

# Sudden unexpected death in epilepsy: sudden death risk decreased by physical activity

Morte súbita nas epilepsias: resultados inspiradores revelados pela atividade física

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## ABSTRACT

Epilepsy is the most commonest serious chronic neurological condition and sudden unexpected death in epilepsy (SUDEP) is probably the most common direct epilepsy-related cause of death. Several suggestions have been made concerning the mechanisms behind SUDEP, most involving speculations on the possible role of autonomic effects such as cardiorespiratory disturbances. Clinical and experimental studies have shown that physical activity can decrease seizure frequency, as well as lead to improved cardiovascular and psychological health in patients with epilepsy. This article reviews the SUDEP phenomenon and the possible contribution of exercise in on the prevention of SUDEP among patients with epilepsy.

**Keywords:** Epilepsy; Death, sudden; Exercise

## RESUMO

A epilepsia é a doença neurológica crônica grave mais comum e o fenômeno da morte súbita nas epilepsias (SUDEP) é uma das causas de morte mais comuns nesta síndrome neurológica. Várias propostas têm sido feitas com o intuito de esclarecer o fenômeno da SUDEP, e a maioria envolve o possível papel dos efeitos autonômicos, tais como distúrbios cardiorrespiratórios, tendo recebido especial atenção. Nesse sentido, estudos clínicos e experimentais têm demonstrado que a atividade física pode diminuir a frequência de crises epilépticas, assim como melhorar a função cardiovascular e psicológica fisiológica dos pacientes com epilepsia. Dessa forma, este artigo de revisão aborda o

fenômeno da SUDEP e a possível contribuição da atividade física sobre para a prevenção da SUDEP entre os pacientes com epilepsia.

**Descritores:** Epilepsia; Morte súbita; Exercício

## SUDDEN UNEXPECTED DEATH IN EPILEPSY

Epilepsy is the most common serious neurological condition. Approximately 50 million people worldwide have epilepsy<sup>(1)</sup>. Epidemiological studies suggest that between 70% and 80% of people developing epilepsy will go into remission, while the remaining patients will continue to have seizures and are refractory to treatment with the currently available treatments/therapies<sup>(2)</sup>. The most common risk factors for epilepsy are cerebrovascular diseases, brain tumours, alcohol, traumatic head injuries, malformations of cortical development, genetic inheritance, and infections of the central nervous system<sup>(3)</sup>. In resource-poor countries, endemic infections, such as malaria and neurocysticercosis seem to be major risk factors<sup>(4)</sup>.

Sudden Unexpected Death in Epilepsy (SUDEP) is defined as sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning deaths in patients with epilepsy, with or without evidence of a seizure and

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excluding documented *status epilepticus*, in which post mortem examination does not reveal a toxicological or anatomical cause of death<sup>(5)</sup>. Comparisons of incidence estimates for SUDEP are difficult as different definitions of SUDEP have been used, not all patients have postmortem examinations, and case ascertainment methods and source populations have varied<sup>(6)</sup>. The incidence of SUDEP has been estimated as 3.5/1000 person-years in a lamotrigine clinical trial<sup>(7)</sup>, 0.5-1.4/1000 person-years in people with treated epilepsy<sup>(8)</sup>, 5.9/1000 person-years in outpatients with epilepsy at a tertiary referral centre<sup>(9)</sup>, 9/1000 person-years in candidates for epilepsy surgery, and 0.35/1000 person-years in a population-based study<sup>(10)</sup>. The National General Practice Study of Epilepsy (NGPSE), a community-based study in the United Kingdom, has seen the first case of SUDEP after 11,000 person-years of follow-up in<sup>(11)</sup>, and the results of the Medical Research Council Antiepileptic Drug Withdrawal Study showed that SUDEP among patients with epilepsy in remission is a rare event<sup>(12)</sup>. Information concerning risk factors for SUDEP is conflicting, but potential risk factors include: age<sup>(7)</sup>, early onset of epilepsy<sup>(13)</sup>, duration of epilepsy<sup>(14)</sup>, uncontrolled seizures, mainly in the TLE<sup>(14-15)</sup>, seizure frequency<sup>(14-15)</sup>, seizure type<sup>(15)</sup>, number of AEDs number<sup>(16)</sup>, and winter temperatures<sup>(17)</sup>. Additionally, potential pathomechanisms for SUDEP is are 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 a potential role<sup>(18)</sup>.

