cats, rodents and arthropods serving as vectors, where the mode of transmission may be sought in the intimate relation to wildlife typical of orienteering and, as in a previous hepatitis B epidemic in orienteers, parenteral transmission between persons may be evident. The study includes no data on transmission, however.

The 31% seropositivity to *B. elizabethae* among elite orienteers (123) indicates a widespread exposition to that agent, or to cross-reacting infectious agents. Little is known on the prevalence of antibodies to *B. elizabethae* in other populations. In 630 inner-city intravenous drug users from Baltimore, MD in which 80% are HIV positive, the seroprevalence was 33% in comparison with 15% in healthy blood donors from Seattle, WA (38). Epidemic spread of parenterally transmissible infections, such as hepatitis B, has been documented in orienteers and homeless persons (the latter group are often drug users) (5, 158). There is evidence that the state of being homeless is a significant risk factor for *B. quintana* infection (28, 97). Homelessness was reported in 44% of the drug users cited above. Both orienteers and people who are homeless frequently visit places usually inhabited by wild animals and their ectoparasites. *B. elizabethae* has only been associated with human disease in one case of endocarditis (44) but has recently been isolated from sewer rats (*Rattus norvegicus*) captured in urban Baltimore and other places (39, 54). It is noteworthy that the genetically related variant *B. tribocorum* have also recently been isolated from wild rats (e.g., *Rattus norvegicus*) (76). In addition to having antibodies to *Bartonella* spp., 16% of the Baltimore drug users had antibodies to *Rickettsia akari*, a spotted fever rickettsia, which is associated with urban rodents and their bloodsucking mites (*Liponyssoides sanguineus*). It may be speculated that blood sucking arthropods, including ticks (110,
(Ixodes ricinus in Sweden), fleas, lice, or mites dwelling on rodents or in their surroundings or even others, such as mosquitoes or deer keds (Lipoptena cervi), may transmit Bartonella to orienteers. Both zoonotic/vector-borne and parenteral man-to-man transmission of Bartonella may exist in parallel and contribute to high prevalence within the group.

Questions raised for further investigations
• The present data justifies further surveillance of orienteers with reference to cardiac death and those having symptoms suggestive of arrhythmias, especially in the elite orienteer.
• The development of a database monitoring all deaths in orienteers by coordination with the Swedish cause-of-death register is urgently recommended.
• Further investigation in individual deaths that occur is indicated.
• Fast identification, preferably within 24 hours, of future SUCD cases is necessary for relevant microbiological testing.
• The collection of sera from orienteers for reference purposes in individual cases, as well as for epidemiological reasons is desirable.
• Orienteers and other persons having cardiomyopathy compatible with ARVC merit microbiological testing especially for Bartonella spp.
SUMMARY
A 20 to 40 fold increased incidence of SUCD was found in Swedish male elite orienteers 18 to 35 years of age from 1979 to 1992. The incidence was 30 SUCD cases per 100,000 person years. A re-evaluation of the autopsies and clinical histories demonstrated subacute myocarditis in 75% of the cases, which in some mimicked arrhythmogenic right ventricular cardiomyopathy. Advanced fibrofatty replacement and inflammatory lesions were seen predisposing for malignant arrhythmias. Concurrent changes in the thyroid gland were observed in three cases. Initially, an association to Chlamydia pneumoniae infection was indicated, but further investigations suggested chronic or relapsing Bartonella infection to be an important pathogenetic factor for development of electric instability in the hearts. DNA sequences from the gltA (citrate synthase) gene of Bartonella spp., were amplified by PCR from the hearts of four of five cases of cardiac death in orienteers and from the lung in a fifth case. In one case, the hyperplastic thyroid gland tested positive as well. The sequences were identical to B. henselae (Houston-1 isolate) in three cases and close to B. quintana (Fuller-strain) in two cases. Four of the five cases revealed antibodies to Bartonella, with the titers being higher for B. elizabethae, than for B. henselae or B. quintana. Two elite orienteers diagnosed with malignant arrhythmias and suggestive ARVC had antibodies to Bartonella spp. Testing of antibodies to B. elizabethae, B. henselae, and B. quintana was positive in 31% of 1,136 ranked orienteers, as compared with 6.8% in 322 healthy blood donors (p<0.001).

It is hypothesized that Bartonella infection is an important factor in the pathogenesis of inflammatory cardiomyopathy (myocarditis) and ARVC-like disease in orienteers succumbing to SUCD. The deaths were chiefly detected in the male elite group as opposed to the much larger group of recreational orienteers of the same ages. Symptomatic Bartonella infection has an altered clinical spectrum in the immunocompromised, which explains why immunomodulation by high intensity training without resting periods may be a co-factor. Bartonella infection is a zoonosis associated with cats, rodents and arthropods serving as vectors, where the mode of transmission may be sought in the intimate relation to wildlife typical of orienteering. As in a previous hepatitis B epidemic in orienteers, parenteral transmission between persons may be evident. It is also concluded that SUCD of the same type was evidenced in orienteers 35 years or older, but the occurrence is concealed in the mortality from ischemic heart disease.
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A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series *Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine*. (Prior to July, 1985, the series was published under the title "Abstracts of Uppsala Dissertations from the Faculty of Medicine.")