Session 4: From unwitnessed fatality to witnessed rescue: pharmacological intervention

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Abstract

The mechanisms of SUDEP have been difficult to define, as most cases occur unwitnessed, and physiological recordings have been obtained in only a handful of cases. However, recent data obtained from human cases and experimental studies in animal models have brought us closer to identifying potential mechanisms. Theories of SUDEP should be able to explain how a seizure starting in the cortex can sometimes lead to changes in brainstem cardiorespiratory control mechanisms. Here we focus on three major themes of work on the causes of SUDEP. First, evidence is reviewed identifying postictal hypoventilation as a major contributor to the cause of death. Second, data are discussed that brainstem serotonin and adenosine pathways may be involved, as well as how they may contribute. Finally, parallels are drawn between SIDS and SUDEP, and we highlight similarities pointing to the possibility of shared pathophysiology involving combined failure of respiratory and cardiovascular control mechanisms. Knowledge about the causes of SUDEP may lead to potential pharmacological approaches for prevention. We end by describing how translation of this work may result in future applications to clinical care.

This manuscript focuses on mechanisms of SUDEP, as revealed by animal and human studies. Analysis of data from monitored human cases has refined our understanding of the final events leading to death. It is now clear that seizures immediately preceding SUDEP often lead to rapidly developing hypoventilation and bradycardia. More extensive use of animal models, including ones that more closely replicate the human condition, provide a detailed understanding of the pathophysiology of seizure-induced changes in cardiorespiratory function. Increasing our knowledge of the mechanisms of SUDEP is our

best hope for developing pharmacological approaches for prevention, and for guiding targeted translation of research to clinical care. We will address three main themes.

First, recent evidence supports the hypothesis that apnea/hypoventilation plays a significant role in SUDEP, and in some cases may be the primary cause of death.[1] Some investigators previously assumed SUDEP to be exclusively due to cardiovascular mechanisms (asystole, bradycardia, arrhythmia, hypotension, etc.), but data from monitored cases of SUDEP do not support the conclusion that the initial inciting event is usually cardiac.[1] The relative importance of cardiovascular versus respiratory mechanisms is unknown, but both appear to be involved, possibly reflecting a global neurovegetative dysfunction induced centrally by seizures.[1] In addition, impaired arousal mechanisms have not received much attention, and yet the deep post-ictal unresponsiveness, of which post-ictal generalized EEG suppression (PGES) may be a correlate,[2] may also play an important role by preventing protective reflexes.[3–5]

Second, serotonin and adenosine pathways are promising targets for pharmacological therapy[4,6–9]. It is unclear whether either one is central to the pathophysiology, but drugs targeting one or both of these two systems might reduce the risk of SUDEP in high-risk populations. Sites of interaction between these two neurotransmitter pathways may be particularly effective targets for treatment. Two other neurotransmitter pathways of potential interest are that of endogenous opioids and γ-aminobutyric acid (GABA).

Third, and separate from any possible cardiac susceptibility to sudden death, there are similarities between SUDEP and SIDS that may lead to a better understanding of the mechanisms of both, and may help guide preventive measures.[4, 5, 10–12] Recent data suggest that some cases of SIDS may be due to seizures that go unrecognized.[13, 14] SIDS and SUDEP have both been linked to the 5-HT system,[4, 11, 15–20] and together with other similarities in presentation and diagnostic criteria, this has led to the suggestion that they may share a final common pathway leading to death.[4,5,12]

Respiratory dysfunction in SUDEP

It has long been known that changes in cardiovascular function occur during and after seizures. Since most sudden deaths in non-epileptic patients without structural cardiac disease are due to arrhythmias, this led some to assume that SUDEP is usually a result of seizure-induced cardiovascular dysfunction, such as tachyarrhythmias, asystole or parasympathetic vasodilation and hypotension.[21] The possible contribution to SUDEP of genetic susceptibility to sudden cardiac death is discussed in detail by Goldman et al in this supplement,[22] but it is nevertheless worth considering that some genes implicated in cardiac arrhythmias may also be expressed in brainstem respiratory nuclei.

In some witnessed SUDEP cases, respiratory difficulties were seen prior to death.[1, 23–25] For more than a century, it has been known that seizures can induce significant hypoventilation.[26] Recently it has been found that apnea and O_2 desaturation are much more common than previously realized after generalized convulsive or partial seizures.[27,28]

Direct observations of SUDEP are limited. Until 2013 there were only eight published cases of SUDEP monitored at the time of death,[2, 23, 29–33] and in that year the MORTEMUS study added another six while systematically reanalyzing five previously published cases.[1] In none of these 14 cases were oronasal airflow, impedance plethysmography, tidal volume, ventilation, end tidal CO_2, O_2 saturation or blood gases recorded. In 10 cases, respiratory rate was estimated by watching chest and abdominal movements on video, together with respiration-induced artifact on EEG,[1] but this method is not able to rule out airway obstruction, paradoxical breathing or shallow breathing. Measuring respiratory rate alone does not allow an estimate of alveolar ventilation, which requires knowledge of tidal and dead space volumes.

Data from patients who died of SUDEP while being monitored in epilepsy monitoring units (EMUs) have yielded highly valuable information about pathophysiological mechanisms. These data, such as from the MORTEMUS study,[1] reveal that apnea/hypoventilation and bradycardia/asystole both occur as terminal events. Methodological limitations have made it difficult to draw firm conclusions from these observations. However, among the many important results from this study, one of the most valuable was that central apnea occurred prior to death, and changes in breathing were not those that occur in response to global hypoperfusion.[34] Another was that every case of monitored SUDEP occurred after a generalized tonic-clonic seizure (GTCS). Therefore, it is reasonable to conclude that changes in respiratory and cardiac physiology induced by GTCS are relevant to SUDEP, and these can be studied in patients who do not die.