## EPILEPSY AND EXERCISE: HUMAN'S STUDIES IN HUMANS

Although the favourable effect of physical fitness on general health is unquestionable, patients with epilepsy are often excluded from participation in physical activity. This is surprising because for many high-risk patients such as those with coronary heart disease and diabetes, physical exercise has proved quite beneficial. This reluctance of both patients and physicians is due in part to fear of injuries and in part to fear that exercise will cause seizures<sup>(19)</sup>. 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<sup>(20)</sup>.

The attitude towards restriction and protection of the patient with epilepsy has, however, changed dramatically in the last decades and general recommendations have been recently reviewed. In 1968, the American Medical

Association Committee on Medical Aspects of Sports advised that people with epilepsy not controlled by medication should avoid not only collision sports, but also non-contact sports<sup>(21-22)</sup>. In 1974, the Committee revised its instance, describing that people with epilepsy with rational seizure control should be allowed to play any sport except activities in which chronic head trauma may occur<sup>(23)</sup>. In 1983, the American Academy of Pediatrics allowed for further individual consideration and stated that, "epilepsy *per se* should not exclude a child from hockey, football, basketball and wrestling"<sup>(22)</sup>. The International League against epilepsy recommended in 1997 that the only prohibited sports for athletes with epilepsy are skydiving and scuba diving<sup>(24)</sup>. In order to give epileptic patients satisfactory advice about sports, it is essential to understand the factor in sports that could affect the epileptic disorder. Many circumstances during physical activities or sports are presumed factors and have not been investigated. Likewise, it is rather difficult to indicate the specific effects of epilepsy will have on sports participation and to draw general conclusions.

Some studies have been designed to study the relationship between epilepsy and exercise comparing physical and social activities among patients with epilepsy based on questionnaires and/or clinical studies<sup>(25)</sup>. They also assess physical fitness by using standardized tests of physical endurance<sup>(25)</sup> and physical training programs<sup>(20)</sup>. With few exceptions, regular physical exercise is beneficial to the individual with epilepsy. For instance, a study conducted by Nakken et al.<sup>(20)</sup> reported that 4 weeks of a physical training program at an intensity of 60% of  $VO_{2max}$  for 45 min a day, did not change the average frequency of seizures<sup>(20)</sup>. Another study evaluating physical exercise in woman with intractable epilepsy demonstrated that aerobic physical training decreased the number of seizures during the exercise period<sup>(26)</sup>.

The degree of participation in physical activity among patients with epilepsy appears to be low<sup>(27)</sup>. In a study of epileptic patients in Norway, only 23% participated in organized physical activity<sup>(19)</sup>. 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<sup>(28)</sup> analyzed the degree of participation in physical activities among Brazilian patients with epilepsy. Although only 15 percent of patients were classified qualified as active, that is, they exercised regularly, more than half of the patients participated in physical activities once or twice per a week or on the weekends. While the main concern with regarding to physical exercise by persons with epilepsy has been exercise-induced seizures, other factors such as lack of training facilities, problems with transportation,

low motivation, reduced energy due to medication, and being afraid of provoking a seizure, lack of qualified instructors who know how to handle such problems were noted as important explanatory factors<sup>(19)</sup>.

## EPILEPSY AND EXERCISE PHYSIOLOGY

Most experiments on brain electrical activity have shown that abnormal discharges disappear in most patients during physical activity but returns at rest<sup>(29)</sup>. It has also been also observed that fewer seizures occur during both mental and physical activity compared with periods of rest<sup>(30)</sup>. The increased vigilance and attention involved in exercise could explain the reduction in the number of seizures<sup>(29)</sup>. Another hypothesis relates the  $\beta$ -endorphins released during exercise with inhibition of epileptic discharges<sup>(31)</sup>.

