Effects of Seizures on Autonomic and Cardiovascular Function

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Parial and generalized seizures often affect autonomic function during seizures as well as during the interictal and postictal periods. Activation or inhibition of areas in the central autonomic network can cause cardiovascular, gastrointestinal, cutaneous, pupillary, urinary, and genital manifestations. Autonomic dysfunction during or after seizures may cause cardiac and pulmonary changes that contribute to sudden unexplained death in epilepsy.

Partial and generalized epilepsies alter autonomic function during ictal, postictal, and interictal states. All aspects of autonomic function can be affected, including the parasympathetic, sympathetic, and adrenal medullary systems. Autonomic changes are the most common symptoms of simple partial seizures but may go unrecognized. Seizures typically activate sympathetic nervous activity, increasing the heart rate and blood pressure, although parasympathetic activation or sympathetic inhibition may predominate during partial seizures. Seizure-induced cardiovascular dysfunction, pulmonary edema, and postictal depression of autonomic respiratory reflexes and cardiovascular function may contribute to sudden, unexplained death in epilepsy.

Seizures that arise from or spread to areas in the central autonomic network can mimic stimulation of autonomic afferents or modify autonomic expression. The central autonomic network encompasses cortical limbic areas, including the amygdala, anterior insula, anterior cingulate cortex, and posterior orbitofrontal cortex (1). These areas directly connect with subcortical regions of the central autonomic network, including the hypothalamus, periaqueductal gray, parabrachial region in the pons, solitary tract nucleus, and ventrolateral medulla. Electrical stimulation and spontaneous seizures arising from or spreading to cortical limbic areas can alter autonomic functions and evoke visceral and emotional feelings.

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Ictal autonomic changes can cause cardiovascular, respiratory, gastrointestinal, cutaneous, pupillary, urinary, and genital manifestations (2). They also can elicit visceral, emotional, and sexual feelings. Ictal activation of the central autonomic network often leads to the hallucination, and less often the illusion, of visceral or corporeal sensations. These feelings are often painful, but many are vague and poorly localized, and even articulate patients cannot describe them. When autonomic phenomena are the sole manifestation of partial seizures, the diagnosis is often delayed or missed. Diffuse sensations (e.g., a cool feeling rising from the legs) may result from stimulation of areas that receive input from autonomic afferents. Real or hallucinatory autonomic phenomena such as palpitations, tachycardia, tremor, and piloerection reproduce the peripheral accompaniments of the "fear response" and may contribute to the experience of fear commonly reported with partial seizures.

Sympathetic responses predominate during most seizures, causing tachycardia, tachypnea, increased blood pressure, pupillary dilatation, diaphoresis, and facial flushing. From infancy to adulthood, tonic–clonic seizures and complex partial seizures of temporal or extratemporal origin often lead to sympathetic activation. However, ictal parasympathetic activity or sympathetic inhibition can predominate, causing increased salivation, gastric acid secretion, peristalsis, miosis, reduced heart and respiratory rates, and decreased blood pressure (3). Combinations of sympathetic and parasympathetic activation and inhibition may occur simultaneously or sequentially during individual seizures.

Several studies suggest hemispheric lateralization of autonomic cardiovascular control. The right hemisphere may predominantly modulate sympathetic tone, whereas the left hemisphere modulates parasympathetic tone (4). In epilepsy patients, this pattern is supported by results of insula stimulation (5) and intracarotid amobarbital studies (6). It is difficult to localize and lateralize the seizure focus on the basis of autonomic phenomena alone. Activation of the amygdala triggers fear and increases sympathetic outflow (7). However, fear and sympathetic activation occurs with seizures involving other cortical limbic areas. In adults, nondominant temporal lobe epilepsy (TLE) is most likely to cause vomiting and retching, spitting automatisms, and ictal urinary urge. Data regarding a left- or right-sided predominance of ictal tachycardia and electrocardiogram (ECG) abnormalities are conflicting (8–10).

Cold shivering and piloerection, infrequent symptoms of partial seizures, are most often associated with a left temporal lobe focus but also occur with a right temporal, as well as a

frontal or parietal lobe, focus (11,12). Piloerection can occur ipsilateral to the seizure focus, and the march documented during invasively monitored seizures suggests a somatotopic organization of limbic autonomic areas, at least in anterior cingulate cortex (11). Mydriasis is the most common pupillary change, and miosis and ptosis also can occur (see section entitled *Other Ictal Autonomic Changes*).

