Breath-Holding Spells

Galen N. Breningstall, MD

Two particularly common, and frequently frightening, forms of syncope and anoxic seizure in early childhood are pallid and cyanotic breath-holding spells. Pallid breath-holding spells result from exuberant vagally-mediated cardiac inhibition. Cyanotic breath-holding spells are of more complex pathogenesis, involving an interplay among hyperventilation, Valsalva maneuver, expiratory apnea, and intrinsic pulmonary mechanisms. The history is the mainstay of diagnosis; videotape documentation may be possible. Performance of an electrocardiogram to evaluate for prolonged QT syndrome should be strongly considered. In patients with pallid breath-holding spells, a characteristic sequence of changes may be documented on an electroencephalogram with ocular compression, if this study is performed. Spontaneous resolution of breath-holding spells, without sequelae, is anticipated. Reassurance is the mainstay of therapy. Occasionally, pharmacologic intervention may be of benefit.


Breath-Holding Spells

Forms of anoxic seizures occur in early childhood with considerable frequency. Anoxic seizures are dependent on the sudden depression of the function of a population of neurons due to ischemia or asphyxia, in contrast to epileptic seizures which imply the excessive discharge of a population of neurons [1]. Two particularly common forms of anoxic seizure in early childhood have been termed breath-holding spells (BHS). BHS have been subdivided as cyanotic or pallid, based on the coloration of the child during the event [2-4]. Although the fundamental pathophysiology of these two types of BHS is different, along with the clinical scenario anteceding their occurrence, certain patients experience anoxic seizures due to both cyanotic and pallid BHS. With pallid BHS, breath-holding per se is a minor component of the event. Vagally-mediated cardiac inhibition is a major factor in pallid BHS, which may be termed reflex anoxic seizures, infantile syncope, or non-epileptic vagal attacks, instead of BHS [5,6]. The breath-holding that occurs with cyanotic BHS is involuntary and reflexive, occurring in active or full expiration, in contrast to volitional breath-holding which is prolonged inspiration. Despite ample literature regarding these two types of anoxic seizure, parents and practitioners continue to confuse these with epileptic seizures. Indeed, in some children BHS may be the precipitant of an epileptic seizure or status epilepticus, enhancing the confusion.

In a paper that summarized institutional review boards, the occurrence and phenotype of anoxic seizures in human adults was studied in volunteers [7]. A "specially designed inflatable cervical pressure cuff, held down to the lower third of the neck," with a cuff pressure rising to 600 mmHg in 1/8 s, effected a rapid temporary arrest of the cerebral circulation. The sudden inflation of the cuff prevented engagement of the cerebral vessels by occluding arterial inflow before the next heartbeat. In addition to psychiatric patients and prisoners, the investigators and their associates were also studied. Generalized tonic-clonic seizures, "usually relatively mild" and rarely continuing more than 6-8 s were usually occurred in these subjects. Usually, the seizures occurred after release of pressure in the cuff, not during acute cerebral anoxia.

Pallid Breath-Holding Spells

A vivid description of the typical pallid BHS is given by Stephenson [5]:

