Impaired CO$_2$-Induced Arousal in SIDS and SUDEP

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Premature, sudden death is devastating. Certain patient populations are at greater risk to succumb to sudden death. For instance, infants under 1 year of age are at risk for sudden infant death syndrome (SIDS), and patients with epilepsy are at risk for sudden unexpected death in epilepsy (SUDEP). Deaths are attributed to these syndromic entities in these select populations when other diagnoses have been excluded. There are a number of similarities between these syndromes, and the commonalities suggest that the two syndromes may share certain etiological features. One such feature may be deficiency of arousal to CO$_2$. Under normal conditions, CO$_2$ is a potent arousal stimulus. Circumstances surrounding SIDS and SUDEP deaths often facilitate CO$_2$ elevation, and faulty CO$_2$ arousal mechanisms could, at least in part, contribute to death.

Towards a Pathophysiological Understanding of Sudden, Unexpected Death
Sudden, premature death of individuals takes a heavy toll on their families, circle of acquaintances, and society at large. Often, there is an evident cause for premature death, such as accidental injury, inflicted injury (e.g., suicide or homicide), or critical illness. Unfortunately, too often, there is no immediately identifiable cause for death. In some respects, these cases can be even more devastating for loved ones, as the latter are left with the unsettling questions of why their loved one died, and whether anything could have been done to prevent the loss.

For certain patient populations, syndromic sudden death entities have been described and are attributed as the cause of death when other possible diagnoses for death causes have been excluded. Two such entities that have gained considerable attention recently are sudden infant death syndrome (SIDS) (see Glossary) and sudden unexpected death in epilepsy (SUDEP). Despite their notoriety, the pathophysiology of each condition is poorly understood. In both entities the actual death is typically unwitnessed and the victim is found dead, often in bed. The fact that death is commonly unwitnessed makes it challenging to retrospectively piece together circumstances of death. Based on this incomplete information, measures have been proposed and implemented in an attempt to identify high-risk individuals and mitigate death. Yet, the incidence of SIDS and SUDEP remain high.

SIDS and SUDEP share a number of common features, including potential pathophysiological mechanisms. Among these, dysregulation of certain arousal mechanisms may be particularly pertinent. The objective of this Opinion article is to present relevant features of SIDS and SUDEP, highlighting commonalities, and to outline the hypothesis that impaired CO$_2$-induced arousal is a key common feature among these conditions.

SIDS
SIDS is defined as the sudden and unexpected death of an infant under the age of 1 year that remains unexplained after thorough review of the clinical history, death scene investigation, and

Highlights
SIDS and SUDEP are among the leading causes of death in their respective patient populations (i.e., infants under 1 year of age and patients with refractory epilepsy), but their pathophysiology is poorly understood.

Some common features of SIDS and SUDEP have been identified, including impaired cardiorespiratory function and dysfunctional serotonin signaling.

A possible common pathophysiological mechanism is impaired arousal in response to elevated CO$_2$. Individuals at risk for both conditions experience situations in which serum CO$_2$ concentrations rise (e.g., due to physical airway obstruction, or as a consequence of a seizure). However, the physiological mechanisms of CO$_2$-induced arousal from sleep are not fully understood, and whether a definitive link to SIDS or SUDEP exists remains to be validated.

Better understanding of the mechanisms of CO$_2$-induced arousal, and how these impaired mechanisms possibly contribute to death in SIDS and SUDEP, may help address the pressing need for effective prevention strategies in these conditions.

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complete autopsy [1]. It is the leading cause of sudden death in infants under 1 year of age. Considerable work has been done in attempts to understand the risk factors for SIDS and its pathophysiological features. Collectively, this work has produced the triple risk model for SIDS. This model fits into the broad framework of triple-risk models, whereby an individual with an underlying susceptibility is exposed to a detrimental exogenous factor during a critical period (Figure 1). In the case of SIDS, the critical period is the first year of life; particularly the first 6 months or before infants are able to roll over on their own. While considerable work is ongoing to better define at-risk individuals, some genetic, pathophysiological, and environmental features have been identified from babies that died of SIDS and compared with babies that died for other reasons [2].