It is now widely believed that at least some cases of SUDEP are due to hypoventilation induced by seizures. However, it remains necessary to explain why when apnea occurs in around 50% of seizures, whether partial or generalized,[27, 28] SUDEP only occurs once out of thousands of seizures and usually only after GTCS.[1]

Role of 5-HT in SUDEP

Normal function of 5-HT neurons

There is a relatively small number of 5-HT neurons in the brain, located primarily in the brainstem raphe nuclei.[35, 36] Some 5-HT neurons are involved in thermoregulation, others in arousal, mood, appetite or other brain functions.[36, 37] A subset are sensors of arterial PCO_2[37–41] and respond indirectly through a decrease in intracellular pH.[42] They are proposed to be central respiratory chemoreceptors that stimulate breathing to restore CO_2 back to normal.[37, 43–47] A separate subset of serotonin neurons in the midbrain is also sensitive to an increase in blood PCO_2,[48] but instead of stimulating breathing they cause cortical arousal,[3] an important component of the protective response to hypercapnia. If a person is asleep or postictal, and a mattress, blanket or pillow obstructs their mouth and nose, it is important to become more alert so they can move and relieve the airway obstruction.

Rodent 5-HT neurons in slices or in culture increase their firing rate by an average of 3-fold when pH is decreased from 7.4 to 7.2,[39, 40–42] well within the range that stimulates breathing *in vivo*. These neurons are closely associated with the basilar artery and its major

branches where they can accurately monitor arterial PCO_2.[48, 49] 5-HT neurons project to all major respiratory nuclei, and release serotonin, thyrotropin releasing hormone (TRH) and substance P.[37] These neurotransmitters stimulate respiratory neurons,[37] and in some cases induce bursting pacemaker activity in neurons that are rhythmically active *in vivo*.[50, 51] Stimulation of 5-HT neurons *in vivo* causes an increase in ventilation.[52]

Studies of 5-HT neurons have been facilitated by genetically engineered mice deficient in 5-HT neurons (*Lmx1b^{f/f/p}*). *Pet1* is a transcription factor expressed in all 5-HT neurons and only 5-HT neurons.[53] *Lmx1b* is another transcription factor required for survival of many brainstem neurons.[54] To specifically delete all 5-HT neurons[55] one mouse strain that expressed the virus protein cre recombinase (cre) under control of the promotor for *Pet1* (PET1-Cre) was mated with a second mouse strain that contained LoxP sites flanking the LMX1B gene (floxed LMX1B). When bred to produce offspring with two alleles (homozygous) of floxed LMX1B and at least one allele for PET1-CRE, the LMX1B gene was deleted in all embryonic 5-HT neurons.[55] As 5-HT neurons first differentiate during embryonic development, they express cre, the LMX1b gene is then excised, and this causes them to die. Other neurons are unaffected.

The absence of 5-HT neurons causes neonatal *Lmx1b^{f/f/p}* mice to have severe apnea lasting as long as 55 seconds and 30% die in the first few days of life.[56] In those that survive, breathing normalizes after 12 days of age, except that their ventilatory response to inhaled CO_2 is decreased by about 50%.[45] They also no longer wake up from sleep in response to 3–7% CO_2 in the air, and thus lack this important protective reflex.[3] These and other data support the conclusion that some 5-HT neurons in the medulla are central respiratory chemoreceptors, whereas other 5-HT neurons in the midbrain are "central arousal chemoreceptors" that are a component of the ascending reticular activating system.

Evidence that 5-HT mechanisms contribute to SUDEP

The first clue that the 5-HT system might be involved in SUDEP was that mice in which the 5-HT$_{2c}$ receptor is genetically deleted have spontaneous generalized seizures, and during those seizures that progress to a tonic extension phase, these HTR$_{2C}^{-/-}$ mice rapidly die[8, 57] due to respiratory arrest. These mice also provided early evidence that 5-HT can raise the seizure threshold, a conclusion now supported by data from many other approaches.

The DBA/1 and DBA/2 mouse strains with audiogenic seizures often die from respiratory arrest after generalized seizures with tonic extension.[58, 59] Death of DBA/1 & DBA/2 mice can be prevented by brief postictal mechanical ventilation.[9, 59] Pretreatment with fluoxetine, a selective serotonin reuptake inhibitor (SSRI), also prevents respiratory arrest.[9]

The lack of 5-HT neurons in *Lmx1b^{f/f/p}* mice makes them more susceptible to maximal electroshock and to pilocarpine-induced seizures, and when they have seizures they are more prone to respiratory arrest.[60] Thus, defects in the 5-HT system in mice can increase susceptibility to seizures and to seizure-induced death. Seizure-induced death can be reduced in *Lmx1b^{f/f/p}* mice by agonists of 5-HT$_{2A}$ receptors. As would be predicted, SSRIs have no effect in these mice that lack 5-HT neurons.[60]

Similarities between SUDEP and SIDS

SIDS is defined as the sudden and unexpected death of an infant under 12 months of age, usually associated with sleep, that remains unexplained after a complete autopsy, death scene investigation, and review of the clinical history.[61] In the U.S., SIDS is the leading cause of death between 1 and 12 months of age, with an incidence of 0.6 per 1000 live births, or 6 deaths per day in the U.S.A.[11] The risk of SIDS increases (>3 fold) when an infant is prone in bed,[62] an important observation that led to the successful public health campaign to place babies to sleep on their back as discussed by Tomson et al in this supplement.[63]

