COULD SUDDEN CARDIAC DEATH IN EPILEPSY BE RELATED TO THE OCCURRENCE OF THALAMIC DYSFUNCTION OR ANATOMIC CHANGE?

Fulvio A. Scorza[1], Lineu Calderazzo[1], Marly de Albuquerque[1], Ricardo M. Arida[2], Antonio-Carlos G. de Almeida[3], Esper A. Cavalheiro[1]

Abstract – Sudden unexpected death in epilepsy (SUDEP) is the most important direct epilepsy-related cause of death in people with chronic epilepsy. Its physiopathology is still unknown; however, the most commonly suggested potential mechanisms involve cardiac or respiratory abnormalities. As the anatomical substrate of epileptic activity in the central nervous system (CNS) shows a direct relationship with cardiovascular alterations, this may suggests that patients with epilepsy associated with focal CNS lesions may be at particular risk of SUDEP. Currently, experimental and clinical data support an important role for thalamic nuclei in the behavioural manifestations, initiation and propagation of seizures. In view of the above findings, we purpose that SUDEP, at least in some cases, could be related to the occurrence of thalamic dysfunction or anatomic change.

KEY WORDS: epilepsy, cardiovascular abnormalities, heart, thalamus, sudden unexpected death in epilepsy.

A morte súbita cardíaca em epilepsia poderia estar relacionada com a ocorrência de alterações anatômicas ou funcionais do tálamo?

Resumo – A morte súbita e inesperada nas epilepsias (SUDEP) é a mais importante causa de morte em pacientes com epilepsia. A fisiopatologia da SUDEP ainda é desconhecida, no entanto, os prováveis mecanismos estão relacionados com alterações cardiovasculares ou respiratórias. Como o substrato anatômico da atividade epiléptica no sistema nervoso central (SNC) apresenta direta relação com alterações cardiovasculares, esse fato sugere que pacientes com epilepsia e lesões focais no SNC podem apresentar maior risco para SUDEP. Atualmente, dados experimentais e clínicos demonstram um importante papel dos núcleos talâmicos nas manifestações comportamentais, bem como no início e propagação das crises epilépticas. Sendo assim, nós acreditamos que a SUDEP, pelo menos em alguns casos, poderia estar relacionada com a ocorrência de alterações anatômicas ou disfunções talâmicas.

PALAVRAS-CHAVE: epilepsia, alterações cardiovasculares, coração, tálamo, morte súbita e inesperada nas epilepsias.

SUDDEN UNEXPECTED DEATH IN EPILEPSY: GENERAL ASPECTS

Epilepsy is the most common serious neurological condition. Approximately 50 million people worldwide have epilepsy[1]. In the US each year, about 100,000 new cases of epilepsy are diagnosed[2,3]. In the UK between 1 in 140 and 1 in 200 people (at least 300,000 people) are currently being treated for epilepsy[4]. Epidemiological studies suggest that between 70 and 80% of people developing epilepsy will go into remission, while the remaining patients continue to have seizures and are refractory to treatment with the currently available therapies[5,6]. 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[7]. In resource-poor countries, endemic infections, such as malaria and neurocysticercosis seem to be major risk factors[8].

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 excluding documented *status epilepticus*, in which post mortem examination does not reveal a toxicological or anatomi-

[1]Disciplina de Neurologia Experimental, Universidade Federal de São Paulo/Escola Paulista de Medicina, São Paulo SP, Brasil (UNIFESP/EPM); [2]Departamento de Fisiologia, UNIFESP/EPM; [3]Departamento de Engenharia Biomédica, Universidade Federal de São João Del Rei, São João Del Rei MG, Brasil (UFSJ).

