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·Minireview·

Physical activity in sudden unexpected death in epilepsy: much more than a simple sport

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Abstract: Sudden unexpected death in epilepsy (SUDEP) is the most important direct epilepsy-related cause of death. Additionally, potential pathomechanisms for SUDEP is unknown, but it is very probable that cardiac arrhythmia during and between seizures, electrolyte disturbances, arrhythmogenic drugs or transmission of epileptic activity via the autonomic nervous system to the heart may play a potential role. Quite interestingly, clinical and experimental data have shown that physical activity can decrease seizure frequency, as well as lead to improved cardiovascular health in patients with epilepsy. Based on these facts, the purpose of this article is to review the body of literature of the possible contribution of physical exercise to the SUDEP prevention in a comprehensive manner.

Keywords: sudden unexpected death in epilepsy; physical activity; epilepsy; heart; seizure

1 Sudden unexpected death in epilepsy

Epilepsy is one of the most common serious neurological conditions that is associated with a two- to three-fold increase in mortality compared with general population, and sudden unexpected death in epilepsy (SUDEP) is the most important direct epilepsy-related cause of death[1]. SUDEP is defined as sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in patients with epilepsy, with or without evidence of a seizure and excluding documented *status epilepticus*, in which postmortem examination usually does not reveal a toxicological or anatomical cause of death[2]. Comparisons of incidence estimates for SUDEP are difficult, since different definitions of SUDEP have been used, not all patients have postmortem examination, and case ascertainment methods and source populations are varied[3]. SUDEP is responsible for 7.5% to 17% of all deaths in epilepsy and has an incidence of 1:500 and 1:1 000 among adults[4,5]. Information concerning risk factors for SUDEP is conflicting, but potential risk factors include age[6], early onset of epilepsy[7], duration of epilepsy[8], uncontrolled seizures, mainly in the temporal lobe epilepsy[8,9], seizure frequency[8,9] seizure type[9], number of antiepileptic drugs[10] and winter temperatures[11]. Additionally, potential pathomechanisms for SUDEP is unknown, but it is very probable that cardiac arrhythmia during and between seizures, electrolyte disturbances, arrhythmogenic drugs or transmission of epileptic activity via the autonomic nervous system to the heart play potential roles[12-14].

We have to keep in mind that preventative measures other than medical and surgical therapies could be much more useful in the prevention of SUDEP[15]. Among these factors, physical activity may play an interesting role[15,16]. Substantial evidence from animal and clinical studies indicated that physical activity could reduce seizure frequency, as well as lead to improved cardiovascular and psychological health in patients with epilepsy[16]. Based on these facts, the aim of this article is to review the body of literature of the possible

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contribution of physical exercise to the SUDEP prevention in a comprehensive manner.

2 Epilepsy and exercise: experimental and clinical data

Patients with epilepsy are routinely discouraged from participating in sports and exercise. This is surprising because for many high-risk patients such as those with coronary heart disease and diabetes, physical exercise has been proved to be quite beneficial. This reluctance of both patients and physicians is partly due to fear of injuries and fear that exercise will cause seizures[17]. Although the question of a positive or a negative impact of physical exercise on seizure frequency remains unsolved, patients with epilepsy should have the same benefits as others from the positive effects on maximal aerobic and work capacity, body weight, and self-esteem[18].

The attitude towards restriction and protection of the patients with epilepsy has, however, changed dramatically in the last decades and general recommendations have been reviewed. The International League Against Epilepsy recommended in 1997 that the only prohibited sports for athletes with epilepsy are skydiving and scuba diving[19]. In order to give epileptic patients satisfactory advice on sports, it is essential to understand the factors in sports that could affect the epileptic disorder. Likewise, it is rather difficult to indicate which specific effects epilepsy will have on sports participation and to draw general conclusions.

Some studies have been aimed to study the relationship between epilepsy and exercise by comparing physical and social activities among persons with epilepsy based on questionnaires and/or clinical studies[20]. In this line, the existing clinical data concerning the impact of exercise on patient outcomes have some limitations. There is a lack of prospective studies, studies using appropriate controls, studies examining behavioral aspects, and studies using a comprehensive approach in an outpatient setting. As a general rule, regular physical exercise is beneficial to the individuals with epilepsy. For instance, a study conducted by Nakken *et al*.[18] reported that 4 weeks of physical training program did not change the average frequency of seizures[18]. Another study evaluating physical exercise in women with intractable epilepsy demonstrated that aerobic physical training decreased the number of seizures during the exercise period[21].

