



Původní sdělení | Original research article

Sudden cardiac death in children and young adults – epidemiology and prevention

Peter Kubuš, Jan Janoušek

Dětské kardiocentrum, Fakultní nemocnice Motol, Praha, Česká republika

INFORMACE O ČLÁNKU

Historie článku:

Došel do redakce: 24. 4. 2012

Přijat: 30. 5. 2012

Publikován online: 14. 6. 2012

Keywords:

Children

Preparticipation screening

Sudden cardiac death

Klíčová slova:

Děti

Náhlá srdeční smrt

Preparticipační screening

ABSTRACT

Sudden cardiac death is a rare but catastrophic event in children and young adults (< 35 years) with the incidence ranging between 0.8 and 2.8/100 000 person-years. Considering the frequent genetic background of potentially lethal cardiovascular disease in these patients, all attempts should be made to determine the risk for remaining family members. A population-based approach consists of screening young individuals being at higher risk (e.g. athletes) for potentially lethal cardiovascular disorders. The following text will analyse the efficacy of both approaches using currently available data.

SOUHRN

V populaci dětí a mladých dospělých do 35 let věku je náhlá srdeční smrt vzácnou příhodou s četností 0,8–2,8 na 100 000 osobo-roků. Při častém genetickém podkladu jednotlivých potenciálně život ohrožujících onemocnění v této věkové kategorii však zasluhuje maximální pozornost s ohledem na posouzení rizika nejen postiženého, ale i členů jeho rodiny. Snahy o aktivní vyhledávání rizikových jedinců v určitých skupinách (zejména lidé provozující kompetitivní sportovní aktivity) vycházejí z předpokladu, že řada z těchto onemocnění je u dosud asymptomatických jedinců identifikovatelná jednoduchými a pro screening vhodnými vyšetřovacími metodami. V následujícím textu rozebereme účinnost obou přístupů za použití dostupných literárních údajů.

© 2012, ČKS. Published by Elsevier Urban and Partner Sp. z o.o. All rights reserved.

Introduction

Sudden cardiac death (SCD) is a natural death from cardiac causes, heralded by abrupt loss of consciousness within one hour of the onset of acute symptoms [1]. Sudden death of a child and young adult is a tragedy for the rest of his or her family. Considering frequent genetic basis of conditions leading to SCD in the young [2–5] it is of great importance to examine the rest of the family for the presence of a potentially life threatening cardiac disease. The aim of this article is to summarize our current knowledge of the epidemiology and prevention of SCD in children and young adults, focusing on two different

strategies: family risk assessment and screening for persons at risk in the general population.

Epidemiology

The incidence of SCD in children and young adults (< 35 years) varies, according to the literature, between 0.8 and 2.8/100 000 person-years [6]. Ischaemic heart disease and dilated cardiomyopathy is the most common cause of SCD in the elderly population. On the contrary, inherited or congenital cardiovascular disorders are the main cause of SCD in children and young adults [7]. The athletes participating in competitive sports, requiring systematic

Adresa: MUDr. Peter Kubuš, Dětské kardiocentrum, Fakultní nemocnice Motol, V Úvalu 84, 150 06 Praha, e-mail: peter.kubus@lfmotol.cuni.cz

DOI: 10.1016/j.crvasa.2012.05.015

training and regular competition against others, are particularly at higher risk of SCD [8,9].

In 1988 Thiene et al. have published the study of 60 persons (< 35 years) who had died suddenly in the Veneto region (Italy) [10]. They found morphologic features of right ventricular cardiomyopathy (ARVC) in 12 of them. The authors suggested that ARVC might have been more frequent than previously thought and represented an important cause of sudden death in the young. A systematic nationwide pre-participation screening of young competitive athletes was introduced in Italy in 1982. In addition to the personal history and physical examination, 12-lead ECG has been included. The aim was to identify the asymptomatic athletes with a potentially lethal cardiovascular disorder and to prevent SCD through the disqualification from the competitive sport activities in individuals at risk. In a population-based study, Corrado et al. have evaluated the impact of this screening by analysis of the trends in incidence rates and cardiovascular causes of SCD [11]. They focused on athletic and non-athletic population, aged between 12 and 35 years, in the Veneto region (period 1979–2004). A parallel study examined trends in cardiovascular causes of disqualification from competitive sports in 42,386 athletes undergoing preparticipation screening in Center for Sports Medicine in Padua. The annual incidence in athletes decreased from 3.6/100 000 person-years in 1979–1980 (before the screening period) to 0.4/100 000 person-years in period 2003–2004. The incidence of SCD in the unscreened non-athletic population did not change significantly (0.77 and 0.81/100 000 person-years, respectively). The decrease in mortality was due mainly to the reduction of SCD from cardiomyopathies, which were the most common cause of SCD (followed by coronary artery disease, myocarditis, cardiac conduction disease, congenital coronary anomalies and mitral valve prolapse). Potentially inaccurate estimation of a true incidence of SCD, related to a relatively short pre-screening period, was the main limitation of the study.