Even more than SUDEP, it has been exceedingly rare to capture physiological monitoring data from an actual SIDS event. Based on a very small number of monitored cases, a handful of witnessed cases, observations of death scenes, epidemiology, and other sources of information, the leading theories of pathophysiology have focused on paroxysmal events leading to cardiovascular or respiratory dysfunction made worse by abnormal arousal mechanisms.[11, 64] These events are thought to include homeostatic stressors such as airway obstruction, overheating, activation of the laryngeal chemoreflex, etc.[11]

A major step forward in SIDS research resulted from studies of brainstems of infants who died of SIDS. Using non-routine methods (e.g. receptor autoradiography, immunohistochemistry, HPLC, etc) to examine regions of the brainstem thought to be involved in chemosensitivity,[65] a number of abnormalities were found in medullary nuclei that contain 5-HT neurons, such as the raphe and arcuate nuclei. These abnormalities include atrophy[66] and decreased muscarinic receptor binding in the arcuate nucleus,[17] decreased LSD binding,[67] decreased 8-OH-DPAT binding,[18] an increase in immature forms of 5-HT neurons visualized using immunohistochemistry for tryptophan hydroxylase,[18] and a decrease in 5-HT content in brainstem nuclei using HPLC.[68] In addition there have been a number of other studies reporting various abnormalities of the 5-HT system.[11] It is not clear how these occur, but the link between cigarette smoking and SIDS[11] suggests that environmental exposures could contribute.

There are many similarities between SUDEP and SIDS including their definitions.[61, 69] In both it is common for death to occur in the prone position in bed, and both are related, at least at times, to periods of sleep.[70] Theories of pathophysiology for both center around cardiac, respiratory and arousal defects, and both have been linked to the 5-HT system. SIDS and SUDEP are heterogeneous syndromes, but there may be shared terminal mechanisms in many cases in both disorders. The many similarities suggest that SIDS and SUDEP may have similar causes or share a final common pathway.

Recent data suggest that some cases of SIDS may be due to unrecognised seizures;[13, 14] thus, some cases of SIDS could be SUDEP in infants not yet diagnosed with epilepsy. It is common for seizures in infants to manifest only with apnea.[71] An 8-month infant died soon after he was found prone having seizures and in respiratory distress after a sleep period.[13] Had he been found after death, he would have been diagnosed with SIDS. Another infant who died prone at 10 months of age after a sleep period would have been diagnosed with SIDS had he not had hippocampal asymmetry and microdysgenesis on autopsy.[14] Routine

autopsies rarely include such detailed analysis of hippocampal pathology, so there may be other infants diagnosed as SIDS with similar pathology.

By definition, SIDS only occurs before the age of 12 months, but toddlers can die from sudden unexpected death in childhood (SUDC) with a similar definition to SIDS and SUDEP and some common features such as an increase in risk when toddlers are asleep prone.[72, 73] Some of these children have hippocampal and temporal lobe anomalies, and the risk of these anomalies is increased to 82% if they or a family member have a history of febrile seizures.[73]

Taken together, the above suggests that a subset of SIDS and SUDC may actually be SUDEP in infants with occult seizures or their first seizure. If true, this informs research in both fields. SIDS research, for example, should examine a link to seizures, while SUDEP research should focus on brainstem pathology looking for evidence of abnormalities of 5-HT or other neurotransmitter systems.

Role of adenosine in SUDEP

The purine ribonucleoside adenosine is an endogenous homeostatic regulator of network activity.[74–76] Adenosine exerts its action via four different receptor subtypes that exhibit differential distributions within the brain, with some of these receptors only activated by the high levels of adenosine observed during seizures.[77–82] Conditions of excessive energy consumption as occur during a seizure or after an injury to the brain can trigger a surge in adenosine,[78, 83] considered an adaptive response to conserve energy[84] and limit the extent of injury.[85] Accordingly, increased adenosine suppresses neuronal activity as an innate mechanism to stop seizures.[86] Increased levels of adenosine and its metabolites were observed in human TLE patients following a seizure[78] and in the rodent hippocampus with seizures induced by several different convulsant drugs.[77] Changes in adenosine receptor density have also been observed in epilepsy patients and in animal models of epilepsy.[87–89] Importantly, adenosine is also involved in the control of respiration in the brainstem,[90, 91] and suppresses cardiovascular and respiratory functions through increased activation of brainstem adenosine receptors.[92–94] Paradoxically, a decrease in pH in hippocampal slices causes a rise in adenosine, which causes inhibition of glutamatergic excitatory neurotransmission through actions on A_1 adenosine receptors and ATP receptors.[87] However, it has been proposed that a decrease in pH in the brainstem causes release of ATP from a subset of respiratory chemoreceptors, and subsequently stimulates respiratory neurons,[95] leading to the opposite effect on excitability as occurs in the hippocampus. Adenosine also induces sedative actions,[96] which may be relevant to SUDEP. Adenosine agonists prolong post-ictal sedation and adenosine antagonists shorten it.[97] The 'adenosine hypothesis of SUDEP'[98] predicts that a seizure-induced adenosine surge in combination with impaired metabolic clearance can trigger lethal apnea or cardiac arrest. If excessive adenosine triggers SUDEP, then adenosine receptor antagonists, such as caffeine or theophylline, might prevent SUDEP.

