

Human Hypoxia and Seizures: Effects and Interactions

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INTRODUCTION

This chapter will focus on the effects of acute hypoxia on the human nervous system and its interactions with epilepsy. The effects of both ischemic and non-ischemic hypoxia will be considered. Clinical and physiological aspects will be utilized to differentiate loss of consciousness caused by cerebral hypoxia (i.e., syncope) from epileptic seizures. The role of hypoxia in the precipitation of seizures and the role of seizures in precipitation of hypoxia will be studied. Finally, some potential molecular and cellular mechanisms by which hypoxia could precipitate seizure discharges in an epileptic will be discussed.

ACUTE ISCHEMIC HYPOXIA: DIFFERENTIATION OF SEIZURE FROM SYNCOPE

Gastaut and Fischer-Williams (8) provided a detailed analysis of the clinical and electroencephalographic (EEG) profile of acute ischemic hypoxia in nonepileptic humans. In patients referred for syncope, sustained ocular compression was utilized to induce an excessive vagal response. The ensuing parasympathetic discharge resulted in systemic vasodilatation, bradycardia or asystole, and hypotension. Thus impaired cerebral perfusion presumably mediated the loss of consciousness in these patients.

The EEG and electrocardiogram (EKG) were monitored and the patients observed during and following the period of compression. Blood pressure and respiration were not reported. Moreover, subtle alterations in consciousness may have escaped detection in these patients who sat quietly with their eyes closed following ocular compression. Despite these limitations, valuable information was clearly obtained from this work.

Following 7 sec of asystole, synchronous theta and delta activity developed in the EEG in association with apparent mild impairment of consciousness (Table 1). After 14 sec of asystole, the patients exhibited one or two generalized myoclonic jerks followed by decerebrate posturing. This decerebrate posturing consisted of an intense generalized tonic spasm in extension with opisthotonus.

TABLE 1. *Clinical and EEG profile of ischemic hypoxia in man*

Duration of asystole following ocular compression	EEG pattern	Clinical pattern
3-6 sec	desynchronization 2° to pain of compression	no change
7-13 sec	synchronous theta and delta frontally predominant	perhaps mild impairment of consciousness
more than 14 sec	flattening of EEG (electrical silence)	onset of unconsciousness associated with one or two generalized myo- clonic jerks followed by decerebrate rigidity (tonic extension) lasting 10-20 sec
return of heartbeat	synchronous theta and delta for 30 sec	Cessation of tonic spasm associated with a myo- clonic jerk; conscious- ness returns but patient feels faint

The EEG pattern during this tonic extension was absolutely flat, although the sensitivity of the EEG channel apparently remained at $7 \mu\text{V/mm}$. Despite return of the heart beat, the tonic extension persisted for 10 to 20 sec and was followed by a myoclonic jerk, return of consciousness, and a faint feeling. In sum, this is the classic description of syncope, loss of consciousness secondary to cerebral hypoxia.

By contrast, a grand mal or major motor seizure typically begins with sudden loss of consciousness and generalized intense tonic extension. Following the tonic extension is a period of sustained clonic limb movements. Tongue-biting and incontinence of stool and urine often accompany the seizure. On completion of the motor aspects of the seizure, the patient is usually unresponsive for several minutes and gradually becomes oriented in the next 15 to 30 min. Drowsiness, headache, and muscle soreness usually follow a seizure.

The scalp EEG activity reflects the underlying physiology of the two conditions. Flattening of the EEG in syncope parallels animal studies of unit recordings demonstrating relative electrical silence of the cerebral cortex during ischemic hypoxia (8). The classic EEG alteration of a grand mal seizure consists of a crescendo of low-voltage fast activity followed by generalized rhythmic synchronous high-amplitude spikes at a frequency of 8 to 12 Hz during the tonic phase of the seizure (10). The spikes eventually become grouped and separated by slow waves. These spike-and-wave discharges coincide with the clonic spasms of the seizure. Unit recordings of the cerebral cortex in animals during seizures demonstrate excessive neuronal firing in contrast to the decreased firing during ischemic hypoxia (2).

The physician is often confronted with the task of differentiating syncope

from seizure in a patient presenting with a history of transient loss of consciousness. A careful history of the event from the patient and an observer usually provides the data needed to make this differentiation. Consciousness is generally lost much more abruptly in a seizure than in syncope. Although tonic extension may occur in both, sustained clonic movements are seen only in seizure. Confusion, drowsiness, headache, and muscle soreness mark the postseizure state; syncope is not ordinarily followed by such problems. Since the EEG discloses abnormalities in 50% to 80% of seizure patients between attacks, this study may provide additional help in the diagnosis.

ACUTE NONISCHEMIC HYPOXIA

In Normals

The previous section dealt with the effects of hypoxia presumably arising from impaired perfusion of the brain. This section will consider the effects of hypoxia associated with intact perfusion, that is, nonischemic hypoxia. The data utilized in these considerations were obtained mainly from two systematic studies in which human subjects inhaled either pure nitrogen or 93% nitrogen and 7% oxygen (7,11).