Using targeted retrospective searches from various sources, Maron et al. have identified 1,866 athletes from the USA (mean age 19 ± 6 years), who had died suddenly or survived a cardiac arrest in the period between 1980 and 2006 [12]. Sudden death due to cardiovascular disease was probably or definitely found in 1,049 (56%). Of these, 690 deaths could be reliably (and other 359 most likely) attributed to cardiovascular disease. The incidence of sudden death in these individuals (estimated population of 10.7 million athletes aged < 39 years in the USA) was 0.61/100 000 person-years. The absolute number of sudden deaths due to cardiovascular causes was < 100 per year in this population. The authors proposed the introduction of a systematic mandatory national reporting system for SCD in young competitive athletes. Among 690 SCD, hypertrophic cardiomyopathy was the most common cardiovascular cause of sudden death (36%), followed by coronary artery anomalies of wrong sinus origin (17%), possible evidence for hypertrophic cardiomyopathy at autopsy with mildly increased left ventricular wall thickness (8%), myocarditis (6%), ARVC (4%), ion channelopathies (4%), mitral valve prolapse (4%), coronary artery disease, aortic rupture, aortic stenosis, dilated cardiomyopathy and Wolff-Parkinson-White syn-

drome. Among 1,049 cases of probable or definite cardiovascular death, 65% were < 17 years of age, 29% were between 18 and 25 years, 7% were 26 and older. Male athletes represented 89% of cases of sudden cardiovascular death, but the proportion of females has increased to 12% in the period 2000–2006. Despite the absence of ECG as a part of the pre-participation screening in the USA (only personal history and physical examination were used), the study showed a relatively low number of cardiovascular sudden deaths in young athletes, which is in clear contrast with findings of Italian study in the pre-screening period [11].

In a population-based study (2010), Winkel et al. have evaluated the incidence of SCD in all death persons aged 1–35 years in Denmark (5.38 million inhabitants) in the period 2000–2006 [13]. They identified 625 cases of sudden unexpected death (10% of all deaths). Of the 469 autopsied cases, SCD was attributed to 314 (67%), with histopathology performed in 96% of them. The incidence of SCD was 1.9/100 000 person-years (2.8/100 000 after including non-autopsied cases of sudden unexpected deaths, which corresponds to 7% of all deaths in persons aged 1–35 years), thus higher than previously reported in a general population. The median age of the SCD population was 29 years and the risk of SCD was more than 10 times higher for persons aged 30–35 years, compared to persons aged 1–10 years. Male gender was present in 67% of the SCD cases and there was no difference in age distribution between males and females. Of the SCD group, 61% had no previous medical history. Death occurred in awake resting state in 50%, during sleep in 34% and during moderate to high intensity activity including sport in 11% of the cases. Of the 314 autopsied persons suffering from SCD, ischaemic heart disease was the cause of death in 13%, myocarditis in 7%, thoracic aortic dissection in 7%, hypertrophic cardiomyopathy in 6% and ARVC in 5%. Sudden unexplained cardiac death represented the remaining 43%. The authors suggested that a relevant part of these deaths could have been attributed to primary electrical disease.

Steinvil et al. have analysed the impact of the mandatory pre-participation screening of competitive athletes, enacted in 1997 in Israel [14]. The resting and exercise ECG was included in the screening programme. They compared the number of documented sudden death or cardiac arrest in the pre-screening and mandatory screening period (1985–1997 and 1997–2009, respectively), based on a systematic search of the two main newspapers in Israel. The difference in the average yearly incidence of sudden death or cardiac arrest in pre-screening and screening period was not significant (2.54 and 2.66/100 000 person-years, respectively). The method of data collection (uncertain number of cardiac events and a rough estimation of the population of competitive athletes) was the main limitation of this study based on observational data and retrospective analysis.