Clinical relevance of adenosine signalling in SUDEP

Dietary factors have received little attention in the study of SUDEP. Caffeine use is common among the general population; it is thus fair to predict that a proportion of patients with epilepsy regularly consume caffeine. While the chronic use of methylxanthines may increase seizure risk,[99] we suggest that the same stimulants might also reduce the risk for SUDEP. To our knowledge, caffeine consumption has not been studied in case control studies of SUDEP. SUDEP often occurs at night[100, 101] during a physiological time span when plasma caffeine levels are lowest and brain adenosine levels are highest.[102, 103]

Role of metabolic adenosine clearance

Although a seizure induced adenosine surge limits the spatial and temporal extent of a seizure,[85] the resulting excess in adenosine needs to be metabolized effectively to avoid excessive postictal depression. In the adult brain, the metabolic clearance of adenosine under baseline conditions is largely under the control of astrocytes expressing equilibrative nucleoside transporters, followed by metabolism by two adenosine removing enzymes: 1) adenosine kinase (ADK), and; 2) adenosine deaminase (ADA).[7, 84, 104, 105] A seizure-induced adenosine surge, in combination with deficits in the metabolic clearance of adenosine constitutes a candidate mechanism for the development of lethal cardiorespiratory shutdown in SUDEP.[7] The following experimental evidence supports the adenosine hypothesis of SUDEP:

The role of adenosine in a mouse model of postnatal central apnea

Mice with genetic deletion of ADK (Adk−/− mice) have been generated,[106] and 35% of pups die within 4 days of birth. In most cases, death was accompanied by lethal apnea, leading to the suggestion that Adk−/− mice could be a model of SIDS.[106] However, these mice differ from human SIDS in that the latter are normal prior to death and on autopsy, whereas Adk$^{-/-}$ mice have long apneas at baseline and a variety of postnatal abnormalities. These findings, however, provide a direct mechanistic link between impairment of metabolic clearance of adenosine and periods of respiratory distress.

Caffeine prevents lethal apnea after traumatic brain injury

Like seizures, traumatic brain injury (TBI) is a known trigger for an adenosine surge.[83] Importantly, in human subjects exposed to severe TBI, high CSF levels of adenosine are associated with lethal apnea.[83] If this is due to excessive adenosine receptor activation in the brainstem, then caffeine should prevent lethal apnea after TBI. Severe TBI induced by lateral fluid percussion injury (FPI) in rats results in prolonged periods of apnea and a mortality rate of 47%,[107] with apnea significantly longer in animals that died. In contrast, injection of caffeine within 1 minute after the injury prevented extended apnea and lethal outcome.[107]

Deficiency in metabolic clearance of adenosine triggers lethal outcome after seizures

To evaluate whether seizure-induced adenosine release in combination with deficient adenosine clearance might increase the risk of SUDEP, mice were treated with erythro-9-(2-hydroxy-3- nonyl) adenine (EHNA) and 5-iodotubercidin (ITU), inhibitors of the two major adenosine degradation pathways, 15 min prior to the induction of acute seizures with kainic

acid (KA, 35 mg/kg, i.p.). KA-injected animals pretreated with saline instead of EHNA and ITU developed seizures of progressive intensity within 5 minutes after KA. Seizures reached a Racine severity score of about 3 and continued for > 60 min; however, none of these animals died. In contrast, animals treated with EHNA/ITU showed a delayed onset of seizures. However, once seizures developed, all animals rapidly progressed to stage 5 seizures and died within 20 minutes.[98] These data suggest that deficiency in the metabolic clearance of adenosine might reduce seizures but contribute to lethal outcome after seizures.

Chronic recurrent seizures cause changes in adenosine metabolism in the brainstem

To assess the role of adenosine homeostasis in a model of pharmacoresistant temporal lobe epilepsy, intra-hippocampal KA was employed.[108, 109] Four weeks following KA-injection, when animals typically develop hippocampal sclerosis and spontaneous recurrent seizures, prominent upregulation of ADK immunoreactivity was seen in the nucleus tractus solitarius (NTS). Upregulation of ADK in the NTS might be a compensatory response to enhance the metabolic clearance of adenosine in this critical brainstem area.

SUDEP modelled in heterozygous $Adk^{+/-}$ mice

To further investigate whether impaired metabolic clearance of adenosine could contribute to SUDEP $Adk^{+/-}$ mice were chosen, which express only 50% of ADK.[106] Eight $Adk^{+/-}$ mice and 11 wild-type (WT) littermates received intrahippocampal injections of KA to trigger epilepsy. Four weeks after KA injection, intrahippocampal EEG recordings confirmed an epileptic phenotype. Importantly, the epileptic phenotype in $Adk^{+/-}$ mice was less severe than in WT littermates, which experienced more than twice as many seizures. However, $Adk^{+/-}$ mice, despite their attenuated epileptic phenotype, displayed an increased incidence of 'sudden death' with three out of eight animals dying within eight weeks of the emergence of epilepsy. In contrast, none of the 11 WT littermates died during the same time span.

Adenosine and seizure-induced respiratory arrest in mice and rats

DBA/2 mice are susceptible to seizure-induced respiratory arrest (SIRA).[9, 58, 59, 110, 111] In a small percentage of DBA/2 mice that exhibit seizures without SIRA, administration of adenosine (2 mg/kg) significantly increased the incidence of SIRA. Higher adenosine doses, however, reduced the incidence of seizures in DBA/2 mice, so that SIRA could no longer be evoked. In a second group of DBA/2 mice that exhibited seizures without SIRA, administration of ITU caused a significant increase in SIRA at 30 minutes and partial reduction in SIRA at 24 hours. In a third group of DBA/2 mice that initially exhibited SIRA, administration of caffeine at certain doses significantly reduced the incidence of SIRA. Blocking adenosine metabolism with ITU and EHNA in genetically epilepsy prone rats (GEPR-9s) resulted in a significant decrease in post-ictal SpO2% and a significant increase in the incidence of death between 1 and 24 hours post-treatment, compared to untreated GEPR-9s. These data suggest that a seizure-induced rise in adenosine levels may contribute to seizure-induced respiratory depression observed in patients with epilepsy.[27, 28]

