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Out of Hospital Sudden Cardiac Death Among Physically Active and Inactive Married Persons Younger than 65 Years in Slovenia

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Methods: A sedentary life style has been shown to increase the risk of coronary artery disease, a precursor of sudden cardiac death, while regular physical activity prevents atherosclerosis. In an out of hospital cardiac death study in Slovenia, case crossover design was used to investigate physical activity as a potential trigger of sudden cardiac death in connection with certain life style, biological and social risk factors.

Results: In the study, 206 sudden cardiac deaths were selected: 166 men and 40 women with median age at death 57.8 and 59.0 years, respectively. The relative risk of dying during or within one hour after terminating physical activity of at least 6 metabolic equivalents was 3.0 in comparison to time without activity. The relative risk of people who performed 1.5 hours or more physical activity per week was 2.55 (95 % confidence limits: 1.69–3.84), opposed to 49.90 (confidence limits: 18.73–132.96) for persons who performed less activity. According to the observed characteristics the risk of dying for inactive sudden cardiac victims was 17.13 to 25.89 (95 % confidence limits: 11.28–44.60) times higher in comparison to physically active persons. Persons who drank more than 4 international units of alcohol per day, positive family history, ischaemic heart disease and a heart rate of more than 90 beats/minute had the highest risk.

Conclusion: The results confirmed that the risk of dying due to sudden cardiac death during physical activity depends on the degree of physical activity regularly performed and the existing risk factors. *J Clin Basic Cardiol 2003; 6: 63–7.*

Key words: out of hospital, sudden cardiac death, case crossover design, physical activity, triggering factors, married persons

Diseases of the circulatory system are the most frequent cause of death in the Western world, and among them sudden cardiac death (SCD) is a significant public health problem. Approximately 12 % of all natural deaths occur suddenly, and 88 % of them are of cardiac origin [1–3].

The risk factors associated with SCD are the same as those with coronary artery disease (CAD) [4]. Among them, sedentary life style has consistently been shown to increase the risk of CAD [5], while on the other hand regular physical activity plays a role in both primary and secondary prevention of atherosclerotic vascular processes. Exercise increases cardiovascular functional capacity and through affecting autonomic nervous system, by increasing vagal activity [6], decreases myocardial oxygen demands [7–9]. At the same time heavy physical exertion sometimes immediately precedes and indeed appears to trigger the onset of acute myocardial infarction [5, 10].

In the section "Out of Hospital SCD research among persons younger than 65 years in Slovenia", we tried to determine the risk of dying during or within an hour after terminating physical activity of 6 metabolic equivalents (MET) or more among physically active and inactive persons. In both groups we also looked at the risk of triggering SCD according to various characteristics of the deceased.

Methods

Study Design

Case crossover study design [11] was used to assess the effect of 6 or more MET physical activity – measured according to the Physical Activity Rating Scale [12] – on triggering SCD. A one-hour hazard period immediately before the onset of SCD was compared to the total hazard period in the last year of life computed on the basis of the usual frequency approach [11, 13]. Cases were deceased subjects who died due to sudden cardiac death during or within an hour after terminating defined physical activity, and controls were persons who also died due to SCD, but during a time of less or no physical activity.

Study Population

The study population was selected on the basis of underlying cause of death from the Death Register of Slovenia. Cases were residents of the Republic Slovenia in the year 2000 and in the first months of 2001 who died out of hospital due to cardiac disease, and were between 20 and 65 years old at the moment of death.

Data were obtained through two questionnaires. The first was sent to family members and the second to the attending physician of the deceased. Only married persons were included in the study because risk behaviour, usual annual frequency data and also the profile of risk behaviour in the last 24 hours of the deceased's life were needed. We further divided cases into SCD victims and expected deaths. SCD was defined as an instantaneous death or a death within an hour after the onset of cardiac symptoms. When family members were not able to or did not decide whether their relative had died according to the definition of suddenly or not, we also considered the death as sudden when the deceased person could perform physical activity of at least 3 MET on the very last day of his/her life or if SCD was written on any part of the death certificate. We supposed that an individual who could perform very light exertion such as personal care or strolling in the park was not expected to die on the same day. This last criterion was also used for persons who died during night sleeping.

