CARDIAC EFFECTS OF SEIZURES

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Seizures frequently affect the heart rate and rhythm. In most cases, seizure-related cardiac changes are transient and do not appear to cause clinically significant abnormalities for the patient. Great interest in this area of research has been generated because of a possible connection with sudden unexpected death in epilepsy (SUDEP). While there are clear, but rare complications from seizure-related cardiac arrhythmias, such as ictal asystole that causes syncope, the overall risk of seizures on cardiac status and any potential connection between seizures and SUDEP still remain uncertain.

Seizure-Related Cardiac Abnormalities

Considerable interest in seizure-related cardiac abnormalities has developed, particularly since the recognition that the majority of patients with witnessed sudden unexpected death in epilepsy (SUDEP) experience a preceding seizure, suggesting a causal relationship between the seizure and death (1). In adults and children, most complex partial and generalized tonic–clonic seizures cause an increase in heart rate (2–5). Blumhardt et al. reported that 92% of 26 patients with temporal lobe seizures recorded by ambulatory EEG–EKG monitoring were associated with a dominant increase in heart rate (2). Subsequently, Smith and colleagues found that the most common pattern of heart rate change associated with complex partial seizures is that of an initial steep acceleration at the onset of the seizure, followed by marked variations during the seizure and postictally (4). This increase in heart rate was seen not only in the majority of clinically symptomatic seizures, but also in most subclinical seizures as well. The investigators also observed that the patterns of heart rate changes during and after the seizure were markedly similar amongst seizures within the same patient, suggesting that the same type of autonomic stimulation occurred in a stereotyped progression in those individuals. Keilson et al. reported that 93% of 106 lateralized and generalized seizures (in 45 patients who underwent 24-hour ambulatory EEG–EKG monitoring), of at least a 30-second duration, were associated with an ictal tachycardia of greater than 100 beats per minute (6). The investigators found that the ictal tachycardia did not favor one hemisphere over the other.

Seizure-related asystole and bradycardia are much less common. In one retrospective analysis, only 5 out of 1244 patients who underwent video-EEG monitoring had ictal asystole (7). Schuele et al. also observed that ictal asystole is rare, seen in only 0.27% of 6825 patients who underwent video-EEG monitoring (8). Tinuper et al. reported 3 cases of ictal bradycardia and reviewed 60 other cases from the literature and found that, most commonly, temporal or frontal lobe seizures are associated with ictal bradycardia and asystole (9). Another study concluded that ictal bradycardia occurred only in the setting of respiratory changes, particularly apnea, suggesting that cardiorespiratory reflexes are important in the generation of ictal bradycardia (10). In contrast, Tinuper et al. found that ictal bradycardia could occur without significant changes in respiration (9). Also notable in this study is the concomitant finding of decreased blood pressure, which may occur before the onset of bradycardia and persist during the seizure. It is important to recognize that seizures may also rarely cause asystole, resulting in a secondary syncope that could be confused with a secondarily generalized seizure (11,12). Schuele et al. determined that sudden atonia caused by asystole usually occurred late in the course of a typical seizure, at an average of 42 seconds after clinical onset (8). In cases of seizure-induced asystole and syncope, placement of a cardiac pacemaker may aid in preventing trauma that is due to falls (13).

Electrical stimulation of the human insular cortex suggests that the right hemisphere may have greater sympathetic influence, while the left hemisphere may be associated with greater parasympathetic control (14). Intracarotid amobarbital studies are inconclusive, with some data suggesting that there are right and left hemisphere differences in heart-rate control (15), but others not clearly demonstrating a difference in overall autonomic balance between the hemispheres (16). Similarly, while some clinical studies support lateralization of autonomic control (5), others have not definitively shown that control of ictal tachycardia and bradycardia is lateralized (17).