Translating progress in the pathophysiology and pharmacology of SUDEP into clinical trials in patients with epilepsy

The challenge of studying SUDEP prevention in patients with epilepsy

As discussed by Tomson et al in this supplement,[63] any attempt to design a clinical trial targeting prevention of SUDEP needs to fully appreciate the challenges posed by the sample size needed and patient recruitment. If one considers an incidence of SUDEP in patients with refractory epilepsy of about 5/1000 patient-years,[112] the sample size required to demonstrate a 50% reduction in SUDEP rate over one year, with a statistical power of 90% and a 5% type-1 error, would be 25,120. Recruiting that many patients with intractable epilepsy in a one-year long double-blind randomized controlled trial (RCT) is unrealistic, both in terms of cost, recruitment capacities, and ethics, taking into consideration the level of evidence regarding currently proposed prevention strategies. Accordingly, and as discussed below, progress in three areas are needed before a RCT can be considered: 1) identification of a population at higher risk of SUDEP than the general population of patients with refractory epilepsy, 2) determining a safe strategy, the potential effectiveness of which in preventing SUDEP is considered high, and 3) seeking further evidence, both in animals and patients with epilepsy, in support of such effectiveness.

Identifying a population at very high risk of SUDEP

Patients with refractory epilepsy demonstrate the highest SUDEP incidence (about 0.5% per year) culminating in a rate of 9.3/1000 patient-years in those undergoing pre-surgical evaluation or having failed epilepsy surgery,[113] and 6.9/1000 patient-years in patients enrolled in add-on RCTs of antiepileptic drugs (AEDs) allocated to placebo treatment.[114] However, a subgroup of patients, still to be identified, might carry most of the SUDEP burden and suffer an annual risk of up to 2–5% between the age of 20 and 40. Identifying these patients would dramatically reduce the number needed for recruitment in a SUDEP prevention RCT, down to 2420 patients using the same figures as those previously considered (1-year follow-up; 50% reduction of SUDEP rate; $\alpha = 0.05$, $1-\beta = 0.9$). Selection of patients at very high risk of SUDEP should also promote participation of patients to be recruited in such a trial.

The main risk factor for SUDEP is the presence and frequency of generalized tonic-clonic seizures with an odds ratio of above 15 for patients with 3 GTCS per month.[115, 116] This figure was calculated from mixed populations of patients seen at epilepsy centres and community-based cohorts of prevalent epilepsy,[115] both of which suffer SUDEP rates between 1 and 2/1000 patient-years.[117] Considering that 12% of the controls suffered from more than three GTCS per year,[115] one can extrapolate that the subgroup of patients with 3 GTCS/year suffer an annual rate of SUDEP grossly ranging from 5 to 18/1000 patient-years. Thus, we need to identify other biomarkers to select patients with the greatest risk of SUDEP. Those currently considered include the occurrence of nocturnal seizures,[118] prolonged post-ictal EEG suppression, ictal/post-ictal hypoxemia, mood disorders and other biomarkers of serotonergic dysfunction, and gene polymorphisms.[22, 119] For some of these biomarkers, development of medical devices and biosensors that will collect such

information in ambulatory patients might be a prerequisite to the demonstration of their predictive value.

Determining a safe SUDEP prevention strategy with high likelihood of success

Another way to promote the feasibility of RCTs for SUDEP prevention is to increase the effect size of an intervention. Targeting an 80% reduction in SUDEP rate, rather than 50%, would reduce the number of patients to be recruited from 2420 to 760, using the same parameters as above (patients with 5% annual risk; $\alpha = 0.05$, $1-\beta = 0.9$). While such an ambitious objective might sound unrealistic, it is supported by recently published data. Indeed, a meta-analysis of all double-blind randomised placebo controlled trials performed in adult patients with refractory epilepsy showed that patients receiving an add-on AED had an 87% lower risk of SUDEP (0.9/1000 patient-years) than those receiving placebo on top of their baseline AED treatment (6.9/1000 patient-years) during the brief double-blind phase of clinical trials.[114] If simply adding an AED can reduce the risk of SUDEP to such an extent, one can hope that an intervention specifically tackling the pathophysiology of SUDEP might prove as effective.

Potential prophylactic and peri-ictal pharmacological SUDEP intervention strategies

Interventions to be tested in RCTs for SUDEP prevention should first be proved to be highly potent in pre-clinical and proof-of-concept studies. These interventions should also be proved to be reasonably safe, especially regarding their impact on seizure frequency and severity. As discussed in previous sections, targeting mechanisms involved in seizure termination, such as adenosine release, might carry the risk of aggravating seizures. Non-pharmacological interventions are discussed by Rugg-Gunn et al in this supplement[120] as is the role of education (Donner et al).[121] Here we highlight potential pharmacological interventions, prophylactic and peri-ictal.

SSRIs

A bulk of experimental data suggest that potentiation of serotonergic neurotransmission is associated with antiepileptic properties.[122–128] Several studies evaluated the impact of SSRIs on seizure frequency in patients with epilepsy. In a pilot open-label study of fluoxetine in 17 patients with drug resistant focal seizures and no depression, six became seizure-free for a mean period of 14 months, while the remaining patients demonstrated a 30% mean reduction in seizure frequency.[129] Three other series evaluated the risk of seizure aggravation in a total of 181 patients with epilepsy and comorbid depression treated with either sertraline, citalopram, or fluoxetine for a mean period of 4, 10 and 25 months.[130–132] Only two, both treated with sertraline, reported a significant increase in seizure frequency[130, 132]. In one of these studies, seizure frequency decreased in 39 of 45 treated patients.[131] Overall, using SSRIs in patients with focal epilepsy at risk of SUDEP appears safe, regardless of whether or not patients are depressed.

