Autonomic Consequences (Including SUDEP) of Seizures

M Stewart, State University of New York Downstate Medical Center, Brooklyn, NY, USA

© 2009 Elsevier Ltd. All rights reserved.

Introduction – Seizures Cause Autonomic Disturbances

Seizure-induced autonomic dysfunction could cause serious clinical consequences, yet may occur only transiently and escape detection. Signs of autonomic nervous system dysfunction are common in epileptic patients, but are often overshadowed clinically by more apparent motor and cognitive effects of seizures. Small focal (i.e., simple partial) seizures may produce flushing, sweating, and piloerection, while complex partial seizures can produce a broader spectrum of autonomic signs, including changes in heart rate and rhythm (often bradycardia; complete AV block has been reported), blood pressure (usually hypertension), and increased or decreased gastrointestinal motility (usually vomiting) and secretion. Complex partial seizures may also induce relative hypoxia, though the mechanism of this change is not understood. Generalized tonic-clonic seizures may be associated with severe increases in blood pressure and changes in heart rate and conduction, such as complete nodal block. In a subgroup of epileptic individuals, however, seizures may trigger more ominous cardiovascular derangements such as marked bradycardia or asystole. At autopsy, pulmonary edema is the most common finding. Although still poorly understood, the causes of sudden unexpected death in epilepsy (SUDEP) are strongly suspected to involve cardiovascular and/or respiratory dysfunction provoked by seizures spreading into the autonomic nervous system.

Mortality among epileptic individuals is 2–3 times greater than among their nonepileptic counterparts. Among individuals with epilepsy, SUDEP is the single most common cause of death, accounting for as much as 10–15% of mortality in this group and exceeding the mortality attributable to status epilepticus. Estimates of the annual incidence of SUDEP among individuals with epilepsy range from 1 in 1000 to 1 in 500. The average age for SUDEP is 28–35 years, and men in their third or fourth decade have the highest annual risk of SUDEP, as high as 1 in 200. SUDEP occurs in different seizure types, and does not show a consistent predisposition for localization-related or primary generalized epilepsy. Further, SUDEP is not restricted to individuals with the most severe seizures. SUDEP incidence, however, is highest in individuals with medically refractory seizures and lowest in individuals with well-controlled seizures. The relative risk of SUDEP in individuals with two or more seizures per year has been reported to be 20 times greater than the risk in epileptic individuals who are seizure-free, and the increase in risk surpasses 50-fold when the number of seizures in a year is more than 50.

Most studies of the autonomic consequences of seizures have focused on cardiovascular consequences, primarily because these changes are seen as the most significant clinically, but also because considerable information can be extracted from analyses of the ECG. Several analyses of the R–R interval (RRI) — the period of time separating successive heartbeats — reveals RRI fluctuations at the respiratory frequencies that are parasympathetically-mediated, and RRI fluctuations at higher frequencies that are mediated by the combined effects of sympathetic and parasympathetic inputs to the heart. A smaller number of studies monitor other parameters, e.g., blood pressure monitoring by tonometry. Using continuous monitoring of various types, autonomic disturbances have been reported during both ictal and interictal periods. Patients with complex partial seizures had large fluctuations in heart rate during interictal periods that were not seen in controls, and acute deterioration of seizure control was accompanied by increased parasympathetic activity (including bradycardia) before seizure onset. Additionally, some of the dynamic complexity of the autonomic consequences, including baroreceptor reflex function, has been explored. Temporal lobe seizures are frequently associated with bradycardia, but the development of tachycardia during temporal lobe seizures can be proportional to the spread of seizure activity to other cortical areas. Complex-partial seizures were found to be associated with a pattern of parasympathetic activity that fell rapidly about 30 s before seizure onset, and sympathetic activity that continued to rise and peaked at seizure onset.

Although it is clear that the autonomic impact of seizures is broad and complex, it is also clear that clinical studies alone cannot entirely assess the connection between seizures and autonomic dysfunction. Clinical investigations are limited because some phenomena of interest are too infrequent for practical prospective studies, and there are limits to the invasiveness of autonomic monitoring that can be performed with human patients.