A major exogenous factor that has been identified is airway occlusion or obstruction, such as could occur if the infant was lying prone in the crib. As such, the ‘Back to Sleep’ campaign was implemented in which it was strongly suggested that infants be placed on their backs to sleep [3–5]. Along with this, it was suggested that other items such as stuffed animals, pillows, and blankets be removed from the crib, and the infant be dressed in tight-fitting clothes. This campaign contributed to a reduction in the incidence of SIDS from 1.2 in 1000 live births to approximately 0.6 in 1000 live births in the USA, where it remains today [3,6].

SUDEP
SUDEP is defined as the ‘sudden, unexpected, witnessed or unwitnessed nontraumatic and non-drowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicological or anatomic cause of death’ [7]. It is the leading cause of death in patients with medically refractory epilepsy [8]. SUDEP is second only to stroke in terms of years of potential life lost to neurological disease, owing in part to the fact that it occurs most often in younger individuals [9]. SUDEP is thought to occur most commonly in patients with mesial temporal lobe epilepsy, but certain epilepsy populations, such as children with the severe myoclonic epilepsy of infancy, or Dravet syndrome [10], have an especially high rate of SUDEP [11]. In 2017, the American Academy of Neurology, estimated the overall global incidence of SUDEP to be 0.58/1000 patient-years, and incidence of 0.22 and 1.2/1000 patient-years in children and adults, respectively, based on review and analysis of literature published before April 2015 [8]. Incidence estimates in more discreet patient populations in which all epilepsy deaths are captured during a defined time window suggest the incidence may be more comparable between children and adults. For instance in Sweden, examination of all epilepsy deaths during 2008 revealed an incidence of 1.2/1000 patient-years [12]. In Canada, a review of all epilepsy death in children from 2014 to 2015 revealed an incidence of 1.17/1000 patient-years [13]. These discreet population-based studies suggest that the incidence is comparable across age groups, whereas an earlier large meta-analysis indicated a higher incidence in the third and fourth decades of life [14].

SUDEP has been subcategorized into definite, probable, and possible SUDEP. In definite SUDEP there is an autopsy that confirms there is no competing cause of death. In probable SUDEP, there is no autopsy. A ‘plus’ designation can be added to definite and probable SUDEP if there was a comorbidity that could have contributed to death, but was not thought to have contributed. In possible SUDEP, there is a comorbidity that could have contributed to death. If it is perceived that a person would have likely died following a seizure, but survived at least for 1 h because of resuscitative efforts, this is termed a near-SUDEP. While in each of these subcategories the definition of SUDEP is applied differently, they can largely be grouped...
together when considering anatomical, pathological, physiological, and electrophysiological features that portend increased risk for SUDEP.

**Similarities between SIDS and SUDEP**

There are a number of similarities between SIDS and SUDEP [15] (Table 1). Both are essentially diagnoses of exclusion. In both, the individual is usually healthy (except for epilepsy in SUDEP). In both, autopsy is normal. Similar etiological factors have been proposed for both, including respiratory demise, cardiac demise, and impairment of arousal. In both, the death is commonly un-witnessed, with the individual being found dead in bed/crib and in the prone position. The incidence is comparable between the two entities. And in both entities dysregulation of the serotonin [5-hydroxytryptamine (5-HT)] system has been identified or proposed. 5-HT is an attractive candidate in the pathophysiology of SIDS and SUDEP because it is involved in modulating many associated factors implicated in these disease entities, including breathing, cardiovascular control, sleep and wakefulness, arousal, circadian rhythms (i.e., both entities occur more commonly at night), and seizures [11,16]. Due to these similarities, especially the association with prone positioning, a ‘Back to Sleep’ campaign, similar to that which was so successful in reducing the risk for SIDS, has also been proposed for SUDEP; however, while it is easy to have a patient with epilepsy start the night sleeping on their back, it is rather difficult to keep them that way throughout the night [17].