Prevention

Using the data of Winkel et al. [13], we may expect about 140 cases of SCD per year in the population aged

1–35 years in the Czech Republic (or 100 cases based on their data of autopsied cases). Taking into account the frequent genetic basis of the conditions leading to SCD in children and young adults [7], every attempt should be made to prevent the repetition of the tragedy in surviving relatives. Furthermore, screening strategies for potentially life-threatening cardiovascular disorders may be considered either in the whole population or in persons being at higher risk (e.g. competitive athletes) based on the evaluation of their effectiveness.

Family risk assessment

Between 10 and 30 (–40) % of sudden deaths in the young remain unexplained after a thorough autopsy thus referred as sudden unexplained death (SUD) or as sudden infant death syndrome (SIDS) in children aged < 1 year [13,15]. According to two recent studies, an inherited cardiac disease (ARVC, hypertrophic cardiomyopathy) or a primary electrical disease (long QT syndrome – LQTS, catecholaminergic polymorphic ventricular tachycardia – CPVT, Brugada syndrome) were found in 22% and 28% of family members of SUD victims, respectively [2,3]. The evaluation of first-degree relatives of SUD victims showed the presence of cardiac symptoms in 27% (palpitations, presyncope, syncope), and sudden unexpected death in 6% [3]. Behr et al. have evaluated 57 consecutively referred families with sudden arrhythmic death syndrome (SADS). They found an inheritable heart disease in 53% of them (LQTS, ARVC, Brugada syndrome, other cardiomyopathies) [4]. Tester and Ackerman have performed a molecular autopsy of 49 victims of SUD (average age at death 14.2 years). They discovered a gene mutation responsible for a potentially lethal arrhythmia in one third of them (LQTS and CPVT-associated mutations in 20% and 15%, respectively) [5].

When SCD is found to be the likely cause of death, it is essential to inform the relatives as soon as possible. The general practitioner should communicate with the family and provide the access to the specialist. The cardiologist should assess the detailed personal and family history and provide a risk assessment for the close relatives in a specialised cardiologic centre, including the genetic testing in accordance to the guidelines or expert consensus statement [16]. The cooperation of the family members is crucial. The pathologist should provide evidence of a structural heart disease, if present, and initiate molecular genetic examination in indicated cases (this examination is not yet routinely performed in this country).

In the Czech Republic, a structural autopsy is mandatory in case of death under 18 years of age, or unexplained death outside the hospital. According to the law recently enacted, the autopsy is performed by the forensic pathologist in case of sudden and unexpected death, unexplained by external inspection of the corpse. A pathologist is obliged to inform a general practitioner in writing about the cause of death. A physician carrying out an inspection of the deceased is obliged to inform a closely related person, eventually the police. If transferred into real life, these regulations may positively im-

pact the process of evaluation of the potentially affected relatives.

Screening

The purpose of screening is early detection of cardiovascular disease potentially leading to SCD. In the population of competitive athletes individuals with such a condition should be temporarily or permanently disqualified from competitive sport activities and, if necessary, treated adequately [17,18].

The evidence about SCD incidence in competitive athletes is generally hampered by retrospective character of the studies performed, as well as by questionable data collection (information from newspapers/media, single-centre studies or registries, problematic definition of the study population, limited pre-screening period, seasonal variation in SCD incidence), both probably leading to an underestimation of a true SCD incidence in this group. In their prospective study, Corrado et al. declared a 2.5 times higher risk of SCD in adolescents and young adults participating in competitive sport activities [11]. Previously asymptomatic cardiovascular abnormalities, especially cardiomyopathies and coronary artery disease, were the main cause of SCD. Similar to other published reports, a significant predominance of males was found, which probably corresponds to a different male to female ratio engaged in competitive sport activities, more vigorous physical exertion in males, and eventually to a higher prevalence and/or phenotypic expression of cardiac abnormalities leading to SCD (cardiomyopathy, ischaemic heart disease, LQTS) in males [8,13,19–21].

If a cardiac abnormality is identified or suspicious, a further non-invasive (echocardiography, 24-hours ambulatory ECG monitoring, exercise testing) or invasive (electrophysiologic study, coronary angiography, ventriculography, endomyocardial biopsy) should be considered to confirm or rule it out.

