Respiratory Physiology & Neurobiology 189 (2013) 315–323

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

journal homepage: www.elsevier.com/locate/resphysiol

Review

Sudden unexpected death in epilepsy: Fatal post-ictal respiratory and arousal mechanisms☆

Levi P. Sowers[a,b], Cory A. Massey[a,b,c], Brian K. Gehlbach[b,c,d], Mark A. Granner[a,b], George B. Richerson[a,b,e,f,*]

[a] Department of Neurology, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, IA 52242, United States
[b] Roy J. and Lucille A. Carver College of Medicine, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, IA 52242, United States
[c] Interdisciplinary Graduate Program in Neuroscience, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, IA 52242, United States
[d] Department of Internal Medicine, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, IA 52242, United States
[e] Molecular Physiology and Biophysics, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, IA 52242, United States
[f] Vetranan Affairs Medical Center, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, IA 52242, United States

ARTICLE INFO

Article history:
Accepted 14 May 2013

Keywords:
SUDEP
Death
Respiratory
Peri-ictal

ABSTRACT

Sudden unexplained death in epilepsy (SUDEP) is the cause of premature death of up to 17% of all patients with epilepsy and as many as 50% with chronic refractory epilepsy. However, SUDEP is not widely recognized to exist. The etiology of SUDEP remains unclear, but growing evidence points to peri-ictal respiratory, cardiac, or autonomic nervous system dysfunction. How seizures affect these systems remains uncertain. Here we focus on respiratory mechanisms believed to underlie SUDEP. We highlight clinical evidence that indicates peri-ictal hypoxemia occurs in a large percentage of patients due to central apnea, and identify the proposed anatomical regions of the brain governing these responses. In addition, we discuss animal models used to study peri-ictal respiratory depression. We highlight the role 5-HT neurons play in respiratory control, chemoreception, and arousal. Finally, we discuss the evidence that 5-HT deficits contribute to SUDEP and sudden infant death syndrome and the striking similarities between the two.

1. Introduction

Estimates suggest that up to 6 people die each day in the U.S. of SUDEP, a devastating condition afflicting patients with epilepsy (Shorvon and Tomson, 2011; Thurman, 2011). In most cases, individuals are healthy (excluding the diagnosis of epilepsy), but are unexpectedly found dead, often in the prone position in bed with evidence of a recent seizure. For such a major public health concern, it is surprising that SUDEP remains largely unknown to the general public and, more alarmingly, to many clinicians. According to a recent report, only 56% of Canadian pediatricians who care for epilepsy patients knew that children with epilepsy were at an increased risk of sudden death, and only 33% knew of the term SUDEP (Donner et al., 2012), indicating a critical need for increased education.

SUDEP is defined as "the sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death of patients with epilepsy with or without evidence of a seizure, excluding documented status epilepticus, and in which postmortem examination does not reveal a structural or toxicological cause of death" (Nashef, 1997). There are three classifications of SUDEP: first is definite SUDEP, which adheres to the aforementioned definition; second is probable SUDEP where there is no post-mortem examination but the other criteria for SUDEP are met; and finally possible SUDEP in which there are competing causes of death but SUDEP cannot be ruled out.

It is becoming apparent that SUDEP is much more common than previously recognized, but it has been difficult to obtain precise estimates of its incidence. There are many epidemiological studies on SUDEP, but these were done among different populations of patients with different types and severity of seizures making them difficult to compare. The reported rates cover a wide range from 0.09 per 1000 person years among unselected incident cases of epilepsy to 9.3 per 1000 person years among epilepsy surgery candidates (Shorvon and Tomson, 2011). The lifetime risk of SUDEP ranges from 10 to 17% in all epilepsy patients to 10–50% in chronic refractory epilepsy patients (Ficker, 2000; Shorvon and Tomson, 2011).

☆ This paper is part of a special issue entitled "Clinical Challenges to Ventilatory Control", guest-edited by Dr. Gordon Mitchell, Dr. Jan-Marino Ramirez, Dr. Tracy Baker-Herman and Dr. Dr. David Paydarfar.

* Corresponding author at: The University of Iowa, 1000 Med Labs, 25 South Grand Avenue, Iowa City, IA 52242, United States. Tel.: +1 319 356 4296.
E-mail address: George-Richerson@uiowa.edu (G.B. Richerson).

1569-9048/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.resp.2013.05.010

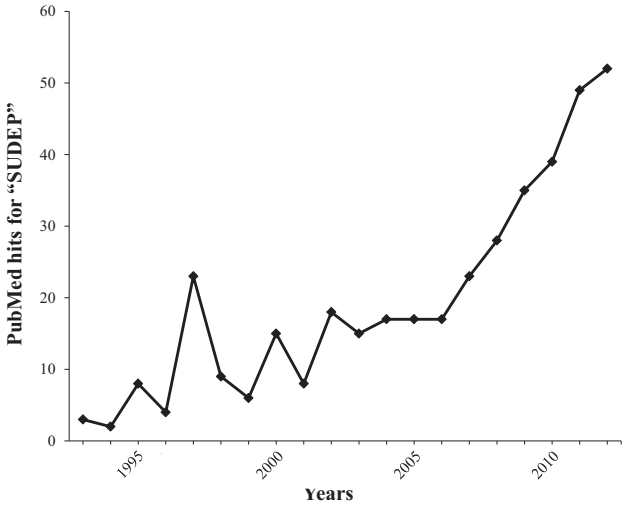

Fig. 1. SUDEP research is growing at a rapid pace. In 1993 there were few publications that appeared in a PUBMED search using the term SUDEP. However, in 2012 there was greater than 50 publications with SUDEP in the title. This graph highlights the increased attention SUDEP research has recently received.