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Dr. Fulvio Alexandre Scorza – Disciplina de Neurologia Experimental - Rua Botucatu 862 - 04023-900 São Paulo SP - Brasil. E-mail: scorza.nexp@epm.br

cal cause of death[9]. Comparisons of incidence estimates for SUDEP are difficult as different definitions of SUDEP have been used, not all patients have postmortem examination, case ascertainment methods and source populations have varied[10]. The incidence of SUDEP has been estimated as 3.5/1000 person-years in a lamotrigine clinical trial[11], 0.5–1.4/1000 person-years in people with treated epilepsy[12], 5.9/1000 person-years in outpatients with epilepsy at a tertiary referral center[13], 9/1000 person-years in candidates for epilepsy surgery and 0.35/1000 person-years in a population-based study[14]. 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[15] 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[16]. Information concerning risk factors for SUDEP is conflicting, but potential risk factors include: age[11], early onset of epilepsy[17], duration of epilepsy[18], uncontrolled seizures, mainly temporal lobe epilepsy (TLE)[18,19], seizure frequency[18-20], seizure type[18,20,21], anti-epileptic drugs (AED) number[17,18,22] and winter temperatures[23]. Additionally, potential pathomechanisms for SUDEP, including pathological changes in the heart, cardiac arrhythmia during and between seizures, electrolyte disturbances, arrhythmogenic drugs or transmission of epileptic activity via the autonomic nervous system to the heart have been extensively investigated (for review see[24]). Overall, in all studies the risk of sudden death in epilepsy is found to be elevated. Clarification of risk factors and establishment of the mechanisms of SUDEP are important so that as many people as possible can be saved from SUDEP.

CARDIAC CHANGES INDUCED BY STIMULATION OR LESION OF SOME CENTRAL NERVOUS SYSTEM STRUCTURES IN THE HEALTHY BRAIN

It has long been believed that, in the healthy brain, stimulation (or lesion) of some central nervous system (CNS) structures is able to promote morphological and functional cardiovascular alterations. Earlier studies have shown that electrical stimulation of the hypothalamus can lead to autonomic cardiovascular disturbances[25] and that hypothalamic lesions can lead to cardiac and gastrointestinal haemorrhages[26]. A variety of stresses applied to cortico-preconditioned rats succeeded in producing a common type of cardiac necrosis[27]. Moreover stimulation of certain brain areas (subiculum, posterior hypothalamus, ventrolateral thalamus and substantia nigra) has been shown to modify heart function without producing disturbances in the activity of the brain[28]. In addition, other workers showed that injections of a small dose of picrotoxin into the lateral ventricle of rabbits and cats leads to a rise in blood pressure associated with various types of ischaemic-like electrocardiographic changes and arrhythmias[29]. In the same year, it was reported that electrical stimulation of the cortex of the left frontal lobe in cats leads to constriction of the coronary blood vessels associated with ischaemic changes in the ECG[30]. Other workers brought about myocardial necrosis by exposing wild rats to tape recorded cat-rat fights and showed that anti-adrenergic drugs protected rats from stress-induced cardiac damage[31]. It has also been reported that angiotensin II, when administered into the lateral ventricle of cats, is able to induce a severe tachycardia[32,33]. Coronary hyperaemia, ventricular tachycardia with chaotic heart activity and evoked marked elevations of blood pressure could be observed when unipolar stimulations of various brain regions of dogs were evaluated[34]. Moreover, electrical stimulation of the stellate ganglion in dogs produced focal myocardial necrosis[35]. Lateral septal lesions have been shown to enhance conditioned bradycardia in the rabbit, suggesting that septo-hippocampal circuits participate in classical conditioning of cardiovascular changes[36]. In 1985, it was also shown that electrical stimulation of insular cortex elicits cardiac inhibition but insular lesions do not abolish conditioned bradycardia in rabbits[37]. In parallel, the role of the insular cortex on cardiovascular changes was confirmed in human studies[38]. Acute chemical lesions of the dorsal periaqueductal gray (DPAG) have been shown to produce a reduction in resting arterial pressure accompanied by an increase in heart rate in conscious rats[39], suggesting that DPAG is involved in the tonic and reflex control of resting arterial pressure and heart rate. More recently, a marked tachycardia immediately after a lesion of the anteroventral third ventricle of rats was demonstrated[40].