The competent working groups of the European Society of Cardiology (ESC) have adopted a proposal for a common European protocol for the initial cardiovascular evaluation of young competitive athletes, which consists of complete personal and family history, physical examination (including blood pressure measurement) and 12-lead ECG [6]. The screening should be performed (by a physician trained in identifying the signs of potentially lethal cardiac abnormalities) at the beginning of competitive sport activity, and repeated at least every two years. The implementation of ECG according to ESC criteria [22] is particularly based on the Italian experience which showed a significant decrease in mortality due to the reduction of SCD from cardiomyopathies in young athletes [11]. ECG abnormalities have been also described in patients with ARVC and some genetic arrhythmic syndromes (e.g. LQTS, Brugada syndrome).

The recommendation of the Council on Nutrition, Physical Activity, and Metabolism, American Heart Association (AHA) consists of 12 items (8 for personal and family history and 4 for physical examination). Positive finding in any of these items justify the examiner to re-

fer the person to a cardiologist. The physicians are currently not mandated to adopt the ESC guidelines. Arguments against a routine application of ECG testing are mainly based on the enormous financial burden of such a nationwide screening programme, which is partly related to the size of the competitive athletes population, partly to the relatively low prevalence of cardiovascular abnormalities leading potentially to SCD, low specificity of ECG as a screening test in athletes (due to high rate of ECG alterations associated with the normal physiological adaptations of the trained heart) and finally to the limited administrative and medical human resources [23]. The generation of borderline or false-positive results (8.8–25% according to different reports) will trigger further diagnostic tests in likely healthy persons and carry an emotional, financial and medical burden for the athlete and his or her family [11,23–25]. The cost-effectiveness of a pre-participation screening programme in young athletes including 12-lead ECG (in conformity with the ESC [6] recommendation) has been recently evaluated by Wheeler et al. [26] calculating a price of 100 000 USD per one life-year saved.

Currently available studies showing a positive effect of the pre-participation screening [6,9] have important limitations including inaccurate data collection, ambiguous subject definition, temporarily limited pre-screening period (the influence of a seasonal variation in SCD incidence), and eventually a mortality bias (false-positive impact of a screening programme linked to the natural variation of SCD incidence within the pre-screening and screening period).

Conclusion

The evaluation of the young (< 35 years) victims of sudden cardiac death and their relatives is an effective strategy for the detection of familiar cardiovascular disorders leading to SCD. As for the Czech Republic, apart from limited access to some diagnostic methods (molecular autopsy), the communication among individual health care providers, as well as the communication towards the affected families, is one of the main problems in this process. The compliance of the affected family will likely play a crucial role as well.

The introduction of a pre-participation screening programme in risk groups (e.g. competitive athletes) with the inclusion of a 12-lead ECG may enhance the detection of asymptomatic individuals with potentially lethal cardiovascular disease. Nevertheless, taking into account the organizational and financial aspects, as well as a high number of false-positive findings, the cost-effectiveness of such an approach has not been definitely confirmed yet. The present ESC recommendations are based on a single large study. The practical implementation of the screening programme requires a large number of the physicians providing the ECG analysis. The implementation of such a screening programme should be thoroughly debated and all interested parties (including professional associations, health care providers, and insurance companies) should participate in the discussion.

Funding

Supported by the project (Ministry of Health, Czech Republic) for conceptual development of research organization 00064203 (University Hospital Motol, Prague, Czech Republic)