Another point to be considered is the low degree of participation in physical activity among patients with epilepsy[22]. In a study in Norway, only 23% of epileptic patients participated in organized physical activity[17]. Despite the fact that several epidemiological studies have been performed on this subject, these patient samples may not be directly applicable to developing countries. A study conducted by Arida and colleagues[23] analyzed the degree of participation in physical activities among Brazilian patients with epilepsy. Although only 15 percent of patients were qualified as active, that is, exercised regularly, more than half of the patients participated in physical activities once or twice per week or on the weekends.

Experimental studies have also demonstrated a positive effect of physical exercise in animals with epilepsy[24-27]. The first study relating the effect of physical exercise on epilepsy used kindling model. In this study, the effect of acute and chronic physical exercise on amygdala kindling development was verified[24]. After this period of training, rats were kindling stimulated 1 min post-exercise. The number of stimulations needed to reach stage 5 was statistically higher in the chronic exercise group when compared with the control one. Consequently, the exercise group spent longer time and shorter afterdischarge (AD) duration during stage 1 than the control group. It was also observed that the time spent in stage 1 was longer and that the AD duration during this stage was shorter in the exercise animals. As a whole, these findings suggest that physical exercise inhibit amygdala kindling development in rats.

A subsequent study, using the pilocarpine model of epilepsy, evaluated the effect of an aerobic physical program on seizure frequency[25]. After the first spontaneous recurrent seizure, animals were submitted to an aerobic exercise program. A reduced frequency of seizures in trained animals with epilepsy was observed (Fig. 1). The main concern with regard to physical exercise by people with epilepsy is exercise-induced seizures. Seizures occur during physical exercise, but apparently infrequently[28]. It is interesting to note that in this study, only 2 animals presented 3 seizures each during the 3 600 h of exercise, and 2 animals presented 1 seizure 1 min post-exercise.

Additional investigations were performed to better clarify the factors that may interfere with this process. By using local cerebral metabolic rates for glucose (LCMRglu), a study

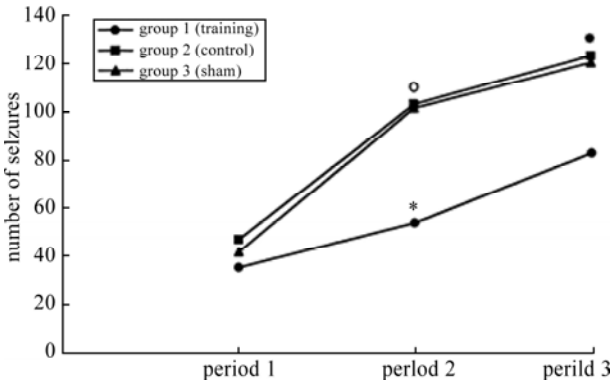

Fig. 1 Mean number of seizures observed for each period of 45 d in each group. Significant increase from period 1 to period 2 (○, $P < 0.05$) and from period 1 to period 3 (●, $P < 0.05$) in group 2 and group 3 (control and sham groups). Significant difference in period 2, between group 1 (training group) (*$P < 0.05$) and group 2 and group 3 (control and sham groups). Adapted by permission of Dr. Arida and colleagues[25].

evaluated whether physical training might modify the functional activity in rats with epilepsy[26]. LCMRglu was measured quantitatively by the [^{14}C] 2-deoxyglucose (2DG) method. To determine changes in cerebral functional activity in trained animals with epilepsy, rats with epilepsy were studied during the interictal phase of the pilocarpine model of epilepsy. The rationale to study brain metabolism during the interictal phase was that all animals present seizures at rest and not during exercise[25]. The premise that animals with epilepsy submitted to a physical training would exhibit a marked metabolic alteration in the interictal phase was, however, not confirmed. An increase in interictal LCMRglu in inferior colliculus and auditory cortex in the trained rats with epilepsy was observed when compared with rats with epilepsy. Although no substantial LCMRglu changes were observed after physical training, exercise did reverse the low metabolic rates in several structures of animals with epilepsy. Electrophysiological study was also performed to study the effect of aerobic exercise on "*in vitro*" hippocampal electrophysiological parameters observed in rats submitted to the pilocarpine model of epilepsy[27]. Trained rats with epilepsy exhibited a reduction in population spikes from CA1 area when compared with nontrained rats. These results indicate that physical training reduces CA1 hyper-responsiveness and may modify synaptic plasticity in rats submitted to the pilocarpine model of limbic epilepsy (Fig. 2).