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Cases were those SCD victims who had died during or within an hour after termination of at least 6 MET physical activity, in comparison to controls who also had died of sudden cardiac death but not during heavy physical activity or within an hour after its termination. Physically active were those SCD victims who performed physical activity of 6 MET or more at least 1.5 hours a week (78 hours per year), as opposed to inactive ones who performed less physical activity of equivalent degree. All subjects were also divided into four classes according to frequency of physical activity performed per week.

Chronic stress was defined as retirement or dismissal from employment in the last year of life or serious disease or death of a close family member in the same time period [14]. On the basis of alcoholic beverages usually consumed per day or per week, the quantity of alcohol consumption measured in international units (IU) was divided into four classes, as can be seen in Table 1.

If immediate relatives died, or survived myocardial infarction or died from SCD before the age of 70, the deceased had a positive family history. Suspected CAD was defined as unclear signs of ischaemia on the electrocardiogram (ECG), but when clear signs of ischaemia on the ECG or medically certified coronary disease were found, CAD was defined as confirmed.

As a criterion for medicine currently taken which could influence the triggering of SCD, we chose those drugs which spouses reported that the deceased had been taking them in the last month of their life and not those just prescribed by a medical doctor.

Table 1. Physically active persons; relative risk of onset of sudden cardiac death during or within an hour after terminating physical activity of 6 MET, according to characteristics of SCD victims; (95 % CI)

Characteristic	Number of SCD victims (127)	Number of deaths during or within one hour after physical activity (23)	Relative risk (95% CI)
Demographic determinants			
Male	111	20	2.43 (1.57–3.77)
Female	16	3	3.85 (1.24–11.94)
Life style characteristics			
0–1 IU alcohol/week	19	4	7.09 (2.66–18.89)
2–6 IU alcohol/week	21	3	1.89 (0.61–5.86)
1–3 IU alcohol/day	41	5	1.49 (0.62–3.58)
≥ 4 IU alcohol/day	29	8	3.46 (1.73–6.92)
Body mass index > 25	102	19	2.70 (1.72–4.23)
Stress yes	52	11	3.00 (1.66–5.42)
Stress no	73	11	2.08 (1.15–3.76)
Ischaemic heart disease and family history			
Family history positive	40	8	3.69 (1.85–7.38)
Family history negative	71	10	1.70 (0.91–3.16)
Suspected or confirmed IHD by clinical signs	10	5	3.08 (0.99–9.55)
IHD confirmed by *post mortem*	32	7	3.94 (1.88–8.17)
Circulatory and biochemical parameters			
Heart beat/minute > 89	9	3	4.86 (1.57–15.07)
Systolic blood pressure > 139 mmHg	61	10	2.52 (1.36–4.68)
Diastolic pressure > 95 mm Hg	39	6	2.22 (1.00–4.94)
Cholesterol > 5 mmol/l	27	6	2.93 (1.32–6.52)
Triglycerides > 1.8 mmol/l	18	4	2.86 (1.07–7.62)
Drugs			
No acetylsalicylic acid or other anticoagulant drugs	89	17	2.59 (1.61–4.17)
No beta receptor blocking agents or amiodarone	41	9	3.65 (1.85–6.84)
No ACE inhibiting drugs	88	16	2.45 (1.50–4.00)
No hypolipaemic drugs	98	19	2.43 (1.55–3.81)

Questionnaire

In the period from one to three months after death, data were collected by mailing the questionnaire to spouses of the deceased and to the attending physician.

Closed type questions were used with detailed instructions for filling in the questionnaire. Before each question dealing with coffee drinking, cigarette smoking, physical activity or alcohol consumption in the last 24 hours of deceased life, and for this purpose requiring the filling in of a time line, a similar event was chosen from everyday life, and written down as an example.

Data on premonitory signs or symptoms of death, life style, physical activity, medical and family history, eventual medication and stressful events were collected from the spouses. The frequency and duration of physical activity (from night sleeping to extreme exertion) [5] in the last year before death were also collected. A detailed description of the level of physical activity in the last 24 hours before death, in two hour intervals, was required to be indicated on the time line. Interviewed spouses did not know the exact topic being researched (SCD); they only knew that cardiovascular diseases were the subject of the study.

In case we did not receive a response within the three week period, another request for participation was mailed to the same address. If the response did not follow despite the second request, the case was considered to be non-respondent. The attending physician was asked for data on the haemodynamic and biochemical parameters of the deceased and some health issues. Before data were entered into the data base, the questionnaires were checked by the study coordinator and coded by professional coders. The protocol of the research was approved by the Ethics Committee at the Ministry of Health of the Republic Slovenia, and all interviewed persons received a letter in which their rights concerning data protection and non-participation in the research were stated.