There are disease entities that may lie on a continuum of sorts bookended by SIDS and SUDEP. These include: apparent life threatening events (ALTEs) in infancy/childhood (which may be the SIDS analog to near-SUDEP, i.e., an event where the victim would have likely died but survived at least for 1 h because of resuscitative efforts); sudden unexplained death in childhood (SUDC) [18] or sudden unexplained death in the young (SUDY); and near-SUDEP [2,7]. SIDS is a specific subcategory of sudden unexpected infant death (SUID) that encompasses all sudden deaths in infants [19,20]. There are case reports of witnessed seizures in infants who have ultimately died as a consequence of the seizure [21]. If these seizures had not been witnessed then it is likely that the baby would have died, been found dead in the crib in the
morning, and SIDS would have been listed as cause of death on the death certificate. This raises the question of how many SIDS deaths may actually be SUDEP, with the baby either experiencing a first and fatal seizure, or the baby having had unrecognized seizures and then having a final fatal seizure. Indeed, seizures in infants can often be bland and unrecognized. Also recently, mutations in the SCN1A gene that encode the voltage gated sodium channel (Na\textsubscript{v},1.1) have been identified in two babies whose deaths were attributed to SIDS [22]. Such mutations also occur in Dravet syndrome, the epileptic encephalopathy with a particularly high incidence of SUDEP [10]. At the time of their death, these babies were too young to have begun to display the seizures and other features of Dravet syndrome.


| Table 1. Similarities between SIDS and SUDEP\textsuperscript{a} |
|-----------------|-----------------|-----------------|
| Diagnostic method | Diagnosis of exclusion | Diagnosis of exclusion |
| Baseline health | Normal | Normal expect seizures |
| Routine autopsy findings | Normal | Normal; pulmonary edema |
| Incidence | ~0.6 per 1000 live births | 0.2–1.2 in 1000 persons with epilepsy |
| Proposed mechanism of death | Respiratory | Respiratory |
| | Cardiac | Cardiac |
| | Arousal impairment | Arousal impairment |
| | Thermoregulatory dysregulation | |
| Circumstances of death | Often found prone | Often found prone |
| Link to 5-HT | Yes | Yes |

\textsuperscript{a}Adapted, with permission, from [15].


natomical abnormalities in the hippocampus and temporal lobe have been identified in many cases of SIDS and SUDEP [18,23–27]. In addition, such abnormalities, including mesial temporal or hippocampal sclerosis are among the hallmarks of temporal lobe epilepsy (TLE); a common form of epilepsy associated with SUDEP. Recently, a distinct clinicopathological entity was described in a cohort of children aged 1–6 years that died in association with a febrile seizure. This has been dubbed hippocampal maldevelopment associated with sudden death (HMASD), and is characterized by sudden, sleep-associated death in a child that had been born at term and found in the prone position [18,26]. Specific abnormalities seen in these cases include bilamination of the dentate gyrus [26], which can also be seen in SIDS [25] and TLE [28,29].

**CO\textsubscript{2}-Induced Arousal from Sleep**

Among the proposed etiologies for SIDS and SUDEP, one that is especially intriguing, and that has garnered little attention, is impaired arousal, especially to CO\textsubscript{2}. CO\textsubscript{2} is expelled by the lungs as one breathes. Drive to breathe is dictated in large part by the serum CO\textsubscript{2} concentration, which is tightly regulated. In addition to potently driving breathing, CO\textsubscript{2} is a powerful arousal stimulus [30]. As can be imagined, acute rises in CO\textsubscript{2} levels occur when an individual is unable to expel CO\textsubscript{2}, such as in the setting of an airway obstruction that might occur when an individual is lying prone in a crib or bed perhaps with a pillow and bedclothes covering the nose and mouth. It has been proposed that such a rise in CO\textsubscript{2} would activate arousal circuitry in a normal baby to wake the baby up, cause them to cry out, summoning a caregiver who would come to their aid, and ostensibly correct the airway blockage to allow resumption of normal breathing.
It has been proposed, among other possibilities, that there is an impaired CO2-arousal system in SIDS-susceptible babies such that when they rebreathe CO2 as described above, they do not arouse, and thus do not cry out, and the blockage is not corrected [16,32]. They thus become acidic and hypoxic and ultimately succumb. We posit that similar such mechanisms could be at play in SUDEP. CO2 rises in association with a convulsive seizure, especially a convulsive or generalized tonic-clonic seizure, with which SUDEP is more commonly associated [8]. It has been suggested that the rise in CO2 is part of the seizure cessation mechanism [33]. In patients at risk for SUDEP, it is possible that there is a dysfunctional CO2 arousal system contributing to seizure-related demise. This would be exacerbated by situations that cause airway obstruction, such as ending up in the prone position or having a physical barrier present, such as a pillow [34–36]. In patients with epilepsy, seizures can also lead to laryngospasm, which could cause airway obstruction and lead to SUDEP [37–39].