An unsteady toddler on his own trips and falls. His mother hears the bump but no succeeding cry and hurries to him. She finds her child lying dead faint, with eyes fixed upwards, lips dusky. As she lifts him, he suddenly stiffens into rigid extension with jaw clenched and hands fisted. He gives a few jerks, and after what seems an age (in fact it is less than half a minute) relaxes limply with an absent far-away look. Then he opens his eyes, at once recognizes his mother, cries a little, and drifts off to sleep, his face distinctly pale.
The precipitant for pallid BHS is usually a sudden, unexpected, unpleasant stimulus, frequently a mild injury to the head. Crying, if present, is not prominent. Generally, cyanosis is not present. Pallor and diaphoresis are common. The patient may be semiconscious or go to sleep following the episode. In children experiencing BHS, whether pallid or cyanotic, the first episode usually occurs by 18 months of age [4]. Parental observations of bradycardia during pallid BHS suggested that an excessive vagal nerve discharge (vagotonia) was present in these patients [8]. The ocularcardiac reflex, elicited by ocular compression, involving transmission of afferent signals to the brainstem via the trigeminal nerve and efferent parasympathetic signals via the vagus nerve, has been utilized to study breath-holders [2,5,9]. With some frequency in patients with pallid BHS, ocular compression would induce an anoxic seizure, which appeared to the parents observing it identical to the child's regular episodes. In those patients not proceeding to anoxic seizure, ocular compression would often induce a prolonged asystole (4 s). These observations supported vagal cardiac inhibition with consequent cerebral anoxia as the pathophysiology of pallid BHS. Cardiac monitoring during spontaneous pallid BHS also reveals prolonged asystoles [2,6,10]. As anticipated, several investigators found prolonged asystoles to occur compression in a greater percentage of pallid breath-holders than cyanotic breath-holders (61-78% versus 23-36%) [2,5]. Ocular compression-induced asystole of up to 32 s duration has resolved without need for resuscitation [6]. The only reported ophthalmologic complication of ocular compression occurred in an elderly patient to whom this procedure was applied in order to terminate ventricular tachycardia [6].

Cyanotic Breath-Holding Spells

Whereas pallid BHS are characterized by syncope, in cyanotic BHS loss of consciousness is but a possible end point. Breath-holding, per se with attendant cyanosis is the characteristic feature of cyanotic BHS. Rousseau describes a cyanotic BHS which terminates, as frequently these do, before syncope is reached [11]:

I shall never forget how once I observed one of these ominous screamers whom his nurse had stopped. He suddenly became quiet; I thought he was intimidated. I said to myself: One day this will be a terrible man which will be influenced only by sternness. But I was wrong; the unhappy child was suffocating from anger and had lost his breath; I saw him turn purple. A moment later a piercing scream erupted. All the signs of indignation and desperation of this age could be heard in his screaming. I was afraid he would succumb to this excitement... I am sure a firebrand accidentally falling on the child's head could not have excited him more than the rather light slap which had been delivered with the apparent intention of chastising him.

The pathophysiology of cyanotic BHS is more complicated than that of pallid BHS. Cyanosis occurs in these patients with surprising rapidity. Peiper, by feeding mashed bananas, which the subject disliked, to a resistant cyanotic breath-holder in a plethysmograph, established that the breath-holding occurs in expiration [11]. There were repeated small movements of the diaphragm during the expiratory apnea without change in the cyanosis. Cinefluorography subsequently revealed the diaphragm to be elevated during cyanotic BHS [12]. Accordingly, cyanotic breath-holding involves a diminished pulmonary oxygen reserve. Two infants with cyanotic BHS studied by Gauck et al. [12] were reported to experience pronounced oxygen desaturation with arterial hypertension and no significant alteration in pulse rate. Anoxic anoxia (cerebral anoxia) consequent to decreased oxygen saturation per se was deemed to be the mechanism for the loss of consciousness in these patients. However, critical inspection of the data indicated that consciousness was lost when the oxygen saturation was close to 90% [10]. A mechanism for cyanotic BHS was then advanced involving violent crying leading to hypopnic cerebral ischemia and respiratory spasm (Valsalva) leading to increased intrathoracic pressure, as well as apnea proceeding to hypoxemia [2]. The hypopnic and Valsalva maneuver combine to decrease arterial inflow and to increase resistance to outflow in the cerebral circulation. A similar combination of physiologic alterations comprise the "nose trick" or "fainting loss," wherein a loss of consciousness is induced for self-stimulation or for the amusement of others [13]. One such induced syncope in the recreational setting resulted in head injury and death [14]. The phenotype of anoxic seizures has been studied in research subjects self-inducing syncope in this manner [15]. The increase in cerebral venous pressure resulting from a Valsalva maneuver has been documented in patients with massive syncope [16].