Background

Animal Studies of Autonomic Nervous System Dysfunction During Seizures

Animal models offer the advantage of invasive monitoring, but come with the disadvantage of perhaps involving...
Autonomic Nervous System (ANS)

Pathways for Spread of Seizures to the Autonomic Nervous System (ANS)

Neocortex and limbic cortices are heavily connected with structures that constitute the ANS, or with regions that project into autonomic structures. The central nucleus of the amygdala and bed nucleus of the stria terminalis are major inputs to hypothalamic, pontine and medullary structures that control preganglionic autonomic neurons of both the sympathetic and parasympathetic branches of the autonomic nervous system. They are positioned to relay cortical activity into the ANS. Neocortex and limbic cortices, especially subiculum, also have direct projections to hypothalamus. Autonomic pathways are integrated in the hypothalamus and influence all visceral systems, including cardiovascular, genitourinary, endocrine, and digestive, as well as peripheral involuntary muscles such as pilomotor and pupillary sphincters.

Projections of hypothalamic, including pontine and medullary neurons to preganglionic parasympathetic and sympathetic neurons controlling cardiac and respiratory function, have been studied anatomically and physiologically. Hypothalamic cells project onto medullary structures (ventrolateral medulla and periaqueductal gray) that project directly to sympathetic preganglionic cell bodies.
located in the intermediolateral horn of the spinal cord. Activity of hypothalamic and medullary neurons correlates with sympathetic nerve activity. Some hypothalamic cells themselves project directly into the spinal cord.

For the parasympathetic system, central nuclei of the amygdala and hypothalamus (PVN and SON) project directly into the dorsal motor nucleus of the vagus and the nucleus ambiguus, the sites of parasympathetic preganglionic cell bodies. Furthermore, the sympathetic and parasympathetic paths can influence each other. For example, efferents of the nucleus ambiguus and dorsal nucleus of the vagus (preganglionic parasympathetic neurons) project to the nucleus of the solitary tract which has a relayed projection to intermediolateral horn (sympathetic preganglionic neurons).

It is not surprising, then, that thalamic/hypothalamic discharges elicited by penicillin-G application would be associated with bursts of activity in vagus nerve recordings. We also found bursts of activity in vagus nerve recordings during the slow spiking period at the end of the limbic seizure, although the total amount of vagus nerve activity at these times was much less than we found earlier in each seizure episode. Interestingly, while the types of seizures in these two animal models are quite different, a pathway from hypothalamic areas through the medulla and into the periphery is common, and can account for similarities in vagus nerve discharge.

**Methods – Our Acute Rat Model**

Our rat model for acute studies of autonomic consequences replicates many features of autonomic disturbances seen in epilepsy patients, and offers some unique advantages. Using kainic acid as the convulsant drug on a background of urethane anesthesia, we produce a prolonged period of recurring limbic seizures that do not significantly involve the neocortex. As a result, animals can be kept in a stereotaxic frame without paralytic agents. The lack of motor convulsions permits stable recordings from the brain, spinal cord, and peripheral nerve, as well as accurate, invasive monitoring of systemic parameters such as blood pressure. We have also developed a simple method for reversibly suppressing seizures in one or both hemispheres repeatedly. The preparation is described briefly here, and more details are given in the readings.

We use male Sprague-Dawley albino rats for most experiments. Six to 8 week old animals (200–350 g) are commonly used. Animals are anesthetized with urethane (1.5 g kg \(^{-1}\) ip), fitted with an endotracheal tube, and maintained at 37 °C. Blood pressure is monitored with an intra-aortic line (polyethylene tubing, 0.5 mm id, 0.8 mm od, inserted into the femoral artery) and pressure transducer. An increase in mean arterial pressure, systolic or diastolic pressure (with no increase in pulse pressure) indicates an increase in sympathetic vasoconstrictor tone. Likewise, a decrease in blood pressure reflects a decrease in sympathetic tone. Increases in pulse pressure reflect increased cardiac stroke volume, which occurs physiologically through two mechanisms: At slow heart rates, stroke volume increases through increased diastolic filling time. At increased heart rates, increased stroke volume reflects increased cardiac emptying from increased cardiac contractility produced by increased sympathetic input to the cardiac muscle and increased circulating catecholamines.

ECG is recorded with parasternal electrodes. Heart rate will increase in response to increased sympathetic and/or decreased parasympathetic outflow to the heart. Decreases in rate are mediated by decreased sympathetic and/or increased parasympathetic outflow. Heart rate changes can occur as a direct response to descending inputs to sympathetic or parasympathetic preganglionic neurons, or changes can be reflexively driven by baroreceptor activity. The presence of abnormally shaped QRS complexes indicates ectopic beats (i.e., patterns of contraction not following the typical conduction pathways). Rates are calculated from the number of beats per unit time and rhythm is assessed by looking at P waves and associated QRS complexes for variations in beat-to-beat intervals and atrial-ventricular coupling. Successive R-R intervals will increase if the heart is under predominant parasympathetic control. Successive R-R interval decreases indicate relative sympathetic nervous system control of the heart. An added benefit of using anesthetized animals is that transthoracic echocardiography can be used to study the mechanical properties of the heart during seizures. The force of contraction, filling and emptying properties, and chamber sizes, are some of the measurements that can be readily made in an echocardiographic study. Ultrasound probes are now quite good for small animal imaging studies, even at the high heart rates seen in mice or rats.