Adenosine receptor antagonists and promoters of adenosine clearance

Conversely, the therapeutic use of the non-selective adenosine receptor antagonist caffeine may be a double-edged sword. Caffeine (as all methylxanthines) may exacerbate seizures via

blockade of the 'anticonvulsant' A_1Rs[99] in the limbic system. In patients with epilepsy, case reports also suggest that caffeine and aminophylline might increase seizure frequency.[133] Caffeine was also found to potentiate the length of seizures triggered by electroconvulsive therapy.[134] The use of region-selective or receptor subtype selective (e.g. $A_{2A}R$ vs. A_1R) agents may capitalize on the anti-SUDEP effects of adenosine antagonists while avoiding any proconvulsant effects. An innovative strategy might be the enhancement of metabolic clearance of adenosine. Human patients with severe combined immunodeficiency syndrome (SCID) lack ADA and receive a stabilized form of the enzyme (PEG-ADA) as an enzyme replacement therapy to prevent this otherwise lethal condition.[135, 136] PEG-ADA therapy might be sufficient to enhance the metabolic clearance of adenosine to avoid overactivation of adenosine receptors in the brainstem. This extremely expensive treatment currently requires intra-muscular injection.

Importantly, adenosine homeostasis in the brain is influenced by factors such as diet, sleep, and exercise.[75] It would thus be of considerable interest to investigate the potential role of such lifestyle choices as modifiers of SUDEP risk.

Opioid receptor antagonists

Convincing evidence points to a role for opioids in post-ictal seizure inhibition. Potentiation of endogenous anti-ictal mechanisms by opioids has been shown in animal models of epilepsy.[137] Kainic acid-induced seizures elicit dynorphin release in rodent hippocampus and activation of presynaptic kappa-opioid receptors (KOR) inhibits glutamate release and limits the spread of excitability in this region.[138, 139] Similarly, several reports indicate that enkephalin release is induced by epileptiform activity[140] and that mu-opioid receptor (MOR) activation can induce anticonvulsant effects.[141] In humans, ictal and immediate post-ictal modifications of opioid receptor binding have been demonstrated using $[11^C]$diprenorphine positron emission tomography in patients with reading-induced epilepsy,[142] absence epilepsy[143] and temporal lobe epilepsy,[144, 145] suggesting an increase of synaptic opioid levels at the time of seizures. Overall, there are convincing data to conclude that endogenous opioids are released during focal and generalized seizures,[146, 147] suggesting that the latter might also contribute to the pathophysiology of SUDEP.[119] Indeed, the impact of opioids on the control of respiration is well known[148] and respiratory depression is one of the cardinal symptoms of opioid overdose.[149] Respiratory patterns in patients exposed to high doses of opioids demonstrate alterations of rhythmic breathing, with irregular respiratory patterns and/or transient apnea reminiscent of that observed in monitored SUDEP.[148] This effect is related to direct inhibition of respiratory neurons by activation of opioid receptors.[148, 150]

Opioid-mediated respiratory distress can be very rapidly reversed by application of naloxone, an antagonist of opioid receptors, leading to patient awakening between 30 seconds and 2 minutes post-injection.[149] There is no major safety issue reported with naloxone, including no risk of seizures. Naltrexone is another antagonist of MOR and KOR used in the chronic management of alcohol dependence and opioid dependence since 1994.[151, 152] It is usually given orally at a standard dose of 50 to 100 mg/day,[151] and an intra-muscular extended-release formulation is also available.[153] As with naloxone, no life-threatening side effects have been reported with naltrexone,[151] including no epilepsy-related

alert in patients with chronic alcoholism who suffer a high risk of seizures.[154_156] However, neither naloxone nor naltrexone has been specifically investigated in patients with epilepsy.[149, 151]

Proof-of-concept studies in patients with refractory epilepsy

The current stage of investigation of SUDEP prevention in patients with epilepsy consists of testing interventions on ancillary biomarkers, in particular peri-ictal hypoxemia. This strategy allows testing the potential of such interventions on much smaller populations. However, the predictive value of peri-ictal hypoxemia on the risk of SUDEP remains to be established.[119]

The effect of SSRIs on peri-ictal respiratory function was recently examined in epilepsy patients admitted to an EMU. Patients were divided into two groups based on whether they were taking any SSRI on admission. Those on an SSRI had significantly less frequent peri-ictal hypoxemia below 85% than those who were not (6% compared to 20%).[6] Interestingly, there was no difference in peri-ictal apnea between groups. However, this was not a randomized trial. Patients on an SSRI probably had an indication for it, such as depression. There is evidence that there is overlap between the pathology of epilepsy and depression, and that both may involve the 5-HT system.[12, 157, 158] Thus, there were likely differences between the two groups in 5-HT signaling at baseline. Furthermore, differences in peri-ictal hypoxemia between groups were only observed for partial seizures without secondary generalization, and not for generalized tonic-clonic seizures, which usually trigger SUDEP.[6]

In order to further investigate the potential of SSRIs in preventing peri-ictal hypoxemia, two double-blind RCTs have been launched, including one in the US that failed to achieve appropriate recruitment (https://clinicaltrials.gov/ct2/show/NCT00986310?term=SUDEP&rank=7), and another led by one of the co-authors (PR) that is still ongoing.

Using a similar approach in patients undergoing video-EEG monitoring coupled with pulse oximetry, a recently approved double-blind RCT will test the impact of naloxone 0.4 mg versus placebo, injected immediately following a generalized tonic-clonic seizure, on the occurrence, duration and intensity of post-ictal hypoxemia (PI S Rheims, Lyon, France). To the best of our knowledge, no clinical study testing the impact of adenosine modulation has yet been performed.