Quite interestingly, to investigate whether the type of physical activity, voluntary or forced, would promote different morphological changes in hippocampal formation, Arida and colleagues[29] performed an immunocytochemical study using the parvalbumin (PV) distribution as a marker. Control rats and rats with epilepsy were submitted to a voluntary (wheel running) and forced (treadmill) exercise for 10 d (acute physical exercise) or 45 d (chronic physical exercise). In animals with epilepsy, the number of PV-positive cells and staining intensity of PV-fibers in the hilus was significantly higher only in the acute physical exercise (voluntary and forced) group. Altogether, these findings demonstrate that acute physical exercise, both voluntary and forced, leads to prominent positive plastic changes in the hippocampal formation of rats with epilepsy (Fig. 3).

In sum, in these animal models of temporal lobe epilepsy, it seems that physical activity in general cannot be considered a seizure-inducing factor. Thus, the mechanisms by which physical training is able to induce such changes are not completely understood and deserve further investigations.

3 Final considerations and future aims

As mentioned before, people with epilepsy present two- to three-fold increase in the probability to die prematurely than those without epilepsy, and the most common epilepsy-related category of death is SUDEP. The exact pathophysiological causes of SUDEP are unknown, but it is very probable that cardiac abnormalities during and between seizures may play a potential role[12]. In accordance to this reasoning and based on the experimental and clinical evidences suggesting that physical activity *per se* is able to reduce cardiac arrhythmias in animal and human studies[30], we postulated the following question: is there an association between physical inactivity and SUDEP?

At the present moment, there is only a case report study that evaluated a witnessed case of probable SUDEP in an individual who was performing exercise[31]. Although this isolated fact, some beneficial effects of physical exercise against SUDEP phenomenon can be speculated.

Firstly, it is believed that cardiovascular diseases are often associated with overactivity of the sympathetic nervous system[32], and increases in physical activity will produce beneficial effects on the cardiovascular system in normal and diseased individuals via alterations in neural control of the circulation[30]. These effects include reductions in blood pressure and sympathetic outflow in human beings[33] as well