One recent estimate suggests that the annual incidence of SUDEP in refractory epilepsy patients (which make up one-third of all epilepsy patients) is 1/1000 which translates into about 2000–3000 deaths per year in the U.S. (Thurman, 2011). When this incidence is compared to other major neurological disorders (Alzheimer's disease and stroke each occur at a rate of about 70,000–80,000 deaths per year in the U.S.), SUDEP is relatively uncommon. However, the peak incidence of death for SUDEP is 30 years, so when quantified as years of potential life lost, SUDEP accounts for 73,000 years lost, second only to stroke among neurological disease (Thurman, 2011). From a public health perspective SUDEP is a major problem, yet this has only recently resulted in increased research into the mechanisms of SUDEP. For example, there were only 4 publications in 1993 (Fig. 1) that appeared in a Pubmed search using the term SUDEP. In 2012 there were >50 publications that used SUDEP, showing a significant increase in interest in studying this syndrome (Fig. 1).

Although research on SUDEP has recently begun to expand, many fundamental questions remain unanswered. What are the risk factors for SUDEP? What are the pathophysiological mechanisms underlying SUDEP? How do we effectively study SUDEP in epilepsy patients, and how representative of the human condition are animal models of SUDEP that are utilized for research? How can respiratory physiologists contribute to this field? Are there ways to prevent SUDEP or definitively diagnose it when it does occur? Moreover, there is a crucial need to better standardize research methods from bench to bedside so that definitive conclusions can be made about SUDEP. With increased research and awareness of SUDEP, it is likely that many cases can be prevented.

There have been many risk factors proposed for SUDEP, including: poor compliance with antiepileptic medications, young age at onset of seizures, chronic refractory epilepsy, male sex, and sleeping in the prone position (Shorvon and Tomson, 2011; Thurman, 2011). The most consistent risk factor for SUDEP is the frequency of generalized tonic clonic seizures (GTCS) (Hesdorffer et al., 2011). However, patients who do not experience any GTCS remain at considerably higher risk than the general population. Many of these risk factors are inconsistently reported throughout the literature, highlighting a need to better understand the underlying mechanisms of SUDEP. It is beyond the scope of this review to fully describe all potential mechanisms of SUDEP. Therefore, we will briefly describe cardiac and postictal generalized electroencephalogram (EEG) suppression (PGES), then concentrate on the potential respiratory mechanisms underlying SUDEP for this special issue of *Respiratory Physiology and Neurobiology*. Furthermore, we highlight the need for a codified methodology for studying SUDEP, in order to appropriately understand this condition.

2. Potential pathophysiological mechanisms in SUDEP

It is important to remember that there are only two ways to die, either you stop breathing or your heart stops. If one occurs then the other is soon to follow. There are many different ictal events that could potentially lead to one of these two outcomes in SUDEP. For example, there is good evidence that seizures can sometimes induce arrhythmias or peri-ictal respiratory depression. Research to date indicates all SUDEP is not caused by a single mechanism, but that different mechanisms can occur in different people. These mechanisms can then cause death by inducing cardiac or respiratory dysfunction or both.

2.1. Cardiac dysfunction in SUDEP

Peri-ictal cardiac dysfunction is thought to play a role in a subset of SUDEP cases (Brotherstone et al., 2010; Neufeld et al., 2009; Surges et al., 2010a, 2010b, 2010c; Surges and Walker, 2010). Tachycardia is the most common ictal autonomic event. In one study of 76 patients tachycardia occurred in 57% of seizures and in 76% of patients at least once, and was significantly correlated with seizure generalization (Rowe, 1987). Seizures can also induce peri-ictal bradycardia or asystole (Lee, 1998; So et al., 2000). Although case studies report a frequent occurrence of post-ictal bradycardia with asystole, in one study patients monitored in an EMU displayed bradycardia in only 2% of seizures (Moseley et al., 2010; Rowe, 1987). Asystole was even more rare, with a rate less than 0.5% (Moseley et al., 2010; Rowe, 1987). In a study of 56 patients with 250 recorded seizures, there was only one episode of ictal bradycardia with asystole. That event was associated with oxygen desaturation below 50% (Bateman et al., 2008), which can be assumed to be due to hypoventilation. Since respiratory monitoring was not done it is not known if the respiratory dysfunction, such as central apnea, was the primary event and asystole was then secondary to the resulting hypoxemia, but that is the most likely scenario. Although some reports give the perception that primary cardiac dysfunction causes a large percentage of SUDEP deaths, the studies described above and others suggest that severe cardiac dysfunction as a primary event actually occurs at a much lower rate (Moseley et al., 2010; Rowe, 1987).

An area of considerable emphasis in SUDEP research is long QT syndrome (LQTS) and the genes underlying that disorder. Mutations in more than 10 different genes cause LQTS (Goldenberg and Moss, 2008). These mutations affect ion channels expressed throughout the body and typically cause a long QT interval in the electrocardiogram (EKG) (Goldenberg and Moss, 2008). This prolonged QT interval can lead to cardiac arrhythmias and sudden death in patients without epilepsy (Goldenberg and Moss, 2008). However, some patients with epilepsy carry these LQTS gene mutations (*e.g. KCNH2*) and some of those patients have a higher rate of SUDEP (Le Gal et al., 2010). Thus, LQTS gene mutations increase the risk of SUDEP (Goldman et al., 2009). However, every patient with a mutation in one of these genes who dies did not necessarily have a fatal cardiac arrhythmia. Many of the LQTS genes are expressed in both the heart and brain (Cheah et al., 2012; Goldman et al., 2009; Holth et al., 2013), and a mutation in one of them could potentially affect breathing or other vital brain functions. For example, KCNQ1 is expressed in brain stem nuclei that are important for autonomic