In a contemporary study of patients with "prolonged expiratory apnea," Southall et al. again demonstrated sustained extreme cyanosis in both spontaneous and induced breath-holding (\( P_{O_2} < 20 \) mm Hg in 20 s) [17]. Patients experienced continued expiratory activity at low lung volumes, frequently with partial or complete glottic closure. Adult controls, however, generated only mild hypoxemia with volitional end-expiration breath-holding. Some of the patients experienced continued episodes of severe hypoxemia despite continued air flow and endotracheal intubation (see also Gauck et al. [18]). Krypton infusion scintigrams have demonstrated the appearance of krypton outside the lung fields in patients with prolonged expiratory apnea, suggesting a right-to-left shunt [17]. Contrast echocardiography failed to demonstrate a right-to-left shunt through a patent foramen ovale in patients with cyanotic BHS.

Larapulmonary shunting involving ventilation perfusion mismatch or flow through bronchopulmonary or other anatomic arteriovenous anastomoses seemed to most probably account for the rapid onset and progression of severe
hypoxemia. Low pressure arteriovenous shunting, with the vessels forming the shunts up to 60 μm in diameter, has been demonstrated in postmortem studies of infants [19].

The pulmonary neuroendocrine system may be comprised of cells which may influence ventilation to perfusion matching. In the fetus, these cells may help to maintain pulmonary vasoconstriction. Pulmonary vasoconstriction may be mediated by adrenergic pathways [17]. It is proposed that interactions among central sympathetic activity, brainstem control of respiration and vasomotor activity, reflexes arising from around and within the respiratory tract, and the matching of ventilation to perfusion account for the intrapulmonary shunting and expiratory apnea occurring in these patients [17].

Diagnosis

Obtaining an accurate and detailed history of the episodes of concern is critical in the diagnosis of BHS. Pallid BHS occur in the context of an injury, frequently an unexpected blow to the head. Cyanotic BHS occur in the setting of anger and upset. Any losses of consciousness or seizure in early childhood that are provoked by either of these antecedents are primarily suspected to be anoxic in character. Epileptic seizures are generally not provoked by anger or injury. In the setting of a normal general and neurologic examination, laboratory testing usually adds little information. Difficulty in diagnosis may arise when certain of the episodes are not witnessed by the instigator. Another diagnostic difficulty, to be discussed later, occurs when BHS in turn provoke epileptic seizures. Videotape documentation of a typical episode may be of considerable value. Patients with pallid BHS have frequently been studied with an electroencephalogram (EEG) during which ocular compression is performed. Generally, firm pressure is applied with the thumbs to the closed eyes of a supine patient for 10 s, while the EEG and cardiac rhythm are monitored [9]. Should this maneuver provoke a pallid BHS, a limited cardiac asystole, along with a stereotypic sequence of EEG alterations, is observed. The earliest EEG sign of cerebral hypoxia is hypersynchronous slowing and increased amplitude of the background. Clouding and loss of consciousness with lumpsness or ocular supraversion may occur with a high voltage delta background. There may then be an interval of profound electrodecrementation of the background, reflecting more profound hypoxia. During which decorticate or decerebrate posturing, as well as convulsion or myoclonic jerking, may occur. A high amplitude hypersynchronous slow background then reemerges, following which the background normalizes (Figs 1-3). A singular ventricular escape beat occurring in the midst of prolonged asystole may prevent or delay both the tonic fit and the isoelectric pattern [10]. If respiration is monitored during ocular compression, there is usually forced expiratory effort exerted simultaneously with cardiac arrest, which is maintained until after EEG recovery has begun [10]. Patients with cyanotic BHS may follow this EEG evolution without significant bradycardia or asystole. Spontaneously recorded BHS recapitulate this sequence of EEG alterations [2,6,10]. Although prolonged asystole per se, without the above sequence of clinical and EEG alterations, may suggest a tendency to anoxic seizures, this depends upon the availability of good normative data [6].