A POSSIBLE ROLE OF THE THALAMUS IN SUDDEN UNEXPECTED DEATH IN EPILEPSY

SUDEP is the most important direct epilepsy-related cause of death in people with epilepsy. Its cause is still unknown; however, the most commonly suggested mechanisms involve cardiac. As the anatomical substrate of epileptic activity in the CNS shows a direct relationship with cardiovascular alterations, this may suggests that patients with epilepsy associated with focal CNS lesions may be at particular risk of SUDEP[10,41]. It has been shown that epileptic activity originating in the amygdala, cingulated gyrus, insular cortex, frontopolar or frontoorbital regions may induces arrhythmias (such as supraventricular tachycardia), sinus tachycardia, sinus bradycardia, sinus arrest, atrioventricular block and asystole[42], which could be implicated in SUDEP.

Currently, experimental and clinical data support an important role for thalamic nuclei in the behavioural

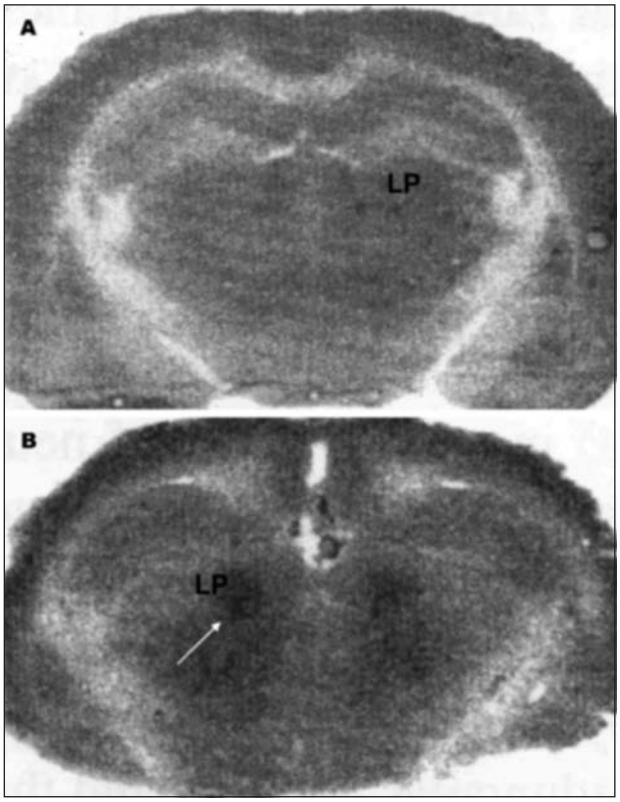

Fig 1. Representative [^{14}C]2DG autoradiographs of the lateral posterior thalamic nuclei (LP). (A) [^{14}C]2DG autoradiographs prepared from control animals. (B) [^{14}C]2DG autoradiographs prepared from animals with epilepsy. Note the activation of the LP (arrow).

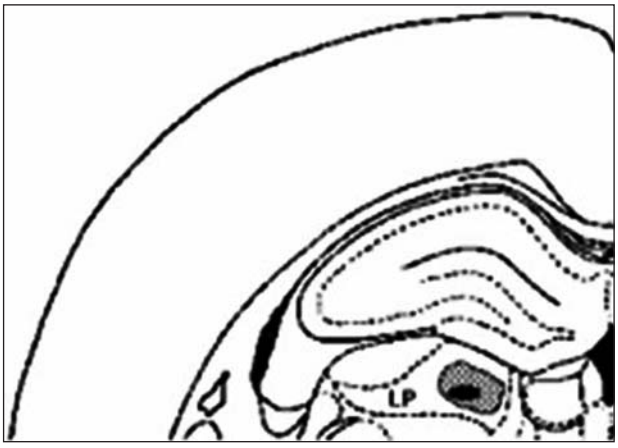

Fig 2. Diagrammatic representation of the extent of the lesioned area following ibotenic acid injection in the lateral posterior thalamic nuclei (LP). The hatched area represent the larger lesion while black area depict the smaller lesion.