In addition to seizure-related rate abnormalities, seizures also may cause rhythm and conduction abnormalities. Keilson et al. reported that among 17 patients in whom 56 electrographic seizures of greater than 10 seconds were recorded, no

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ventricular ectopy or conduction abnormalities occurred (18). However, patients with refractory epilepsy appear to have a higher risk for seizure-related cardiac rhythm and conduction abnormalities. Thirty-nine percent of 43 patients with refractory focal epilepsy had cardiac rhythm and/or repolarization abnormalities during or immediately after seizures observed on video-EEG recording (19). These abnormalities included atrial fibrillation, supraventricular tachycardia, bundle branch block, atrial premature depolarizations, ventricular premature depolarizations, ST-segment elevation, and asystole. Potentially serious abnormalities, including junctional escape rhythm, atrial fibrillation, ST-segment elevation, and asystole, were seen in 14% of individuals; both longer seizure duration and generalized tonic–clonic seizures were associated with an increased occurrence of EKG irregularities. Tigaran et al. reported that 40% of patients with refractory focal epilepsy had seizure-related ST-segment depression, suggesting that cardiac ischemia might occur during seizures (20). Despite this finding, a related study found that cardiac troponin levels were not elevated after complex partial or generalized tonic–clonic seizures (21), indicating that significant ischemia (i.e., resulting in myocardial injury) is unlikely to occur during uncomplicated seizures. However, rarely, in individuals with underlying coronary artery disease, the physiologic stress associated with a seizure may result in significant cardiac ischemia and myocardial infarction in this setting, as has been reported (22).

While seizure-related rate and rhythm disturbances occur immediately after the onset of the seizure and may even precede the ictal pattern seen on a scalp EEG (17), these abnormalities may long outlast the seizure itself (23). Analysis of seizure clusters reveals that increased heart rates associated with seizures may persist for several minutes to hours after the seizure, and if additional seizures occur before the heart rate returns to baseline, there can be incremental heart rate increases as well as more frequent abnormal complexes associated with each subsequent seizure within the cluster (19,24). These data suggest that significant arrhythmias might occur late after a seizure and could have clinical consequences.

Recently, long-term cardiac recording of patients with epilepsy have suggested that arrhythmias may be more common in this population than previously suspected. Rugg-Gunn et al. utilized an implantable loop recorder to monitor EKG data over a median of 18 months in patients with refractory focal epilepsy. Ictal bradycardia of less than 40 beats per minute was recorded in 7 of 19 patients; the bradycardia was deemed to be sufficiently severe to warrant placement of a permanent pacemaker in 4 of these patients. Currently, the clinical indications for pacemaker placement, particularly when the bradycardia or asystole is brief in duration and unassociated with syncope, have not been clearly established. In one study, patients with ictal asystole identified via video-EEG monitoring, who were implanted with a pacemaker, did not have recurrent asystole or bradycardia sufficient to trigger the pacemaker during a mean follow-up of 5 years (25). However, at times, pacemaker placement can result in clinical improvement in preventing syncope (13).

Interictal Cardiac Status

Ambulatory EEG–EKG recordings of patients with epilepsy suggest that serious cardiac arrhythmias are rare. Keilson et al. reported 20–24 hour ambulatory EKG–EEG data on 338 consecutive patients with epilepsy and found that potentially serious cardiac arrhythmias were identified in 5.3% of patients, increased with age, and did not exceed numbers seen in the general population (18). This study comprised a general population of patients with epilepsy. Long-term data for patients with refractory epilepsy also suggest that serious cardiac arrhythmias during the interictal period are rare but that early morning bradycardia and asystole may occur (26,27), probably in part related to increased vagal tone associated with sleep. While such observations are intriguing in that these abnormalities happen during sleep, when the risk for SUDEP appears highest, the clinical significance and potential association with SUDEP of these findings is unknown. It will be important to compare such data to similar long-term findings in normal control individuals.

Cardiac Autonomic Data in Epilepsy

Several studies have documented abnormalities in cardiac autonomic status during the interictal state of epilepsy. Assessments of heart rate and blood pressure during deep breathing and the Valsalva maneuver suggest that the function of the parasympathetic and sympathetic nervous systems, which mediate these responses, are diminished among patients with epilepsy, as compared with a control population (28). In a subsequent study, Ansakorpi and colleagues evaluated similar testing and found that patients with refractory temporal lobe epilepsy appear to have greater dysfunction of cardiovascular autonomic regulation than those with well-controlled temporal lobe epilepsy (29).