Acknowledgments

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Key points

1. Seizures immediately preceding SUDEP often lead to rapidly developing hypoventilation and bradycardia.

2. Peri-ictal apnea/hypoventilation plays a significant role in SUDEP. Brainstem serotonin, adenosine and opioid pathways may be involved.

3. Potential pharmacological prevention strategies influencing the above pathways can be tested in randomised clinical trials.

4. For such trials to be feasible, identification of biomarkers in high risk individuals is needed.

5. Interventions tested need to safe with a high likelihood of success as shown by animal studies and surrogate clinical scenarios as in epilepsy monitoring units
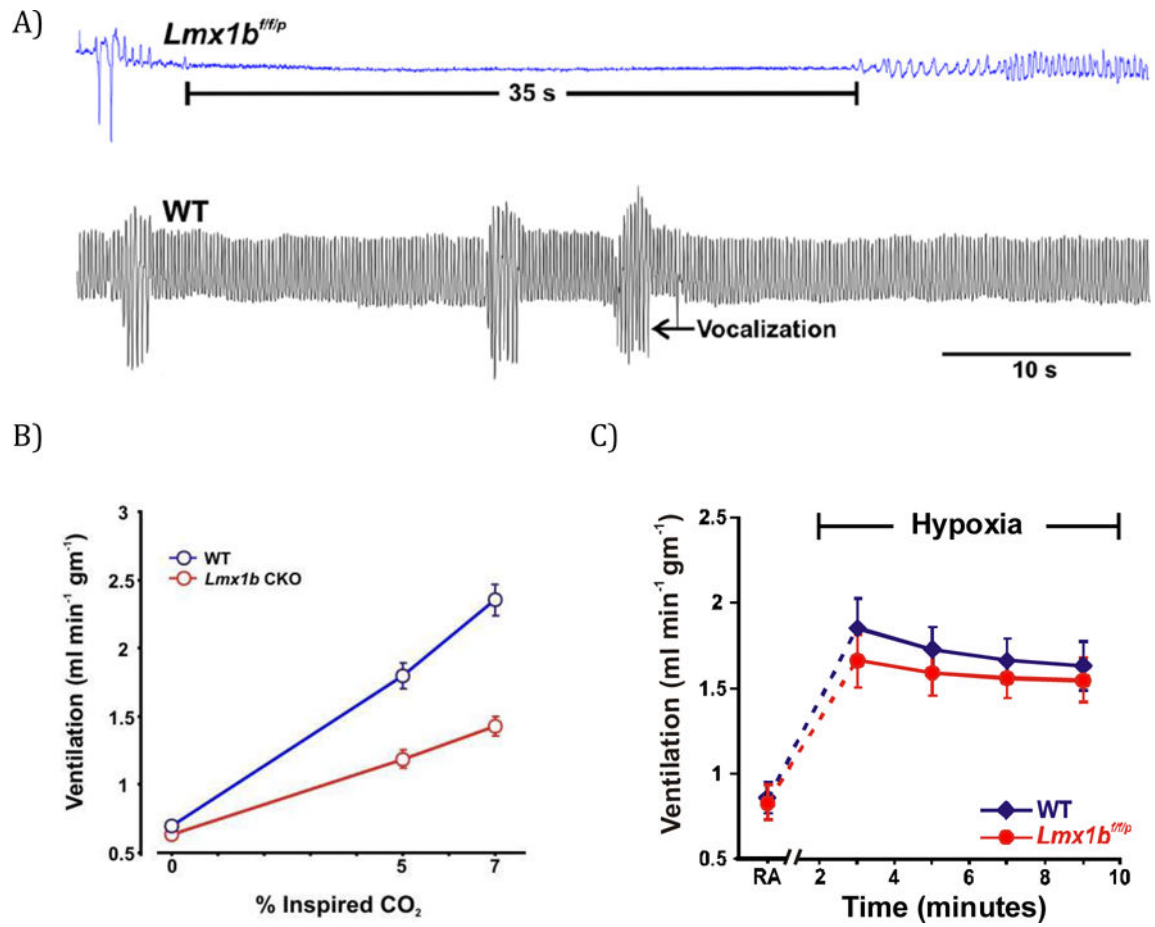
Figure 1.

Figure 2.