Cardiovascular Changes

Palpitations can occur without heart-rate changes. Sinus tachycardia can occur in more than 85% of complex partial and tonic–clonic seizures (9,10). Among partial seizures that do not generalize, ictal tachycardia may be more prominent after mesial temporal than after nonlesional or extratemporal seizures (10). Ictal tachycardia may be significantly higher and abnormalities of rhythm or repolarization (see following discussion) more frequent during, or immediately after, generalized than nongeneralized seizures (9,13). Ictal heart-rate increase can precede the electroencephalogram (EEG) seizure onset by ~13 seconds in TLE patients and ~8 seconds in patients with extratemporal epilepsy (10). Ictal bradycardia occurs in fewer than 2% of seizures, usually of temporal or frontal lobe origin, and may be more frequent in male patients and in patients with left-sided foci (8–10,13,14). Syncope, which has a 5:1 male predominance (14), may result. Seizure-induced asystole is very rare (15). A preexisting cardiac disorder may increase the risk for ictal asystole.

Ictal ECG abnormalities may occur in 35% of generalized seizures. Although most ECG changes are benign, potentially serious changes (e.g., ST-segment depression and T-wave inversion) have occurred in 6% to 13% of seizures (9,13). In patients who have severe rhythm or repolarization abnormalities, seizures can be significantly longer than in those without such changes (13). Approximately 40% of patients with refractory epilepsy have one or more abnormalities in rhythm or repolarization during or immediately after seizures (13,16). ST-segment depression is associated with a higher maximal heart rate during seizures (16). Arrhythmias documented during seizures include total atrioventricular block (17), atrial fibrillation, supraventricular tachycardia, ventricular premature depolarizations, and bundle-branch block (13).

Respiratory Changes

Seizures can alter the perception of respiration and fullness of breath (e.g., shortness of breath), respiratory rate and pattern (e.g., tachypnea, hypopnea, apnea), reflexes (e.g., coughing), quality (e.g., stridor), and secretions. Neurogenic pulmonary edema may contribute to sudden unexplained death in epilepsy patients (SUDEP—see section entitled *Autonomic Dysfunction and SUDEP*). Apnea and cyanosis are common during tonic–clonic seizures and prolonged tonic seizures. Brief apnea occurs during many complex partial seizures (3,18). Isolated apnea is a rare type of neonatal seizure. Hyperventilation and postictal cough are more common with mesial than with neocortical TLE (19). Rarely, nocturnal partial seizures trigger laryngospasm or choking.

Postictal nose wiping is a common automatism, possibly to clear nasal secretions, and involves mainly the hand ipsilateral to the seizure focus, with the contralateral hand showing weakness or neglect. With TLE, this reflex usually results from ictal spread to the amygdala (20). Postictal nose wiping and coughing are most common with TLE.

Gastrointestinal Changes

Visceral auras localized to the abdominal regions are among the most common symptoms of partial epilepsy. Rarely, painful epigastric auras, usually occurring in children, are the sole manifestation of partial seizures (i.e., abdominal epilepsy). Rare in adults, ictal vomiting is commonly associated with early-onset, benign occipital epilepsy (symptoms include nocturnal seizures, vomiting, and tonic eye deviation) (21) and idiopathic photosensitive occipital epilepsy (seizures induced by photic stimuli, associated with head and abdominal discomfort and vomiting) (22).

Other Ictal Autonomic Changes

Cutaneous manifestations of seizures include flushing, pallor, sweating, and piloerection. These are often accompanied by sensations of warmth, coolness, or discomfort. Mydriasis, as well as miosis and ptosis, can occur ipsilateral or contralateral to the seizure focus (23,24). In most cases, however, pupillary changes are bilaterally symmetric.

Seizures with sexual feelings, arousal, or orgasm often combine autonomic and emotional elements and are more common in women and possibly with right-sided foci (25). Urinary incontinence commonly complicates the end of the clonic phase of a tonic–clonic seizure when the sphincter muscle relaxes in a patient with a full bladder (26). Urinary incontinence occasionally complicates absence and partial seizures, possibly resulting from a combination of increased intravesicular pressure and loss of cortical inhibition of the micturition reflex.