For peripheral nerve recordings, we use a linear array electrode that consists of 4 platinum/iridium wires embedded in a small epoxy trough. Wires pierce large nerves as they lay in the trough. Smaller nerves (e.g., renal nerve) are ‘woven’ between electrodes. Excellent multi-unit recordings, occasional single unit recordings, and even simultaneous stimulation and recording are possible with this electrode. Vagus or cervical sympathetic electrodes are placed through a ventral neck incision. Renal sympathetic nerve electrodes are placed through a retroperitoneal incision near the kidney. The renal sympathetic nerve contains postganglionic sympathetic fibers to the renal vascular supply. Splanchnic nerve exposure is also through a flank incision on the left side. Greater splanchnic nerve recordings give access to sympathetic
Seizures are induced with systemic kainic acid by using a stereotaxic frame, multiple electrodes can be implanted for recording seizure activity from limbic cortical structures. These electrodes are placed using stereotaxic coordinates through craniotomy holes. Depending on the experiment, we use dorsal and/or ventral hippocampal electrode placements. Electrodes are generally 75 μm teflon-insulated stainless steel wires (tip impedances ~100 kΩ). Typical stereotaxic coordinates for EEG electrodes are 5.2 mm anterior to lambda, 3 mm lateral to midline, 2–3 mm below skull surface (dorsal CA1); and 2.7 mm anterior to lambda, 5 mm lateral to midline, 7 mm below skull surface (ventral CA1, ventral subiculum).

Seizures are induced with systemic kainic acid (10–12 mg/kg). A single dose of kainic acid causes a period of recurring seizures that lasts more than 4 h. We found that unilateral common carotid artery occlusion will suppress seizure activity ipsilaterally, and our setup allows for brief occlusion episodes to be repeated and alternated. Our carotid occluder is built from a 0.5 ml syringe, the needle of which is removed and a narrow notch is cut near the top of the syringe. The barrel is shortened and the plunger is removed, but the rubber top of the plunger is left inside the barrel. The short barrel is closed by fusing it to the top of a second syringe, leaving the needle to connect to a length of PE tubing. Air movements in the PE tubing (by a remote syringe) cause the rubber plunger tip to press against the top of the syringe, compressing the artery.

**Recent Results**

**Findings Using Our Model**

Kainic-acid-induced seizures were associated with massive increases in parasympathetic (vagus nerves) and sympathetic (cervical sympathetic ganglion, renal sympathetic nerve, splanchinic nerve, cardiac sympathetic nerve) activity. Peripheral nerve activity increases during seizures were much greater than increases that were induced by administration of nitroprusside or phenylephrine, which produced mean arterial pressure changes of >50 mm Hg. Increases in c-fos expression have been found in both sympathetic and parasympathetic medullary regions (as well as hypothalamic areas). Baroreceptor reflex function was impaired during seizures: Changes in nerve activity induced by blood pressure increases or decreases were smaller or absent during tests made with phenylephrine or nitroprusside in the seizure state compared with pre-seizure conditions. In echocardiographic studies, striking acute cardiac dilatation accompanied a profound bradycardia. Finally, a significant fraction of the animals die during seizures, and the mechanism of death was defined through ECG, BP, and echocardiographic measures — to be profound mechanical dysfunction coupled with sinus bradycardia and AV nodal block, leading to hypoperfusion of the brain and finally hypoperfusion of the heart itself.

Our preparation has an advantage in that the consequences of severe limbic cortical seizures can be studied in animals that breathe spontaneously. This is a critical feature for observing and manipulating respiratory activity. We have been able to define the additive roles of seizure-induced autonomic activity and respiratory dysfunction in this seizure model. We have proposed that the massive parasympathetic and sympathetic outflow that occur during a seizure can be compounded by respiratory distress (driving both ANS divisions in the same direction) to impair mechanical function and slow the heart sufficiently to hypoperfuse the brain. The time scale for seizures to impact the heart is seconds, and the development of cardiac dilatation with bradycardia and eventual death occurs on a time scale of minutes. We suggest that this sequence of events is the most common mechanism for sudden death in epilepsy.