Statistical Analysis

The risk of SCD due to heavy physical activity during physical activity and in the one-hour hazard period immediately before death was calculated. To estimate the relative risk, the ratio of the observed frequency of deaths during the hazard period to the expected frequency from the information on the control period was used. The amount of person time spent in heavy physical activity (hazardous person time) was estimated by usual annual frequency

and duration of physical activity. Unexposed person time was calculated by subtracting the hazard period in hours from the number of hours in a year. The ratio of observed non-exposed hours to expected exposed hours was calculated with confidence intervals (CI) [11]. The calculated ratio reflects the risk of becoming an SCD victim during a period of heavy physical activity or within one hour after terminating it in comparison to the risk during lighter or no activity.

Relative risk was calculated only for those variables which at least three or more deceased persons had while performing heavy physical activity. The data were processed on personal computer using the SPSS.10 for Windows and Excel 97 statistical packages.

Results

276 responses out of 376 mailed questionnaires were received from widowed spouses, giving a 73.4 % response rate. Among the 276 responses, 238 SCD were evidenced; 193 men and 45 women with median age at death of 57.5 years (50.8 and 62.2 in 5 % and 75 %) in male and 58.4 years (53.8 and 61.0) in female. Among the 238 SCD evidenced we received 206 responses on the degree of physical activity performed in the last year of the deceased's life, ie hours per day and the frequency of physical activity per week. The same number of responses, ie 86.6 % were obtained for the number of hours before death when deceased was physically active 6 or more MET.

The highest physical activity level that SCD victims were able to perform within the last 24 hours of their life was distributed over a range from sitting and carrying out normal easy tasks to extreme exertion such as exhaustive work or high-activity sports (Figure 1).

We found a three-times higher relative risk of dying during or within an hour after terminating physical activity in comparison to time with no exertion when we looked at all SCD victims together. For physically active SCD victims relative risk was about 18 % lower than that of the entire SCD victims population, but for inactive persons it was about 17-times higher (Table 2).

The majority of characteristic-specific relative risks in physically active persons lay within the 95 % confidence limits of the calculated total relative risk. Everyday physical activity approached the lower confidence limit and close to the upper one were female gender, drinking more than 4 IU of alcohol per day, positive family history and cardiac or antihypertensive therapy without beta receptor blocking agents or amiodarone.

At the highest risk of dying during physical activity, looking only at weekly hours of physical activity, were people who performed less than everyday physical activity, persons who did not drink alcohol or drank only one unit per week, those with heart frequency more than 90 beats per minute and persons whose *post mortem* examination confirmed CAD. The relative risk of triggering SCD during physical activity increased as the level of physical activity decreased. A U-shaped curve was observed between the risk of dying during physical activity and amount of alcohol drunk per day. High chronic stress elevated the risk of dying during physical activity by 44 % (Table 1).

Our analysis was limited by a small number of inactive persons who died during or within an hour after terminating physical activity. Among them the risk of dying during vigorous physical activity was from 17.13 to 25.89 (95 % CI: 11.28–44.6) times higher in comparison to those who were physically active. At the highest risk were persons who did not use prescribed acetylsalicylic acid or other anticoagulant drugs or hypolipaemic drugs 26.89 (CI: 16.21–44.60) and at the lowest were those with a body mass index (BMI) of more than 25 kg/m^2 (Table 3).

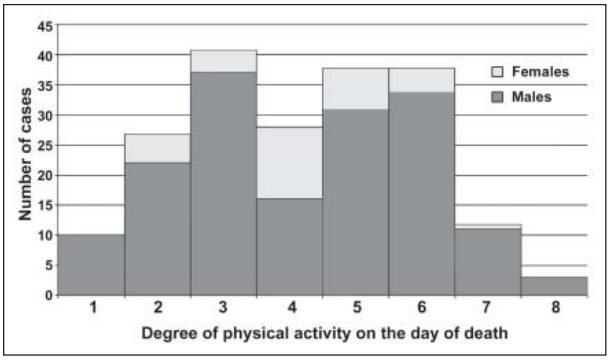

Figure 1. Highest level of physical exertion (Physical Activity Rating Scale) performed by sudden cardiac death victims on the day of death by gender (1: sitting or lying awake; 2: sitting performing easy tasks; 3: very light; 4: light exertion with normal breathing; 5: moderate exertion with deep breathing; 6: vigorous exertion with panting, overheating; 7: heavy exertion with gasping, much sweating; 8: extreme or peak exertion)