Although exercise has been shown to reduce the number of seizures and epileptic activity on the EEG and the number of seizures, there are numerous factors that could cause seizures during sports and exercise, and any links at this point are largely speculative. It appears that these factors occur as the result of a disturbed balance of physiological parameters. Fatigue is one such issue. In sports, general fatigue and local muscular fatigue must be distinguished. The stress of competition has been discussed commented on. Physical, and especially psychic stress is generally accepted as factors that precipitate seizures<sup>(32)</sup>. In competitive sports, this stress can induce seizures in stress-sensitive patients<sup>(30,33)</sup>. Hypoxia, hyperhydration, and hypoglycaemia are other possible considerations. Hypoxia does not occur during normal sporting activities, although it may occur in climbing or alpine skiing at high altitudes (> 2000 m)<sup>(33)</sup>. Hyperhydration can result from a great ingestion of water or from an extreme loss of sodium and is a well-known factor in provoking seizures. Hyperhydration can occur during swimming or prolonged physical exercise, such as marathon running and the triathlon. Over ingestion of isotonic or hypotonic liquids may lead to hyponatraemia<sup>(34)</sup>. Hypoglycaemia can occur during long- distance running, cycling or swimming, especially when regular liquid and food intake is reduced<sup>(35)</sup>. Hyperthermia is also known to trigger seizures. Prolonged exercise (marathon, triathlon) at high temperatures and under humid conditions puts people at risk<sup>(36)</sup>. One factor that is raised frequently, but inappropriately raised, is that of hyperventilation. Because hyperventilation in the laboratory may provoke epileptiform discharges on EEG and even seizures, especially absence seizures, some have erroneously believed that increased ventilation during exercise may cause seizures<sup>(37)</sup>. However, increased ventilation

during physical training is a compensatory homeostatic mechanism; the respiratory alkalosis of induced hyperventilation does not occur<sup>(38)</sup>. In these lines along this line, seizures during exercise may be related to acute metabolic and respiratory changes. How Just how efficient the respiratory control systems are in untrained subjects is not known, but untrained persons lose homeostatic balance more easily than trained persons.

## EFFECT OF PHYSICAL EXERCISE IN ON EXPERIMENTAL MODELS OF EPILEPSY

Experimental studies have also demonstrated a positive effect of physical exercise in animals with epilepsy<sup>(39-42)</sup>. The first study reporting relating the effect of physical exercise on epilepsy used the kindling model. In this study it was verified the effect of acute and chronic physical exercise on amygdala kindling development<sup>(39)</sup>. To assess the acute effect of exercise on kindling evolution, animals were submitted to a daily bout of aerobic exercise which consisted of 40 min of running on the treadmill at 20 meters per min. One minute post-exercise, animals were kindling stimulated. To For the chronic effect of exercise, animals were submitted to an aerobic exercise program (45 sessions of 40 min of running on a treadmill at 20 meters per min, 7 days per week). After this period of training period, the animals were submitted to 40 min of running at the same speed and kindling stimulated one min post-exercise. The number of stimulations required to reach stage 5 was statistically higher for the chronic exercise group when compared to the acute exercise group and control group. The number of stimulations required to reach stage 5 in the acute exercise group was higher, but not statistically different from the control group. Thus, the acute and chronic exercise groups spent a longer more time and had shorter after-discharge (AD) durations during stage 1 than the control group.

Some factors could probably be contributing to this effect. Several lines of evidence show that brain neurotransmission is influenced by exercise. For instance, an increase in noradrenaline levels in whole brain has been reported<sup>(43)</sup>. It is well known that among catecholamines, noradrenaline displays has a tonic inhibitory effect on kindling development but not on the kindling state<sup>(44)</sup>. Bortolotto and Cavalheiro<sup>(45)</sup> observed that the depletion of noradrenaline induced by DSP4 facilitated the propagation of epileptiform activity and the rate of hippocampal kindling. Although most of these studies relate associates the brain noradrenergic system with kindling development<sup>(46)</sup>, Welsh and Gold showed that a single intraperitoneal injection of epinephrine, administered 30 min or 24 h prior to the first trial, retarded the development of seizures, suggesting that endogenous

peripheral catecholamines may play an important role in regulating epileptogenesis. Evidence in favour of changes in synthesis and metabolism of catecholamines during exercise and the inhibitory involvement of this neurotransmitter system in the amygdala kindling support the hypothesis that the effect of chronic exercise on brain catecholamines can contribute to retarding the kindling development.

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 general rule, the rate of kindling seems to be related to the length of the initial AD, i.e., the longer the initial AD, the more rapidly kindling appears<sup>(47)</sup>. Thus, the assessment of different stages is important, since the catecholamine effect is primarily observed during the development of kindling and it does not act after stage 5 seizures are established<sup>(44)</sup>. Taken together, these findings suggest that physical exercise inhibits 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<sup>(40)</sup>. After the first spontaneous recurrent seizure, animals were submitted to an aerobic exercise program of 45 sessions on a treadmill, 7 days per week at the intensity of 60%  $VO_{2max}$ . A reduced frequency of seizures in trained animals with epilepsy was observed. The main primary concern with regard to physical exercise by people with epilepsy has been exercise-induced seizures. Seizures occur during physical exercise, but apparently are infrequently<sup>(48)</sup>. In this study, only two animals presented 3 seizures each during 3600 hs of exercise, and 2 animals presented 1 seizure each, 1 min post-exercise.