**Both Divisions of the ANS are Overactive**

The notion that autonomic dysfunction arises from differences in activity of the two hemispheres pre-dates suggestions that asymmetric seizure activity may contribute to sudden death in epileptic patients. The ‘brain-laterality hypothesis’ was proposed to account for cases of sudden cardiac death, wherein patients died during extreme stress. The brain-laterality hypothesis suggested that emotional arousal could trigger ventricular fibrillation and sudden death by inducing a net lateralized imbalance of activity in some brain areas, leading to uncompensated sympathetic outflow to the heart. Hemispheric inactivation studies have supported this idea.

Differences in activity in the two hemispheres have also been proposed as a contributor or cause for autonomic disturbances — including death — in seizure patients. Controlled lateralized differences in activity are difficult to find (or cause) in studies of seizure activity because seizures can spread rapidly in the brain, and most examples of death during or after a seizure involve generalized seizure activity. A different kind of asymmetry involves differential activation of dorsal and ventral portions of the limbic cortices. Part of this notion comes from data that ventral hippocampal areas (in rodent) have a greater tendency to generate seizure activity than dorsal areas. The connectivity of hippocampal formation with...
brain regions having autonomic impact — e.g., insular cortex — is also heaviest from ventral areas.

Other studies in people and animals suggest that the extent of the cortical involvement, not lateralization of seizure activity, is important for significant heart rate changes. The study by Epstein and colleagues describes predominantly heart rate increases in patients, but also mentions patients that deviated from the majority, showing heart rate slowing and sinus pauses. Ictal bradycardia was found to most often occur in patients with temporal lobe seizures when the seizure activity was bilateral. In kindling animal models, however, arrhythmias were often seen early in the kindling progression (e.g., stage 2 seizures), when seizure spread is limited; however, none of these arrhythmias were fatal.

Although we have seen differences in ANS activity depending on the hemisphere exhibiting seizure activity, our nerve recordings and c-fos data indicate that both divisions of the ANS are strongly activated during kainic acid-induced limbic seizure activity in rats. Further, our data indicate that death results from massive combined ANS overactivity, with the overall result being a parasympathetic-dominated cardiovascular state. In our opinion, cardiovascular complications depend on the degree and duration of increased autonomic activity, and therefore likely depend on the extent and duration of the seizure.

**Death is Mainly a Parasympathetic Phenomenon that Resembles Asphyxia**

Death in our animal model does not resemble most of cases of sudden cardiac death. Although the literature spans some three decades, there is almost universal agreement that 80–85% of cases of sudden cardiac death are due to ventricular arrhythmias. Sudden death from fatal arrhythmia is most commonly a ventricular tachyarrhythmia. In some patients, a ventricular tachyarrhythmia is triggered by an acute myocardial ischemic event, and in other patients, a ventricular tachyarrhythmia is related to an anatomical substrate (e.g., scarring from a previous myocardial infarct). Prevention is aimed at preventing the heart disease that can precipitate cardiac events, and treatment is mainly defibrillation. There are fewer treatment options, other than a pacemaker, for the bradyarrhythmias.

It is interesting that the picture we find during seizures resembles the picture found during asphyxiation. In fact, the respiratory distress during a seizure is a form of asphyxiation, and works pathophysiology in the same direction as the seizures to drive the sympathetic and parasympathetic divisions simultaneously. Respiratory distress causes an increase in vagal activity because of the increase in arterial carbon dioxide, and it increases sympathetic activity (and blood pressure), which also favors an increase in vagal outflow via any functional baroreceptor activity. The combination clearly can be rapidly lethal. Some intense bursts of parasympathetic activity are likely to be large enough to make nodal blockade the initial or predominant first event. In the absence of sustained seizure activity or respiratory distress, a transient arrhythmia may be all that occurs.

In light of these data, one obvious question is whether seizures alone are enough to cause death. In our acute experiments and kindling studies in freely-moving rats, seizures sometimes cause serious arrhythmias, but each episode is usually transient, and therefore not life-threatening. We have not seen evidence for apneaic periods caused by seizures in our urethane-anesthetized animals or in animals that have motor convulsions (animals anesthetized with ketamine/xylazine or unanesthetized animals). The very sudden death that has been described in some mice makes us wonder whether complete respiratory arrest — in addition to or leading to cardiac arrest — is possible. More severe autonomic disturbances might result when seizures occur on the background of a damaged brain, rather than the background of a normal brain. Another possibility is that episodes of arrhythmia predispose to more serious arrhythmias.