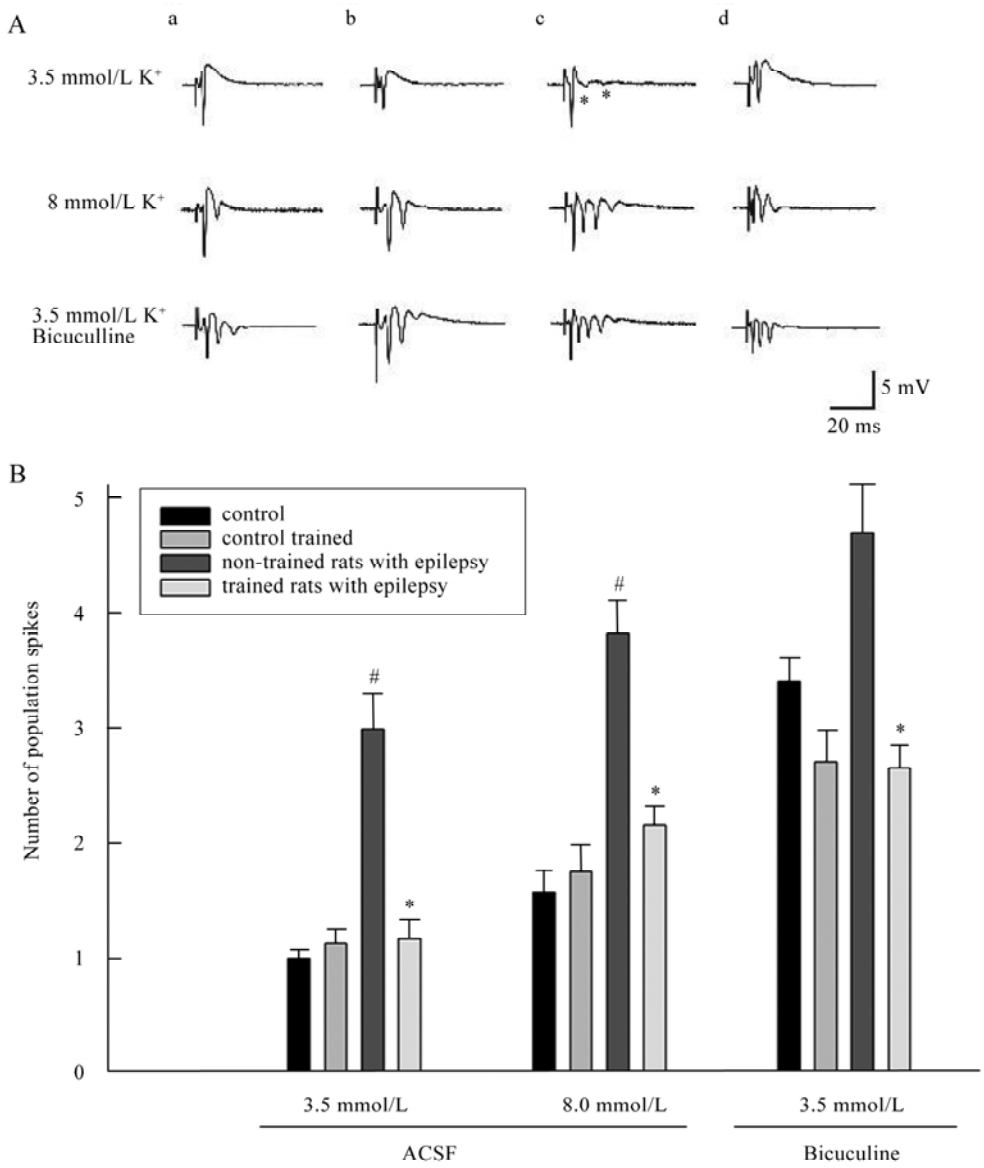

Fig. 2 Population spikes recorded in CA1 area under different experimental manipulations. Panel A shows electrophysiological recordings in control (a) and control trained (b), non-trained rats with epilepsy (c) and trained rats with epilepsy (d). Notice a single population spike under 3.5 mmol/L K^+ and normal responsiveness to 8 mmol/L K^+, and bicuculline application in (a) and (b). Non-trained rats with epilepsy (c) exhibited hyperresponsiveness characterized by multiple population spikes (*) in normal 3.5 mmol/L K^+ and higher responsiveness to 8 mmol/L K^+ and bicuculline. Trained rats with epilepsy (d) showed hyperexcitability and apparently normal responsiveness to 8 mmol/L K^+ and bicuculline. Panel B shows statistical analysis confirming a reduction in the number of population spikes in trained rats with epilepsy when compared to non-trained rats with epilepsy in extracellular 3.5 mmol/L K^+, 8 mmol/L K^+ and 3.5 mmol/L K^+ bicuculline concentrations ($^*P < 0.05$). An increase in number of population spikes in non-trained rats with epilepsy was observed when compared with control rats at 3.5 mmol/L K^+ and 8 mmol/L K^+ concentrations ($^\#P < 0.05$). Repeated measure ANOVA analysis followed by multiple comparisons was used. Data are expressed as mean±SEM. ACSF, artificial cerebrospinal fluid containing. Adapted by permission of Dr. Arida and colleagues[27].

as in animal models of exercise training[34]. As morbidity and mortality in cardiovascular disease are often associated with elevations in sympathetic nervous system activity[35], the beneficial effects of physical activity are likely related, in part, to reductions in sympathetic activity. Quite interestingly, a study developed by our group evaluated the heart rate, *in vivo* ECG and isolated *ex vivo* preparation (Langendorf preparation) of rats with epilepsy[36]. The results showed differences in the mean heart rate *in vivo*, but surprisingly, no differences in heart rate could be observed in the isolated *ex vivo* situation, suggesting a central nervous system modulation on the heart, which could explain the SUDEP[36]. Taken