References

- [1] R.J. Myerburg, A. Castellanos, Cardiac arrest and sudden death. In: E. Braunwald (Ed.), *Heart Disease: A Textbook of Cardiovascular Medicine*, WB Saunders, Philadelphia, 1997, pp. 742–779.
- [2] H.L. Tan, N. Hofman, I.M. van Langen, et al., Sudden unexplained death: heritability and diagnostic yield of cardiological and genetic examination in surviving relatives, *Circulation* 112 (2005) 207–213.
- [3] E. Behr, D.A. Wood, M. Wright, et al., Cardiological assessment of first-degree relatives in sudden arrhythmic death syndrome, *Lancet* 362 (2003) 1457–1459.
- [4] E. Behr, C. Dalageorgou, M. Christiansen, et al., Sudden arrhythmic death syndrome: familial evaluation identifies inheritable heart disease in the majority of families, *European Heart Journal* 29 (2008) 1670–1680.
- [5] D.J. Tester, M.J. Ackerman, Postmortem long QT syndrome genetic testing for sudden unexplained death in the young, *Journal of the American College of Cardiology* 49 (2007) 240–246.
- [6] D. Corrado, A. Pelliccia, H.H. Bjornstad, et al., Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: proposal for a common European protocol, *European Heart Journal* 26 (2005) 516–524.
- [7] P. Schwarz, L. Crotti, Can a message from the dead save lives?, *Journal of the American College of Cardiology* 49 (2007) 247–249.
- [8] B.J. Maron, W.C. Roberts, M.H. McAllister, et al., Sudden death in young athletes, *Circulation* 62 (1980) 218–229.
- [9] D. Corrado, C. Basso, G. Rizzoli, et al., Does sports activity enhance the risk of sudden death in adolescents and young adults?, *Journal of the American College of Cardiology* 42 (2003) 1959–1963.
- [10] G. Thiene, A. Nava, D. Corrado, et al., Right ventricular cardiomyopathy and sudden death in young people, *The New England Journal of Medicine* 318 (1988) 129–133.
- [11] D. Corrado, C. Basso, A. Pavei, et al., Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening programme, *Journal of the American Medical Association* 296 (2006) 1593–1601.
- [12] B.J. Maron, J.J. Doerer, T.S. Haas, et al., Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980–2006, *Circulation* 119 (2009) 1085–1092.
- [13] B.G. Winkel, A.G. Holst, J. Theilade, et al., Nationwide study of sudden cardiac death in persons aged 1–35 years, *European Heart Journal* 32 (2011) 983–990.
- [14] A. Steinvil, T. Chundadze, D. Zeltser, et al., Mandatory electrocardiographic screening of athletes to reduce their risk for sudden death: proven fact or wishful thinking?, *Journal of the American College of Cardiology* 57 (2011) 1291–1296.
- [15] R. Puranik, C.K. Chow, J.A. Duflo, et al., Sudden death in the young, *Heart Rhythm* 2 (2005) 1277–1282.
- [16] M.J. Ackerman, S.G. Priori, S. Willems, et al., HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies, *Europace* 13 (8) (2011) 1077–1109.
- [17] B.J. Maron, D.P. Zipes, 36th Bethesda Conference: eligibility recommendations for competitive athletes with cardiovascular abnormalities, *Journal of the American College of Cardiology* 45 (2005) 1313–1375.
- [18] V. Chaloupecký, O. Reich, J. Janoušek, et al., Pohybová a sportovní aktivita u dětí a mladistvých s kardiovaskulárním onemocněním, *Cor et Vasa* 53 (Suppl 1) (2011) 86–103.

- [19] B.J. Maron, J. Shirani, L.C. Poliac, et al., Sudden death in young competitive athletes. Clinical, demographics, and pathological profiles, *Journal of the American Medical Association* 276 (1996) 199–204.
- [20] K. Miura, H. Nakagawa, Y. Morikawa, et al., Epidemiology of idiopathic cardiomyopathy in Japan: results from a nationwide survey, *Heart* 87 (2002) 126–130.
- [21] A. Nava, B. Bauce, C. Basso, et al., Clinical profile and long-term follow-up of 37 families with arrhythmogenic right ventricular cardiomyopathy, *Journal of the American College of Cardiology* 36 (2000) 2226–2233.
- [22] D. Corrado, A. Pelliccia, H. Heidbuchel, et al., Recommendations for interpretation of 12-lead electrocardiogram in the athlete, *European Heart Journal* 31 (2010) 243–259.
- [23] B.J. Maron, P.D. Thomson, M.J. Ackerman, et al., Recommendations and considerations related to preparticipation screening for cardiovascular abnormalities in competitive athletes: 2007 update, *Circulation* 115 (2007) 1643–1655.
- [24] D. Corrado, C. Basso, M. Shavon, G. Thiene, Screening for hypertrophic cardiomyopathy in young athletes, *The New England Journal of Medicine* 339 (1998) 364–369.
- [25] B.J. Maron, S.A. Bodison, Y.E. Wesley, et al., Results of screening a large group of intercollegiate competitive athletes for cardiovascular disease, *Journal of the American College of Cardiology* 10 (1987) 1214–1221.
- [26] M.T. Wheeler, P.A. Heidenreich, V.F. Froelicher, et al., Cost-effectiveness of preparticipation screening for prevention of sudden cardiac death in young athletes, *Annals of Internal Medicine* 152 (2010) 276–287.