Table 2. Relative risk of onset of sudden cardiac death (SCD) during or within an hour after terminating physical activity of 6 MET, all SCD victims, physically active and inactive persons

Characteristic	Number of SCD victims	Number of deaths during or within one hour after physical activity	Relative risk (95% CI)
All	206	27	3.00 (2.06–4.37)
Physically active (> 78 hrs/year)	127	23	2.55 (1.69–3.84)
Physically inactive	79	4	49.90 (18.73–132.96)
Physically active			
7 times/week	64	13	1.70 (0.99–6.70)
3–4 times/week	38	7	5.62 (2.68–11.79)
1–2 times/week	40	3	6.93 (2.24–21.49)
Less than once/week	73	4	51.44 (19.31–137.06)

Table 3. Physically inactive persons. Relative risk of onset of sudden cardiac death during or within one hour after terminating physical activity of 6 MET, according to characteristics of SCD victims

Characteristic	Number of SCD victims (79)	Number of deaths during or within one hour after physical activity (4)	Relative risk (95% CI)
Socio-economic and demographic determinants			
Male	55	3	49.06 (15.82–152.12)
Stress no	48	3	46.29 (14.93–143.53)
Life style characteristics			
Body mass index > 25	59	3	46.24 (14.91–143.37)
Ischaemic heart disease and family history			
Ischaemic heart disease as an underlying cause of death	48	4	62.80 (23.57–167.32)
Drugs			
No acetylsalicylic acid or other anticoagulant drugs	44	3	65.62 (21.16–203.46)
No hypolipaemic drugs	67	4	62.91 (23.61–197.62)

Discussion

SCD is a special life situation [15] and close family members of SCD victims get over it in very different ways. According to our experience, some of them are willing to talk about the terms and circumstances surrounding this stressful event but others are not. Such a major shock had occurred that some could not concentrate their thoughts and were able to recall particular details of the day of the death of their loved one only a few months later, but others could explain every particular detail at any time. After consultation with a doctor working at a hospice and another one researching mourning due to suicides, we decided to collect data from one to three months after sudden death.

The (in our opinion) good (73.4 %) response rate was the consequence of strong emotions and tensions of the widowed spouses. Possible questions of guilt due to potential missing or overlooking of important signs or symptoms of disease ending with sudden death could also have played a part. We did not insist on 100 % responses to every particular question because the respondents might not know, not remember or not want to respond to some questions which contained unpleasant content for them. Non-participation was due to personal reasons, connected with negative emotions to the research, not knowing the answers to numerous questions or simply no response after the second request. In our country people are not used to participating in research as interviews, especially not in medical epidemiology research.

We classified data on the amount of regular physical activity performed into two categories. Those deceased who performed at least 78 hours of 6 MET physical activity per year were assigned to the first one, those who performed less to the second. We decided to make such broad categories in order to minimise misclassification concerning frequency and duration of deceased physical activity, due to proxy respondents. Physical activity in terms of sports activity or free time engagement is becoming popular as a way of life which can protect health, slow down the course of some illnesses and will help after injury or disease [7]. At the same time physical activity was described as a triggering factor for acute myocardial infarction or SCD [5, 8, 9, 16, 17]. Paterson assigned triggering SCD during extreme physical activity to abnormal regulation of electrolyte and cardiac sympathovagal balance which could increase the incidence of arrhythmia, especially in connection with underlying ischaemia [18].

According to our results SCD victims had a 3-times higher relative risk of dying during or within an hour after terminating physical activity than in periods without activity, and sufficiently physically active persons had a 19.6 times lower relative risk of dying due to SCD during physical activity than those who were not sufficiently active.

In their study on the effect of physical activity on the incidence of SCD, Bartels et al. [19] found the relative risk during highly strenuous physical activity compared to inactivity to be 150 in the sedentary group as opposed to 4.0 in the most active group. Our results showed lower risk in contrast to Bartels. Possible explanation could be different grade of physical activity performed in two groups. Inactive persons in our research performed either no or a few hours of recommended physical activity; we did not include only the sedentary group as Bartels did. Our results are in accordance with the Seattle study where a relative risk of 56 was found during vigorous activity of married men with a low level of habitual physical activity in comparison to 5 for men with a high level of habitual activity [20]. We confirmed the thesis that physical activity could trigger SCD. An increasing level of habitual physical activity was associated with a progressively lower relative risk of SCD, a type of dose response, the same observation as Mittleman found for triggering acute myocardial infarction [5]. The difference in the number of physically active subjects in the categories less or more than 78 hours per year opposed to frequency per week comes from the smaller number of answers assigned to specify hours of physical activity performed per week which we needed to calculate the product hours per year than frequency per week.