manifestations, initiation and propagation of epileptic seizures[43], although the possible role of thalamic nuclei in triggering and spreading epileptic discharges has been discussed over the last four decades[44]. The importance of the thalamus in the genesis of epileptic seizures correlates with its extensive projection to the cortex and other areas, including the basal ganglia, cerebellum, and hippocampus[45,46]. Whilst TLE is the most common form of partial epilepsy, and hippocampal atrophy and sclerosis are the most frequent abnormalities associated with TLE, brain structural changes in patients with TLE are not confined solely to the hippocampus. Indeed, they have been reported to occur in other brain regions, such as the parahippocampal region, entorhinal and perirhinal cortex[47-49]. Interestingly, a recent study demonstrated thalamic atrophy in patients with TLE, which was more prominent in the thalamic nuclei that have strong connections with the limbic system[50]. Moreover, using the pilocarpine model of temporal lobe of epilepsy, our research group has also reported an important role of the posterior thalamus in the cerebral circuits of rats with epilepsy. The first study investigating the interictal cerebral metabolic rate by 14C-2DG autoradiography in chronic pilocarpine-induced rats, found an increase in glucose utilization by several epileptic brain regions[51]. The most relevant finding was a consistent rise of cerebral metabolic rate in the lateral posterior thalamic nuclei (LP), suggesting that the LP may be involved in the cerebral circuitry controlling epileptic activity during interictal intervals (Fig 1). The second study evaluated the contribution of LP to spontaneous recurrent seizure activity induced by pilocarpine[52]. It was shown in this study that bilateral LP lesion by ibotenic acid in chronic epileptic rats (Fig 2) resulted in an increase of seizure frequency, suggesting that LP is one of the most important thalamic nuclei involved in the inhibition of spreading mechanisms (Fig 3). Moreover, subtle thalamic structural abnormalities are also present in patients with generalized idiopathic epilepsies as revealed by MRI volumetric and voxel-based morphometry studies[53,54].

In accordance to the above mentioned findings, it seems plausible to propose that cardiovascular abnormalities and hence SUDEP, at least in some cases, could be related to the occurrence of lateral posterior thalamic morphological or functional changes. As research in this field must be guided by the possible mechanism of SUDEP, a number of arguments might be put forward.

From a morphological point of view, Boyko and coleagues[55] showed that bilateral injections of kainic acid into the thalamus, mainly in the lateral posterior thalamic nuclei, produced myocardial necrosis in adult rats, suggesting that this specific thalamic nucleus has a direct relationship with cardiovascular system. In the same way, it is very important to establish if there is a relation between lateral posterior thalamic nuclei dysfunction and cardiac functioning. According with this reasoning, an experimental study developed by our group could better start to reinforce this idea. In 2005, we evaluated the heart rate, *in vivo* (ECG) and isolated *ex vivo* preparation (Langendorf preparation) of rats with epilepsy[56]. Our results showed