The following measurements were monitored in one or both of these studies: (a) scalp EEG; (b) oxygen saturation with cutaneous spectrophotometry of the ear lobe; (c) partial pressure of exhaled CO₂ with an infrared gas analyzer; (d) EKG; and (e) systolic blood pressure at 10-sec intervals. Ideally, this approach enables one to determine the effects of hypoxia in the absence of hypocapnia or ischemia.

This test was carried out several hundred times in humans without epilepsy. The clinical and EEG results are outlined in Table 2. The parallel with the findings in acute ischemic hypoxia is striking. Both produce graded loss of consciousness associated with slowing and eventual flattening of scalp EEG

TABLE 2. *Clinical and EEG profile of nonischemic hypoxia in man*

Oxygen saturation (estimate by ear lobe spectrophotometry)	EEG pattern	Clinical pattern
>90%	No slowing	Normal
>75%	Mild slowing	No change
60%-75%	Synchronous theta and delta frontally predominant	Slightly clouded consciousness and cyanosis
50%-65%	Slower and lower voltage	
<50%	Flattening of EEG or electrical silence	Onset of unconsciousness associated with clonus followed by decerebrate rigidity (tonic extension)

activity. Both produce motor movements consisting mainly of a tonic extension with one or two generalized myoclonic jerks.

In Epileptics

Similar studies of nonischemic hypoxia were performed on numerous humans with epilepsy (7,11). These studies provide information regarding similarities and differences of the response of epileptic and normal humans to nonischemic hypoxia.

The term epilepsy will be used to refer to a chronic disorder characterized by the recurrent periodic excessive discharge of neurons in the central nervous system. The clinical expression of the epileptic attack is determined by the particular population of neurons discharging excessively and the neural circuits which become involved in spread of this discharge. A useful classification of epilepsy differentiates partial epilepsy (with or without secondary generalization) from primary generalized epilepsy (6). The partial epilepsies are those beginning in a focus of abnormal neurons; the abnormal discharges may spread or generalize to involve the entire brain and be expressed clinically as a grand mal seizure. The primary generalized epilepsies develop from the simultaneous, synchronous involvement of both cerebral hemispheres in the epileptic attack. Primary generalized epilepsy can also be expressed as grand mal seizures.

Many humans with epilepsy respond to nonischemic hypoxia in a pattern identical to that of normals. However, in addition to these effects, nonischemic hypoxia is a potent activator of epileptic discharges in epileptics but not in normals. Gastaut studied the effect of nitrogen inhalation in 29 epileptics with the diagnosis of primary generalized epilepsy [based on EEG criteria of bilaterally synchronous spike-wave discharges (6)]. Hypoxia induced spike-and-wave discharges on the EEG in 16 of the 29 patients, usually in the setting of an oxygen saturation of 60% to 75%. The remaining 13 patients did not display any epileptiform discharges under conditions of hypoxia.

An additional 40 patients diagnosed as partial epilepsy on clinical and EEG criteria underwent nitrogen inhalation. In response to hypoxia, 18 patients developed focal epileptic discharges in the same area that was the site of earlier spontaneous discharges. These discharges consisted mainly of focal epileptic spikes. The remaining 22 patients did not display any specifically epileptiform discharges. Thus nonischemic hypoxia is a potent activator of epileptiform discharges in patients with both partial and primary generalized epilepsy. Neither ischemic nor nonischemic hypoxia provoked epileptiform discharges in humans without epilepsy (7,8).

SEIZURES AS A CAUSE OF HYPOXIA

It is apparent from the preceding discussion that hypoxia can activate seizure discharges in an epileptic. Conversely, abundant evidence indicates that human seizures can cause both ischemic and nonischemic hypoxia.

Generalized seizures are associated with a massive increase in sympathetic output, which mediates systemic arterial hypertension even in paralyzed animals (3). Moreover, the intense tonic-clonic muscle activity of a spontaneous grand mal seizure dramatically increases energy consumption and thus requires increased cardiac output. When there is underlying cardiac disease, such seizures could precipitate myocardial infarction, pump failure, and subsequent ischemic hypoxia. Thus it is not surprising that major motor seizures have precipitated myocardial infarctions, sometimes fatal (1,15). The constellation of systemic abnormalities in a generalized seizure has also resulted in cardiac arrhythmias, another potential source of ischemic hypoxia (4).

Seizures may also induce ischemic hypoxia by a different mechanism. In experimental animals, direct electrical stimulation of some centers in the brain can cause the appearance of arrhythmias and conduction disturbances unrelated to changes in blood pressure, pulse rate, or motor seizures (5). This raises the possibility that partial human seizures could directly trigger potentially fatal arrhythmias in the absence of underlying cardiac disease. Definitive evidence of such a mechanism would require: (a) detailed electrophysiologic cardiac studies to eliminate any inherent cardiac abnormalities; (b) simultaneous EKG and EEG monitoring of an ictal event in which the epileptiform discharges precede the arrhythmia; (c) alleviation of the cardiac arrhythmia by alleviation of the seizure discharges.