Further investigations were performed to better clarify the factors that may interfere in this process. A study evaluated, using local cerebral metabolic rates for glucose (LCMRglu) evaluated, whether physical training modifies the functional activity in rats with epilepsy<sup>(41)</sup>. LCMRglu was measured by the quantitative [<sup>14</sup>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 purpose of studying to study the brain metabolism during the interictal phase was that all the animals presented seizures at rest and not during exercise<sup>(40)</sup>. However, the hypothesis that animals with epilepsy submitted to a physical training would exhibit a marked metabolic alterations in the interictal phase was, however, not confirmed. It was observed an increase in of interictal LCMRglu in the inferior colliculus and auditory cortex was noted in the trained rats with epilepsy when compared to untrained rats with epilepsy. Although no substantial

LCMRglu changes were observed after physical training, exercise did reverse the low metabolic rates in several structures of the animals with epilepsy. Vissing et al.<sup>(49)</sup> reported a higher local cerebral glucose utilization in the auditory and visual cortex during exercise, suggesting that these changes are not related directly to the exercise *per se*, but to a higher mental alertness in rats during exercise rather than at rest in resting rats. Since physical activity does need a certain level of alertness, the increase in attention and vigilance observed during physical activity could reduce the number of seizures<sup>(29)</sup>. Although these changes were observed at rest, the increased metabolic rate in these structures could explain a lower number of seizures number in trained rats with epilepsy in the present and previous papers<sup>(40)</sup>.

A recent study was performed to study analyze the effect of aerobic exercise on *in vitro* hippocampal electrophysiological parameters observed in rats submitted to the pilocarpine model of epilepsy<sup>(42)</sup>. Electrophysiological changes were monitored by extracellular field potentials recorded from the CA1 area. Trained rats with epilepsy exhibited a reduction in population spikes when compared with nontrained untrained rats. These results indicate that physical training reduces CA1 hyperresponsiveness and can modify synaptic plasticity in rats submitted to the pilocarpine model of limbic epilepsy.

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.

## FINAL CONSIDERATIONS AND FUTURE AIMS

As mentioned before, people with epilepsy present a 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 likely probable that cardiac abnormalities during and between seizures play a potential role<sup>(18)</sup>. In accordance to this reasoning and based on experimental and clinical evidences from the last decade suggesting that physical activity *per se* is able to reduce cardiac arrhythmias in animal and human studies<sup>(50)</sup>, we postulated the question: Could exist a relationship exist between physical inactivity and SUDEP?

First of all, it has been believed that cardiovascular diseases have been considered as are often associated with overactivity of the sympathetic nervous system<sup>(51)</sup>,

and increases in physical activity produce beneficial effects on the cardiovascular system in normal and diseased individuals via alterations in neural control of the circulation<sup>(50)</sup>. These effects include reductions in blood pressure and sympathetic outflow in humans<sup>(52)</sup> as well as in animal models of exercise training<sup>(53)</sup>. As morbidity and mortality in cardiovascular disease are often associated with elevations in sympathetic nervous system activity<sup>(54)</sup>, the beneficial effects of physical activity are likely related, in part, to reductions in sympathetic activity. Quite interestingly, a recent study developed by our group evaluated the heart rate, *in vivo* (ECG) and in isolated *ex vivo* preparations (Langendorf preparation) of rats with epilepsy<sup>(55)</sup>. 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<sup>(55)</sup>. Taken considering these findings together, it is reasonable to proupose 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<sup>(6)</sup>, and it is generally acknowledged that cardiac abnormalities between seizures is are the very probably thee cause of SUDEP<sup>(6)</sup>. As physical activity has been considered to act as an anticonvulsant<sup>(28,39-40,42,56)</sup>, it is coherent consistent to proupose that regular physical activity may attenuate the frequency of seizures and cardiac abnormalities that which could culminate in SUDEP.

Finally, the next logical steps are to understand the mechanisms by which exercise training influences 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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