Postictal Changes

Data on postictal autonomic alterations are limited despite evidence that they are among the most dangerous effects of seizures. Neurologic function is depressed after seizures. Postictal dysfunction tends to be greatest in the region from which the seizure arises (27) but may be more diffuse. When seizures arise in areas that inhibit motor, emotional, or autonomic function (e.g., orbitofrontal cortex), postictal hyperactivity (i.e.,

disinhibition) of these systems may occur. After tonic–clonic seizures, patients are often comatose for a brief period, during which time and shortly afterward, the respiratory rate may be decreased and respiratory reflexes impaired. Thus postictal depression of function involves not only the cortical but also the subcortical and brainstem areas involved in seizure spread and propagation. In the rat, cardiovascular regulation is disrupted after recurrent convulsions (28).

Interictally, autonomic modulation is altered, with diminished and more variable parasympathetic and sympathetic cardiovascular responses (29–31). In TLE patients, traditional time and frequency domain measures of heart-rate variability from short-term ECG recordings show cardiovascular dysregulation (29,32). In patients with TLE, not only is heart rate variability reduced, but also is long-term fractal organization (based on chaos theory), and complexity of heart rate dynamics is apparently altered (32). Patients with refractory TLE show greater cardiovascular dysfunction than do those with well-controlled TLE (32), which parallels the relative risk for SUDEP (i.e., greater cardiovascular dysfunction in refractory epilepsy). Variations in blood pressure and heart rate during orthostasis and the cold pressor test are significantly higher in patients with partial epilepsy than in control subjects (31).

Effects of Epilepsy Therapy on Autonomic Function

Antiepileptic drugs (AEDs) can alter autonomic function. Carbamazepine (CBZ), which has anticholinergic properties, and some other AEDs (e.g., phenytoin) in overdosage can cause fatal cardiac arrhythmias. Topiramate and zonisamide can cause hypohidrosis, which can lead to dangerous elevations of core body temperature (33). Abrupt withdrawal of CBZ can increase sympathetic activity in sleep (34). After temporal lobectomy, sympathetic cardiovascular modulation and baroreceptor sensitivity are reduced, possibly as the result of decreased influences of interictal epileptogenic discharges on cortical areas that modulate cardiovascular function (35). Successful TLE surgery may help stabilize cardiovascular control in epilepsy patients by reducing the risk of sympathetically mediated tachyarrhythmias and excessive bradycardiac counterregulation.

Autonomic Dysfunction and Sudden Unexplained Death in Epilepsy Patients

Autonomic dysfunction affecting cardiac or pulmonary systems is postulated to be a major factor in SUDEP. Although seizures and status epilepticus are, by definition, not observed causes of death, tonic–clonic seizures may cause or precede many SUDEP cases. Cardiac arrhythmias and cardiovascular changes are well documented during seizures and may be involved in some cases of SUDEP. However, cardiovascular effects are probably not the major cause of SUDEP. In video-EEG monitoring units, when a life-threatening period or death occurs, it is most often a result of pulmonary dysfunction (36–38). Ictal and postictal apnea (18,36) and neurogenic pulmonary edema (38) are well documented with SUDEP. Pulmonary edema is the result of an increase in pulmonary vascular pressure from increased sympathetic activity, causing some combination of pulmonary vasoconstriction and increased left atrial pressure from systemic hypertension. Status epilepticus and repetitive seizures most often cause pulmonary edema, which can alter pulmonary function for up to 72 hours. When the condition is fatal, pathological study reveals protein-rich exudates and alveolar hemorrhages.

In a patient whose airway is partially obstructed by secretions or the head position blocks the mouth or nares after a seizure (e.g., face down in a bed or pillow), concomitant depression of motor function and respiratory reflexes can be fatal. Normally, if the airway is blocked during sleep, hypoxia or hypercapnia triggers brainstem autonomic reflexes that initiate movement to free the airway and increase the depth and frequency of respiration. Postictal depression of these reflexes allows increased hypoxia, which can further depress all neurologic function, including respiratory drive. The cascade of depressed neurologic and respiratory function is fatal. In a series of 135 cases of SUDEP, 15 witnessed deaths occurred, all during or after seizures, the majority of them generalized, and 12 of which involved respiratory difficulties (39). The available evidence suggests that positioning and stimulation of respiration may help prevent death in some patients.

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