Mechanisms of CO2-induced arousal from sleep have been somewhat controversial (Figure 2, Key Figure). For some time, the general thinking was that arousal from sleep in response to CO2 requires stimulation of breathing, which subsequently activates stretch and mechanoreceptors that in turn activate pathways through the nucleus tractus solitarius (NTS) and other sites to cause arousal [40,41]. More recently, central mechanisms whereby CO2 can be directly sensed by neurons that feed into and influence arousal networks have been proposed [42–45]. A number of possible sites have chemosensory properties and have been implicated in sleep-wake regulation, including 5-HT neurons in the midbrain dorsal raphe nucleus (DRN) or medullary raphe, glutamatergic neurons in the retrotrapezoid nucleus (RTN, or lateral parafacial nucleus), glutamatergic neurons in the NTS, noradrenergic neurons in the locus coeruleus (LC), and orexinergic neurons in the lateral hypothalamus [42–44,46–49]. Whether or how each of these is involved in CO2-induced arousal is unclear, and which site might be the primary sensor of CO2 to incite arousal is unknown.

Serotonin in SIDS, SUDEP, and CO2-Induced Arousal

One candidate for acting as the primary sensor of CO2 in the context of CO2-induced arousal is 5-HT neurons in the DRN (Figure 2). These neurons are robustly chemosensitive in vitro [50] and in vivo [51]. In vitro, most DRN 5-HT neurons tested were chemosensitive and responded with a fourfold increase in firing in response to a pH change from 7.4 to 7.2, well within physiological range [50]. Genetic elimination of 5-HT neurons in the CNS attenuates arousal to inspired CO2 in mice [43]. Direct application of CO2-enriched artificial cerebrospinal fluid (CSF) to the DRN, but not the medullary raphe, causes arousal from sleep in wild-type mice [42]. Stimulation of the DRN in 5-HT-neuron-deficient mice does not cause arousal [42], suggesting that these neurons are important sensors of the pH changes associated with an increase in CO2. Acute inactivation of DRN 5-HT neurons either pharmacologically or optogenetically also attenuates CO2-induced arousal [42]. Mechanisms of CO2-induced arousal downstream of DRN 5-HT neuron activation are unknown. Presumably, these inputs feed into known arousal circuitry, but the specific nature of these connections remains to be clarified [42]. A series of experiments have implicated the parabrachial nucleus (PB), especially the exterolateral PB (PBel) in CO2-induced arousal [45,52,53]. The PB is well situated to activate arousal in response to a variety of arousing stimuli, including increased CO2 concentration. The PB is not known to be chemosensitive itself; thus, some other site might be the primary sensor of CO2 and cause arousal through downstream activation of PB. While the evidence for DRN 5-HT neurons as the primary CO2 sensors is strong, the DRN is not known to project heavily to the PB. Thus, if these two structures are part of a circuit in CO2-induced arousal, a direct connection between the structures is yet to be elucidated, or they may be connected through an intermediary site.
A number of abnormalities in the brainstem serotonergic system have been identified in brains from babies whose deaths were attributed to SIDS. These include reduced binding of ligands to the 5HT1A receptor, an inhibitory autoreceptor in the brainstem raphe nuclei; an increased proportion of immature appearing 5-HT neurons in the raphe; decreased concentration of 5-HT in the medulla; and elevated serum 5-HT [54–61]. However, no differences were found in the concentrations of the 5-HT metabolite 5-hydroxyindoleacetic acid or the 5-HT precursor tryptophan in CSF between SIDS cases and age-matched controls [62]. These studies have
mainly focused on the caudal serotoninergic neurons in the medulla that are thought to be involved in the regulation of breathing. Closer examination of rostral brainstem structures such as the DRN is warranted.