Being female appeared to be riskier for becoming a victim of SCD during intensive physical activity in spite of the same level of recommended health protective physical activity performed annually. There are some morphological and functional adaptations in the anatomy and physiology of the female body which could play a special role not only in pregnancy and childbearing but also in CAD onset in women. Women's cardiovascular system is designed to adapt to the extraordinary demands of pregnancy and childbirth by modifying diastolic cardiac reserve more than systolic [21]. Because of the above mentioned adaptations, there is a question as to what extent the female heart is able to compensate, by means of sympathetic stimulation [22], for the acute extra demands that physical activity no doubt places on it. In the ATRAMI study [6] it was found that depressed baroreceptor stimulation (BRS) and heart rate variability (HRV) were associated with female sex. This finding supported the thesis that low BRS contributes to high risk of cardiac mortality after myocardial infarction. Obesity [23], diabetes [19], tobacco use and alcoholism [24] are known as risk factors, a higher level of which are more predictive for sudden cardiac death in females than in males.

Different extrinsic stimuli may cause similar physiological changes that subsequently lead to acute pathologic events [10]. Depression has been found to be associated with elevated sympathetic tone and decreased vagal tone [10, 25]. This may partly explain the higher relative risk of SCD among those who had experienced prolonged stress in the last year of their life such as illness or death of a close family member or retirement or dismissal from their job.

Heavy drinking increases the risk of SCD [26] with fatal arrhythmia as the most likely mechanism. Subclinical heart muscle injury and hyperadrenergic state, electrolyte abnormalities, impaired vagal heart rate control, repolarisation abnormalities with prolonged QT interval and worsening of myocardial ischaemia or sleep apnoea may also contribute [27]. We did not observe linear dose response in the risk of SCD for physical activity and amount of alcohol consumed per day, but a U-shaped curve linked the relative risk of sudden cardiac death during physical activity and increasing amount of alcohol consumed per day. A similar U-shaped curve was described for alcohol consumption and SCD risk by Albert [28]. We tried to explain the seemingly paradoxical situation that people who did not drink alcohol or drank it rarely had a higher relative risk of dying during physical activity than those persons who drank four or more units of alcohol per day. In addition to not drinking alcohol as a consequence of various illnesses, underreporting of alcohol consumption due to abstention or misclassification by respondents into occasional, regular, ex or never drinkers could play a part.

Taking beta receptor blocking drugs or amiodarone appeared to be some kind of protection against sudden cardiac death during physical activity. We found that persons who were not taking these drugs and at the same time performed sufficient regular physical activity had the highest risk of dying during physical activity than physically active persons who were taking these drugs. We ascribed this to the fact that 91 % of SCD victims had had at least one of the major risk factors for coronary artery disease or CAD had

already been present with them. The antiarrhythmic properties of beta receptor blocking agents possibly reduce the occurrence of severe arrhythmia in some patients with diuretic induced electrolyte depletion and may prevent adrenaline mediated intracellular loss of potassium during cardiac ischaemia [29]. Because of the low number of patients in our analysis who had been prescribed beta blocking agents, we did not separate different indications for beta blocking agents. We could not determine whether not taking beta blocking agents in the case of hypertensive heart or other heart disease increased the risk of dying during physical activity.

Our results, whereupon persons who drink more than 4 IU of alcohol per day, had a positive family history, persons with ischaemic heart disease confirmed by *post mortem* examination and persons with a heart rate of more than 90 beats per minute had the highest risk of dying during physical activity are similar to the most important risk factors for sudden cardiac death described in the Paris study [4]. We calculated the relative risk of dying during physical activity according to the characteristics of the deceased one by one, and we did not examine the interrelations between different characteristics.

Among the SCD victims there were far fewer inactive people who died during hard physical activity then active ones, so we could calculate a relative risk among active as opposed to inactive persons only for a small number of variables. We are continuing our research in order to strengthen our present results and to find other interdependencies between the researched variables.

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