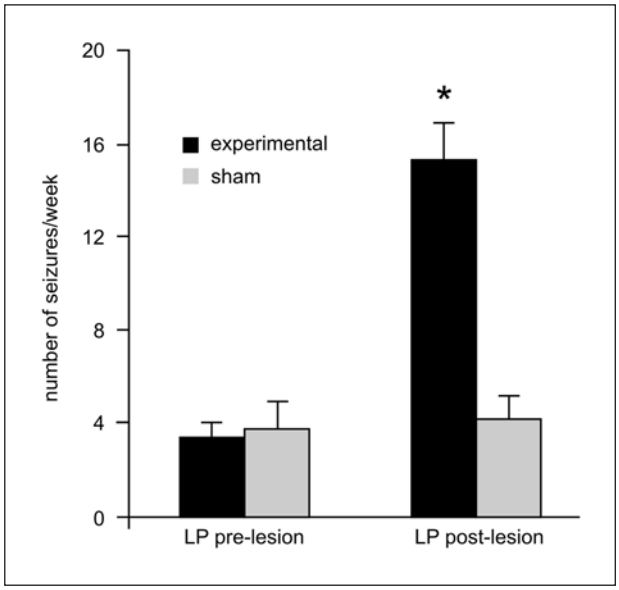

*Fig 3. Graphic representation of the cumulative frequency of spontaneous seizures per week detected in sham and experimental groups, before and after saline or ibotenic acid injections into lateral posterior thalamic nuclei (LP). Data are expressed as mean ±SD. *p<0.05.*

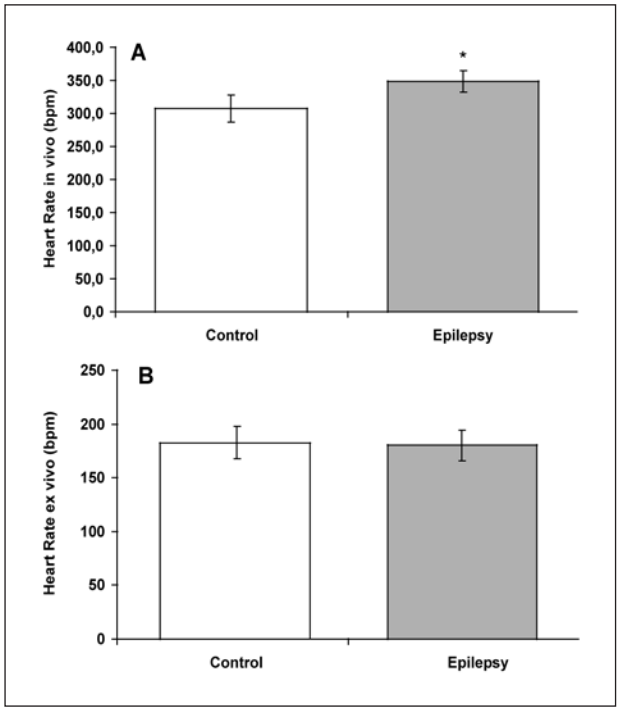

Fig 4. Mean and standard deviation of heart rates of control rats and rats with epilepsy obtained during in vivo (A) and isolated ex vivo situation (B).

significant differences in the mean of heart rate *in vivo* between the groups (control animals: 307±9 bpm; animals with epilepsy: 346±7bpm). In contrast, we did not find differences during isolated *ex vivo* situation (control animals: 175±7 bpm; animals with epilepsy: 176±6 bpm), suggesting a central nervous system modulation on the heart (such as thalamic nucleus), which could explain the sudden unexpected death in epilepsy (Fig 4). Quite interesting and more recently, our group (Scorza and colleagues, *unpublished data*) evaluated the heart rate (*in vivo* and isolated *ex vivo*) of rats with epilepsy before and after bilateral LP lesion. The results showed significant differences in the mean heart rate *in vivo*, but surprisingly, no differences in heart rate could be observed in the isolated *ex vivo* situation. These observations seem to indicate a certain kind of specific thalamic modulation over the heart functioning what could support our hypothesis of SUDEP due to heart failure in consequence of thalamic dysfunction.

In summary, we would like to raise the possibility that the presence of thalamic nuclei lesions in people with TLE could underlie some processes that culminates in SUDEP and that heart failure could have a significant role in this mechanism. However, a clear relationship between TLE, thalamic dysfunction, heart failure and SUDEP still needs to be demonstrated both in experimental and human conditions. In the meantime, strategies, such as taking a detailed cardiovascular history, looking for cardiovascular co-morbidity, cardiovascular risk factors and prior cardiac findings (electrocardiogram and echocardiogram), should be developed in an attempt to prevent SUDEP.

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