A preponderance of evidence has also implicated 5-HT and 5-HT system abnormalities in SUDEP. Until recently this has been more circumstantial evidence including reduced oxygen desaturation following seizures in patients taking selective serotonin reuptake inhibitors [53], and prevention of seizure related respiratory dysregulation in animal seizure models [64–73]. Emerging data have identified anatomical abnormalities, for example, in the serotoninergic nuclei from brains of patients who have died of SUDEP. These abnormalities include reduced functional connectivity networks involving the thalamus, anterior cingulate, brainstem, putamen, and amygdala [74]; excess volume loss in the medulla including in the raphe [75] and other brainstem regions [76]; reduced tryptophan hydroxylase staining in the ventrolateral medulla and reduced 5-HT transporter expression in the medullary raphe in SUDEP cases compared with controls [77]; increased grey matter volume assessed by magnetic resonance imaging (MRI) in anterior hippocampus, amygdala, and parahippocampal gyrus in SUDEP cases and high-risk individuals compared with controls and low-risk individuals [78]; and alterations in expression of a variety of markers in the brainstem [79]. These abnormalities have been identified largely from postmortem analyses. Whether patients at risk for SUDEP display altered arousal or ventilatory responses to CO2 is unknown. Likewise, whether the identified anatomical abnormalities translate into impaired CO2 responses is yet to be determined. It has been demonstrated that seizures can impair breathing by impinging upon circuitry that passes through the amygdala [80,81]. It has been proposed through animal studies that such impingement might occur through spreading depolarization that is incited by the seizure and propagates into the brainstem [82–84]. One could speculate that these could extend to CO2-arousal systems, and by silencing neural activity in these areas impair CO2-induced awakening. Alternatively, as shown in animal models, seizure can directly impair firing of both medullary and midbrain 5-HT neurons that are involved in ventilatory and arousal responses to CO2 [73].

Concluding Remarks and Future Perspectives

Discovery of biomarkers to more easily identify individuals at risk for SIDS and SUDEP is underway [8,54,62]. Once etiological features are clearly defined and at-risk individuals reliably ascertained, prophylactic strategies can be deployed. Converging lines of evidence, as discussed in this article, point at dysregulation of CO2-induced arousal as a shared candidate pathophysiological mechanism in both SIDS and SUDEP. According to this proposed mechanism, prophylactic strategies may include methods to temper the rise in CO2 that may occur in the perinatal period, in addition to ways to lessen the impairment in CO2-arousal mechanisms in susceptible individuals. Before this can be accomplished, however, a clearer understanding of the clinical–pathophysiological deficiencies in these entities and a more precise understanding of the mechanisms underlying CO2-induced arousal are required (see Outstanding Questions). Perhaps an appropriate place to start is with a more concerted comparative analysis of cases representing each aforementioned sudden death entity. Complementarily, modern experimental technology including, but not limited to high field strength MRI, ultra-small scale microscopy, optogenetics, chemogenetics, and calcium imaging, permitting more detailed anatomical and circuit analysis will aid in dissecting mechanisms. These techniques can be first applied in animal models. Insights gained can then be tested and translated for use in patient tissue samples. In the clinical setting, continued efforts are needed to make respiratory assessments more routine in long-term monitoring units, such as those used in epilepsy care and in care of high-risk infants. These monitoring practices could be used not only to assess respiratory responses to CO2 and hypoxia, but also arousal responses. This will allow more

Outstanding Questions

Does SIDS lie on a continuum with SUDEP, and other disease entities such as ALTE, SUDC, and SUDY?

Do some cases of SIDS represent a first presentation of epilepsy, with seizures being previously unappreciated and the fatal seizure being un witnessed?

Are there methods to identify susceptible individuals? What are the biomarkers (e.g., serum/CSF measures, and imaging features) for increased risk of death from SIDS and SUDEP? Once effective biomarkers are identified, what prophylactic measures can be deployed in the relevant individuals?

Are there comparable anatomical and/or pathophysiological changes in the brains from people who die from SUDEP and those from babies who die from SIDS?

How is CO2 arousal circuitry impaired in the first place in individuals at risk for SIDS and/or SUDEP?

Is serotonin key in these processes? Is the DRN the primary CO2 sensor for CO2-induced arousal? What role do other chemosensitive structures (e.g., LC, RTN, medullary raphe, orexin neurons, and carotid bodies) play in this context?

How are the DRN and PB connected to each other in mediating CO2-induced arousal from sleep?

In the setting of airway obstruction and/or respiratory arrest following a seizure, the rise in CO2 level does not occur in isolation, but rather is associated with hypoxia. In fact, the hypoxic component may be more critical in leading to death. Hypoxia can also be a potent arousal stimulus, especially in rodent models. What are the critical roles of hypercapnia and hypoxia in arousal? Will prophylactic measures have to address both hypercapnia and hypoxia?
comprehensive assessment of changes in sensitivity of these systems in patients at high risk for SIDS and SUDEP, and could be extended to examine certain other at-risk populations if and when better biomarkers for other types of sudden and unexpected death are identified.

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