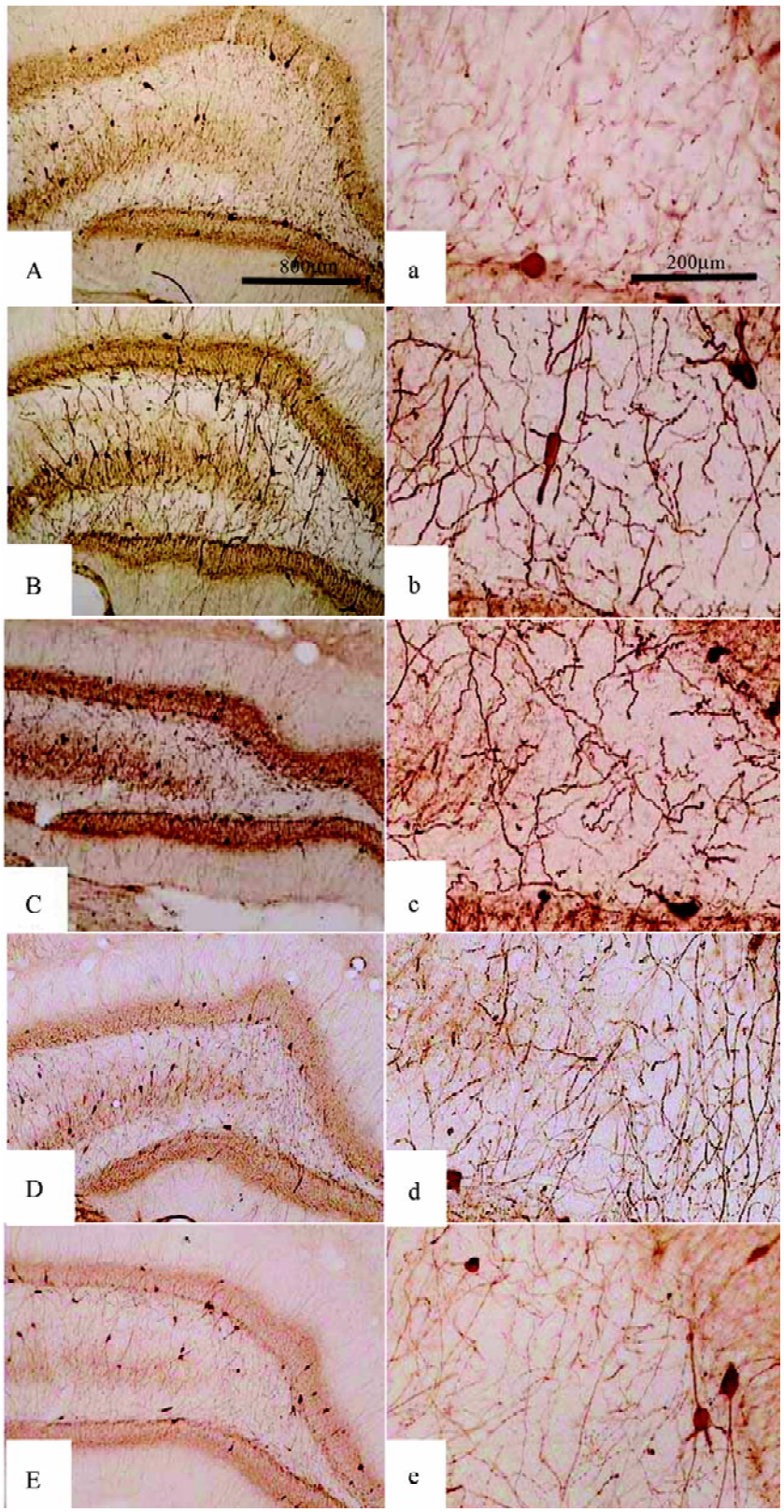

Fig. 3 Photomicrographs of PV stained coronal sections of the DG from animals with epilepsy submitted to acute and chronic physical exercise. A-E: distribution of PV-positive cells in the granular layer (scale bar, 800 μm); a-e: distribution of PV-positive fibers in the hilus of DG (scale bar, 200 μm). A and a: animal with epilepsy; B and b: acute voluntary rats with epilepsy; C and c: acute treadmill rats with epilepsy; D and d: chronic voluntary rats with epilepsy; and E and e: chronic treadmill rats with epilepsy. Adapted by permission of Dr. Arida and colleagues[29].

together, it is reasonable to purpose that regular physical activity is able to attenuate sympathetic nervous system activity, cardiac abnormalities and hence SUDEP.

Secondly, it is clear that premature mortality is increased in patients with epilepsy, particularly in those with more severe seizures[3], and it is generally acknowledged that cardiac abnormalities between seizures is the very probable cause of SUDEP[3]. As physical activity has been considered to act as anticonvulsant[23-25,27,29], it is coherent to purpose that regular physical activity may attenuate the frequency of seizures and cardiac abnormalities that could culminate in SUDEP.

Finally, the next logical steps for us epileptologists are to understand the mechanisms by which exercise training influence the cardiovascular system of patients with epilepsy. These mechanisms are likely to be important for developing new strategies in the prevention of SUDEP.

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体育运动对癫痫猝死症的影响：并非单纯运动

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摘要：癫痫猝死(sudden unexpected death in epilepsy, SUDEP)是癫痫患者最重要的直接与癫痫相关的死亡原因。其潜在病理机制尚未阐明，但癫痫发作时和发作间期的心律失常，电解质紊乱，致心律失常药物或癫痫电活动通过自主神经系统向心脏的传导，很可能与SUDEP的发病机理有关。引人注意的是，临床和实验数据都显示体力活动可以降低癫痫发作频率，并促进癫痫患者的心血管健康。基于上述情况，本文综述了体育锻炼可能预防SUDEP发生的相关文献内容。

关键词：癫痫猝死；体育活动；癫痫；心脏；癫痫发作