Prolonged QT syndrome is a rare, but potentially malignant, cause of anoxic seizure [20,21]. Syncope or sei-
sue may be induced by exercise, excitement, injury, or fright in such patients. Cerebral hypoxia generally results from ventricular tachycardia, although asystole may also occur [6]. Prolongation of the corrected QT interval on an electrocardiogram (EKG) frequently correlates with abnormal T wave morphology [21]. There are, however, patients who experience anoxic seizures due to ventricular tachyarrhythmia even when QT lengthening is not present on a routine EKG. QT shortening may fail to occur with increasing heart rate in such patients [20].

Case Report

A 4 year-old girl fell from her parents’ bed to the floor, cried, and then became apneic. Mouth-to-mouth resuscitation was briefly administered. She was hospitalized but soon discharged. Nine months later, the patient fell, striking her head on a coffee table. Again, an apneic episode occurred. She was hospitalized once more. Presumed hyperventilation syndrome on presentation was treated with rebreathing, phenobarbital, and diazepam. At 5 years of age the patient lost consciousness and became apneic after striking her head against the dashboard when her mother stopped the car abruptly. She was examined in the emergency room and discharged. At 9 years of age, the patient lost consciousness after being struck in the mouth by a door. In the emergency room, an EEG disclosed generalized slowing. An EKG was obtained. A cranial computed tomogram was normal. The patient’s behavior was hicronic and resistant. Psychiatric dysfunction was suspected. Two weeks later, the patient fell at school, striking her head. She sustained a cardiorespiratory arrest and could not be resuscitated. Upon review, the EEG from the emergency room presentation 2 weeks prior to the patient’s death showed a corrected QT interval of 0.50-0.52 (normal 0.44).

This patient’s episodes, like those of breath-holders, were provoked by injury. The age of onset for her episodes was atypical for BHS. Nonetheless, an EKG should be strongly considered in any patient with BHS [22].
BHS occur most commonly within the first 18 months of age and 90% or more of breath-holding have their initial spell by age 2 years [4]. In approximately half of all children with severe spells, the spells terminate by age 4 years. Virtually all breath-holders cease experiencing episodes by 7 to 8 years of age [4]. A family history of BHS may be present [23]. Some investigators have found an increased incidence of syncope in later life in patients with a history of BHS [2,3]. Aside from this, no lasting sequelae of BHS are anticipated [3]. Of children who experience BHS, 54-62% are cyanotic, 19-22% pallid, and 19-24% mixed or unclassifiable [2,3]. In some children BHS at their apex occur many times a day. The peak frequency is generally present in the second year of life. Children with pallid BHS may have other subtle evidence of autonomic dysregulation [24]. Similar findings were also present in a mixed population of breath-holders [25]. Anemia may be a factor contributing to BHS in some children [26]. Febrile illness may also be a precipitant of BHS in some children [27].

Of the 51 infants and young children with recurrent episodes of cyanosis and loss of consciousness described by Southall et al., 8 died suddenly and unexpectedly [17]. Four of these 8 patients died suddenly during or as a direct consequence of a cyanotic episode. This led the authors to assert that "these cyanotic episodes... are a cause of sudden unexpected death in infancy and early childhood."

Of the patients who died in relation to a cyanotic episode, one had undergone tracheoesophageal fistula repair and an aortopexy to treat tracheomalacia; one had been hospitalized repeatedly for assessment and had a history of cleft lip, and the remaining two had tracheostomies in place. The patients studied by Southall et al. were admitted at the severe end of the spectrum and therefore not representative of the whole population of breath-holders. In a prospective population-based study, also conducted by Southall et al., two deaths between 1 and 5 years of age, among 9,856 infants followed, occurred during cyanotic breath-holding (these 2 patients were also among the 4 patients Southall et al., described above) and one occurred after an isolated provoked episode of apnea and cyanosis [28]. Aside from Southall's data, reports of death consequent to BHS are exceedingly rare [11,29].