Another question that remains unanswered is whether the massive sympathetic outflow that occurs in parallel with the vagal outflow is somehow protective, if it makes matters worse, or if it is irrelevant. Koizumi and others have suggested that there are times when parallel (‘non-reciprocal’) activation of the sympathetic and parasympathetic outflow to the heart occurs physiologically, e.g., in response to decreased arterial oxygen (in the presence of constant arterial carbon dioxide). They found a similar parallel activation during hypothalamic stimulation, and co-activation actually enhances cardiac output. In rat and rabbit models of asphyxiation, epinephrine and vasopressin have been used with some success to improve resuscitation. These findings suggest that the sympathetic outflow may be a physiological attempt to promote survival of the organism. However, a background of sympathetic activity can enhance cardiac responses to parasympathetic innervation, either directly or via complex activity within the intrinsic cardiac plexus. Such a synergy could enhance the chronotropic and dromotropic actions of the parasympathetic neuronal transmitter, acetylcholine. Favoring this view of harmful consequence of parallel activation is the fact that we never saw ventricular escape beats, even when heart rates fell to what were lethal levels. Finally, strong coactivation of parasympathetics and sympathetics contributes to the impairment of the baroreceptor reflex. Baroreceptor reflex function was shown to be impaired in patients with temporal lobe epilepsy that were refractory to drug treatment. The interaction of sympathetic and parasympathetic innervation at the heart is complex and this question will not be easily settled.
Future Directions

The ultimate goal of our research is to construct a complete picture of the ANS activity during seizures. The afferent pathways used by different types of seizures need to be fully defined. The long-term consequences of seizures should be studied, including (a) the lasting effects on ANS activity (not during the seizure itself) of multiple seizures, in chronically altered brains; (b) the mechanisms by which changes in the network that generates seizures (e.g., as regions sustain damage or by conversion of previously less active areas) impact the ANS; and (c) the possibility that a newly epileptogenic region is more disruptive for ANS function. These questions must be pursued with a combined approach that involves acute and chronic experimentation in animals as well as corollary studies in patients.

Animal studies will not only be essential for defining the pathophysiology of autonomic consequences in people, but also serve a role in identifying the most significant variables that can and should be monitored in patients. Some of these variables may be critical for identifying a specific immediate risk (e.g., an arrhythmia that will have the potential to be life-threatening); other ANS parameters may even aid in seizure detection. Other approaches, such as functional studies of cardiac function with echocardiography, may be more suitable for defining broader periods of risk, or significant changes in risk during the life of a seizure patient.

See also: Animal models of idiopathic generalized epilepsies (00005); Hormones and seizure susceptibility (00028); Long-term consequences of pilocarpine-induced status epilepticus (00044); Suppression of epilepsy with electrical stimulation (00070); Brain vasculature and seizures (00099); Brain mechanisms linking epilepsy to sleep (00112); Steroid hormones and seizures in WAG/Rij rats (00119); VNS for epilepsy (00135); Neurocardiac dysregulation during seizures (00136); Catastrophic epilepsy syndromes of early childhood (00165); Animal Models of status epilepticus (00210); Hormones and Epilepsy (00217); Catastrophic Epilepsy Syndromes of Early Childhood (00228); Status epilepticus (00276).

Further Reading

Abstract:
Seizure activity that spreads through limbic and neocortical regions also spreads into hypothalamic and medullary brain regions, and finally into the periphery via the autonomic nervous system. The autonomic consequences of seizures include cardiovascular effects that can be life-threatening. Studies of epilepsy patients and various animal models have contributed to a deeper understanding of the autonomic impact of seizure activity, but many features of autonomic involvement, including the mechanisms for sudden unexpected death in epilepsy, are still poorly understood. As our understanding grows, specific autonomic monitoring techniques may become prevalent tools for setting an alert system in seizure patients and for defining patients’ risk for severe cardiovascular consequences.

Keywords: Arrhythmia; Autonomic nervous system; Baroreceptor reflex; Bradycardia; Parasympathetic; Sympathetic; Vagus nerve

Author and Co-author Contact Information:
Mark Stewart
Department of Physiology & Pharmacology, and Neurology
State University of New York Downstate Medical Center
450 Clarkson Avenue
Box 31
Brooklyn
NY
USA