Definitive evidence for such a mechanism is not presently available. However, Goldensohn and his colleagues reported atrial tachycardia developing immediately after epileptiform discharges on the scalp EEG in 2 patients without known cardiac disease (16). Other investigators obtained EKG documentation of sinoatrial arrest lasting 8 sec during a complex partial seizure (14). Although the previously cited criteria have not been satisfied, this evidence suggests that partial seizures can trigger human arrhythmias. It seems likely that arrhythmias induced by partial seizures rarely cause fatal ischemic hypoxia (9).

Seizures can also cause nonischemic hypoxia. Fatalities developing from suffocation with bedding or upper airway obstruction due to massive trauma to the tongue represent examples (17). In addition, direct electrical stimulation of several sites in the human brain including the cingulate gyrus, uncus, and insula have induced transient respiratory arrests (13). Once again, the possibility is raised that partial seizures could trigger respiratory arrest, resulting in non-ischemic hypoxia. In several cases, respiratory arrest of varying duration occurred during spontaneous partial seizures (12,13).

In summary, there are a number of potential means by which seizures could cause hypoxia. Ischemic hypoxia could develop secondary to a myocardial infarction or arrhythmia related to cardiac insult in a major motor seizure. Alternatively, partial seizure involvement of discrete sites in the brain could directly trigger a cardiac arrhythmia. Nonischemic hypoxia could arise from upper airway obstruction complicating a generalized seizure or from a respiratory arrest caused by seizure involvement in selected areas of the brain.

DISCUSSION

The foregoing considerations raise interesting issues of both clinical and fundamental importance. In view of the wealth of potential interactions between hypoxia and seizures in an epileptic, determination of the cause of loss of consciousness can provide a difficult challenge to the most astute clinician. Thus ischemic or nonischemic hypoxia produced by partial seizures could be clinically indistinguishable from other causes of syncope. Alternatively, hypoxia induced by partial seizures could in turn precipitate a generalized major motor seizure. Simple vasovagal syncope in an epileptic could precipitate a seizure. Finally, it is also probable that in rare instances (e.g., prolonged syncope following sleep deprivation), syncope can precipitate a major motor seizure in a patient who will remain free of seizures without anticonvulsants thereafter. An understanding of the precise sequence of events is essential to a rational therapeutic approach. This may necessitate reproduction of the events by a variety of activation procedures including the use of the convulsant agent, pentylenetetrazol.

On a more fundamental level, the observation that hypoxia can activate seizure discharges in epileptics is intriguing. This observation raises the important issue of the molecular and cellular mechanism by which hypoxia mediates this activation. In consideration of the potential mechanism involved, let us make two assumptions: (a) the effects of hypoxia are mediated solely by altering the availability of high-energy phosphates (adenosine triphosphate, ATP) through disruption of aerobic energy metabolism; (b) hypoxia mediates this effect by acting on neurons to the exclusion of other cellular constituents. Even within the framework of these assumptions, disruption of any one of a multitude of biochemical events related to either synaptic or extrasynaptic membrane mechanisms could profoundly alter cell excitation. ATP probably plays an important role in biochemical events related to the synaptic membrane. For example, formation of cyclic (AMP) adenosine monophosphate (from ATP) in the brain seems to be linked to several neurotransmitter membrane receptors. Reduced availability of ATP could reduce formation of cyclic AMP. In addition, a variety of biochemical events that mediate cyclic AMP actions require ATP as a substrate (e.g., cyclic AMP-stimulated protein kinases). It is likely that disruption of any one of these biochemical events ultimately related to the synaptic membrane could profoundly alter normal neuronal function. ATP also plays an important role in some extrasynaptic membrane events essential for normal function. For example, ATP is a substrate for the sodium potassium ATPase which plays a vital role in the maintenance of the resting membrane potential. ATP is also the substrate for the mitochondrial calcium ATPase, which plays an important role in regulation of intracellular calcium. Disruption of either of these extrasynaptic membrane events could profoundly influence cell excitability. Thus hypoxia could influence a myriad of biochemical events critical for normal neuronal function, simply by disrupting aerobic energy metabolism and altering the supply of ATP in neurons.

It must be emphasized that neither one of these two assumptions is necessarily correct. Hypoxia could primarily disrupt glial function and perhaps reduce removal of extracellular potassium, thereby altering neuronal excitability secondarily. Moreover, oxygen per se undoubtedly regulates many biochemical reactions, aside from effects on aerobic energy metabolism and ATP supply. For example, oxygen itself is a substrate for tyrosine hydroxylase, the rate-limiting step in synthesis of catecholamines. In summary, the number of potential mechanisms by which hypoxia could alter cell excitability is tremendous. Although hypoxia activates epileptiform discharges in epileptics but not normals, delineation of the molecular and cellular mechanism by which hypoxia mediates this effect must await elucidation of a fundamental biochemical understanding of epilepsy.

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