Several studies have evaluated heart rate variability, which is a measure of cardiovascular sympathetic and parasympathetic nervous system regulation. Decreased heart rate variability is seen when there is impairment of cardiac autonomic control; the finding is associated with an increased risk for cardiac arrhythmias and mortality in patients with known cardiac disease (30,31). However, it is unclear whether decreased heart rate variability is associated with sudden death in other patient populations, such as epilepsy. Several studies have identified decreased heart rate variability among people with epilepsy, particularly when the epilepsy is refractory, which raises the concern that altered autonomic function might contribute to SUDEP (32–34). In addition, decreased heart rate variability may be a poor

prognostic factor for good postsurgical outcome for temporal lobe epilepsy (34), and some data suggest that that this risk may not be altered by surgery (35). In contrast, Hilz et al. found that temporal lobe epilepsy surgery stabilizes the cardiovascular autonomic control by reducing sympathetic cardiovascular modulation (36). Another study demonstrated reduced variability in the resting heart rate of individuals with subsequent SUDEP, as compared with a control epilepsy population (37).

Chronic vagal nerve stimulation does not appear to significantly affect overall autonomic tone (38,39). Among individuals undergoing vagal nerve stimulation, the reduced heart rate variability seen at baseline in a group of patients with refractory epilepsy was not significantly altered after 1 year of treatment (38). Another study showed that vagal nerve stimulation increased both sympathetic and parasympathetic cardiovascular modulation, thus resulting in no significant alteration in overall autonomic tone related to the treatment (39). Of note, antiepileptic drugs also may affect autonomic tone, and the effects of different medications on autonomic status may be difficult to separate from the effects of the epilepsy. Carbamazepine, in particular, has been shown to affect autonomic tone among patients with temporal lobe epilepsy (28,29), and withdrawal of this drug can increase cardiac sympathetic activity during sleep (40). Lamotrigine affects the cardiac rapid delayed rectifier potassium ion current, but it is not clear that this effect is clinically significant (41). These data as well as studies of SUDEP cases suggest a potential role for specific antiepileptic medications in SUDEP, via a cardiac etiology, but additional studies are needed in this area to clarify these findings (42,43).

Cardiac Rhythms Reported in SUDEP and Near-SUDEP

There are only a few reports of cardiac rhythms of people with SUDEP at the time of death. Cases of ventricular arrhythmias have been described; however, other clinical factors, including prior myocardial infarction and angina, may have contributed to an increased risk for arrhythmia in one instance (44) and only the emergency medical personnel report of ventricular fibrillation (there was no rhythm strip available for confirmation) was available in another case (24). In other studies, EKG recording was not available (45) or revealed initial apnea (46) before bradycardia occurred. In some occurrences of SUDEP, an electrographic seizure was followed by suppression of the EEG postictally (45,47). It has been postulated that persistent postictal suppression may be the result of primary CNS shutdown. Alternatively, seizure-related anoxia and/or decreased cardiac output might prevent the usual postictal recovery of cerebral activity, thus resulting in persistent suppression of cerebral activity and death.

A retrospective review of the ictal and interictal video-EEG and EKG data among individuals who subsequently died from SUDEP revealed no significant increase in the frequency of cardiac arrhythmias, as compared with a control population of patients with refractory epilepsy, but there was evidence of a greater degree of sympathetic stimulation associated with seizures in this group (24). Another study found that there was a statistically significant lengthening of the QTc interval (which might increase the risk for cardiac arrhythmias) on the EKG associated with epileptiform EEG discharges for those who subsequently died from SUDEP, as compared with a control epilepsy population (48).

Cardiac Postmortem Data for SUDEP

Postmortem cardiac examinations of individuals who died from SUDEP have revealed evidence of irreversible pathologic perivascular and interstitial fibrosis (49–51). Additionally, these patients also had evidence of reversible cardiac injury in the form of myocyte vacuolization, which might be the result of excessive adrenergic stimulation associated with seizures. It is possible that if the seizure-related injury is recurrent in individuals with epilepsy, it may cause cardiac fibrosis to develop over time. The fibrosis might then serve as a pathologic substrate, increasing the risk for cardiac arrhythmias as a result of increased sympathetic stimulation related to subsequent seizures. Additional research will be needed to further evaluate this possibility.

Conclusion

Seizures clearly cause both interictal and ictal cardiac abnormalities. Cardiac autonomic status is altered in patients with epilepsy but the clinical significance of these findings, particularly their possible association with SUDEP, is unknown. Both cardiac and respiratory functions are affected by seizures, and dysfunction of the respiratory system during seizures can affect cardiac function. Additional studies, particularly those combining multiple recording modalities to assess respiration, EKG, oxygenation, and EEG simultaneously are needed to further elucidate the relationship of seizures to cardiac status in epilepsy.

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