After the diagnosis of BHS is established, explanation and reassurance to families is the mainstay of therapy [4,6]. The occurrence of BHS per se should not lead to any alteration in the general care of the child [4]. It is neither feasible nor helpful to avoid circumstances which may provoke BHS. If a BHS occurs, placing the child in a lateral recumbent position is appropriate until recovery occurs. Cardiopulmonary resuscitation should generally be avoided. One reported death due to a BHS may have been related to a resuscitation attempt promoting aspiration pneumonia [29]. In the considerable minority of patients with particularly severe BHS, treatment with atropine sulfate or methemoglobin has been utilized [30]. Transdermal scopolamine [31] or even pacemaker implantation [32,33] has also been utilized.

**Case Report**

A boy began to experience episodes of breath-holding and cyanosis at 3 days of age. Such episodes could occur 20-30 times per day. By 13 months of age, the patient had been evaluated by a number of practitioners and hospitalized once for these episodes. The vast majority of the patient's episodes were precipitated by minor injury, frustration, or upset. Five of the episodes had caused loss of consciousness. An EKG and echocardiogram were normal, as was the EEG. An ambulatory EEG disclosed cardiac slowing with EEG background suppression followed by slowing when several episodes occurred. In view of continued episodes, the patient was treated with carbamazepine. The episodes did not diminish in frequency and the patient experienced carbamazepine toxicity. Carbamazepine was discontinued. Video EEG monitoring at 2½ years revealed no evidence for epilepsy, although the heart rate would decrease to the 50s range with episodes of breath-holding. Following cardio-

Bremningall: Breath-Holding Spells 95
evaluation, an endocardial pacemaker was placed. Episodes continued to occur, nonetheless. Propranolol was prescribed but shortly thereafter discontinued when the patient experienced hyperactivity and insomnia. The cardiologist indicated, “Hopefully we can at least prevent arrhythmia which could contribute to marked reduction in cerebral perfusion.”

Anoxic-Epileptic Seizures

Occasionally, patients may experience protracted seizures or status epilepticus following either a cyanotic or pallid BHS [34,35]. Typically, interictal EEG findings in these patients are normal, although one such patient of the author’s acquaintance had vertex spikes on his interictal EEG. Occasionally, an ictal recording on such a patient has been obtained, but most frequently direct observation or videotape reveals the patient to experience the lengthy seizure precipitated by breath-holding. Stephenson [6] termed such episodes anoxic-epileptic seizures. Administration of antiepilepsy medication frequently ablates the lengthy seizures, although BHS may continue to occur.

Conclusion

Pallid and cyanotic BHS are both frequent causes of syncope and anoxic seizures in early childhood. Pallid BHS result from vagal hyperresponsiveness and anoxic BHS result from a complex interplay of hyperventilation followed by inspiratory apnea, increased inotropism, and intrinsic pulmonary mechanisms. Both are generally not only in normal children but also spontaneously resolve without sequelae. History is the mainstay of diagnosis. It is recommended that an EKG be performed for prolonged QT syndrome be done. An EEG with ocular compression may be useful if there is an ambiguous history for pallid BHS. Both pallid and cyanotic BHS proceed to a brief loss of consciousness and seizure. A more protracted loss of consciousness with hypotension may suggest cardiac dysrhythmia requiring further cardiac investigation. A more protracted seizure may be anoxic-epileptic in character, requiring antiepilepsy pharmacotherapy. A subset of patients with cyanotic BHS, children with either anatomic or functional airway abnormalities, may be at risk for morbidity and mortality consequent to cyanotic BHS. Such children may experience life-threatening BHS despite tracheostomy. Ventilatory assistance may be necessary. Patients with particularly severe and frequent pallid BHS may benefit from parasympatholytic medication. Pacemaker implantation is almost never indicated. Pharmacotherapy has little to offer patients with cyanotic BHS.

The author thanks Barbara Bergeron for assistance in preparing the manuscript.

References