A)
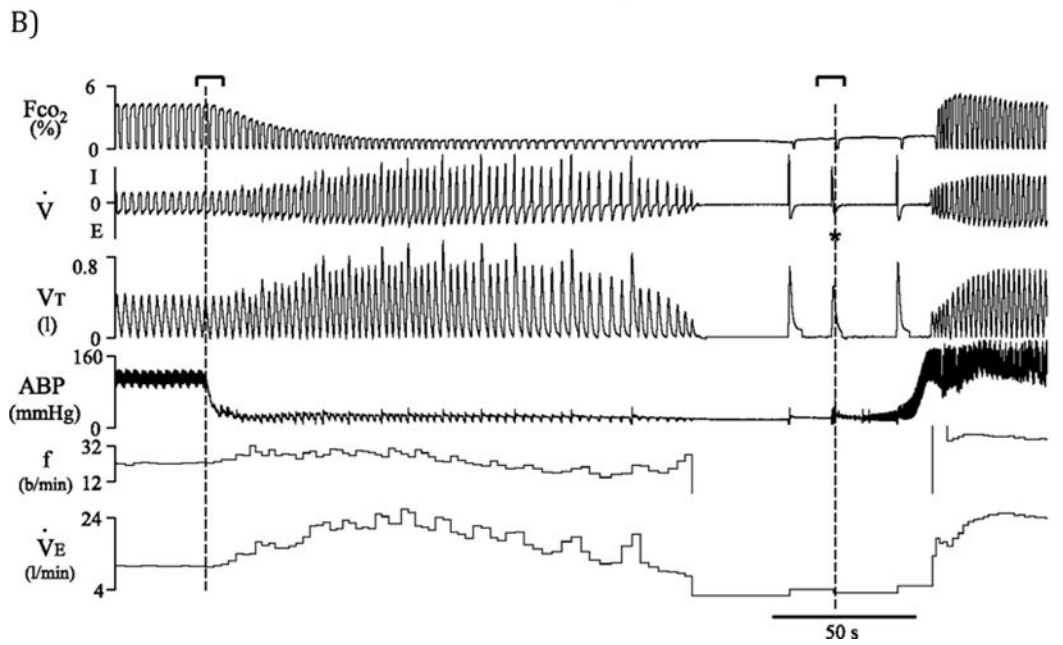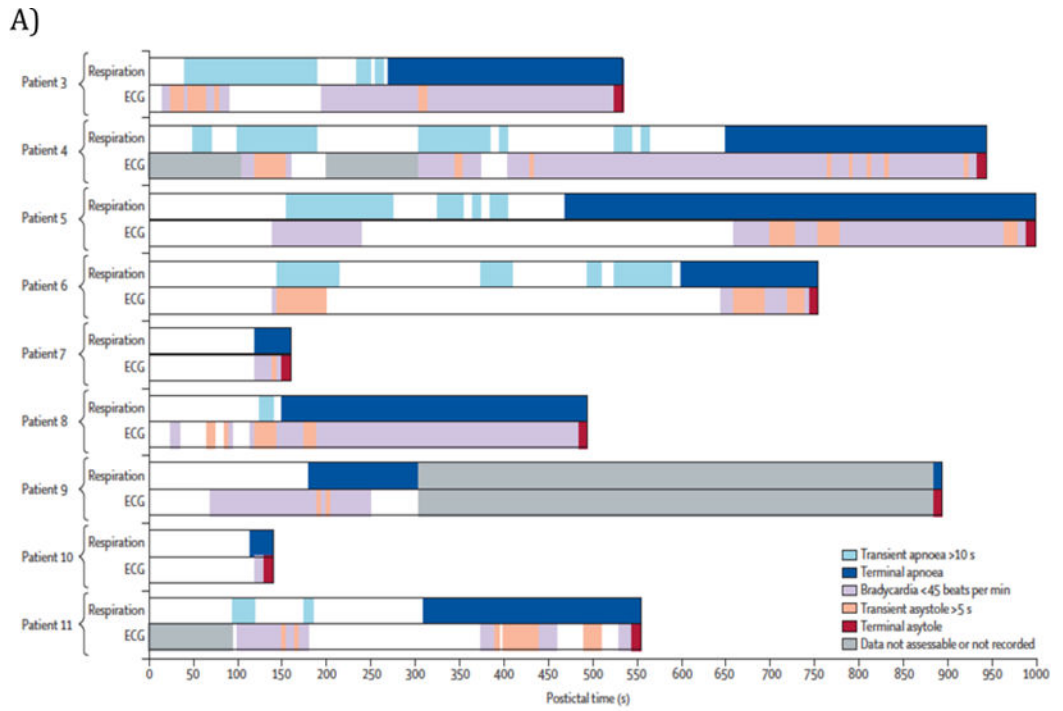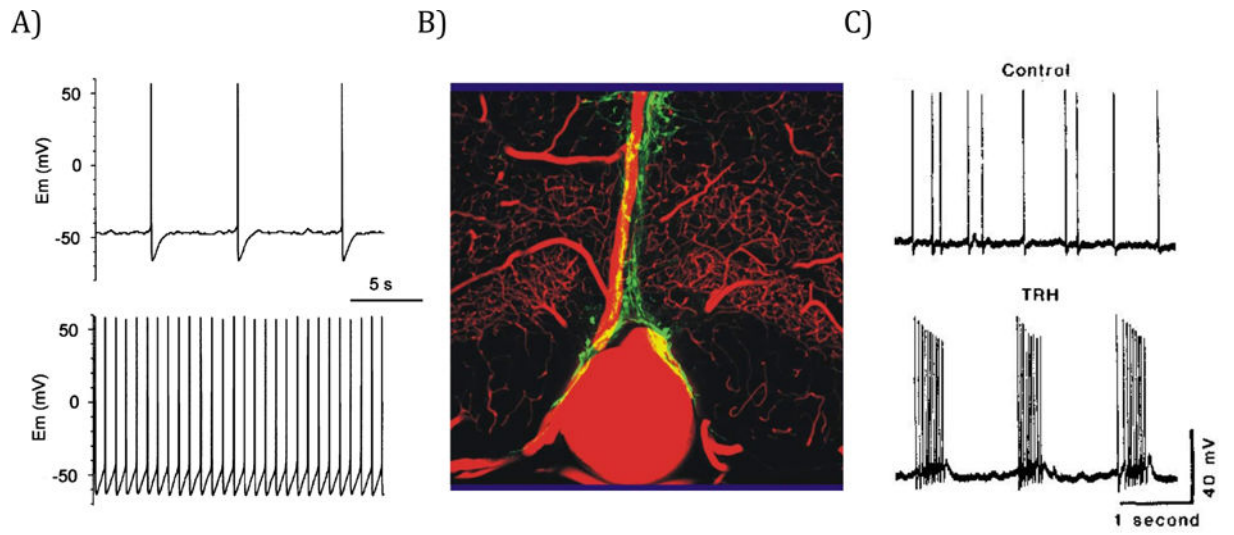
Figure 3.

A)

B)

Figure 4.

Figure 5.