Posthyperventilation Apnea
Associated with Severe Hypoxemia*  

Kenneth F. MacDonnell, M.D., F.C.C.P.;** John T. Bowers, M.D.;† and Robert E. Flynn, M.D.§

We studied a 14-year-old girl who suffered fractures of her mandible and tegmen following a fall from a balance beam. Thirteen days after hospitalization, she developed severe, protracted, recurrent episodes of hyperventilation; subsequently, she suffered posthyperventilation apnea, which at times was prolonged and associated with severe hypoxemia with an arterial oxygen pressure as low as 25 mm Hg. The patient was treated with added dead space and chlorpromazine hydrochloride (Thorazine). Postulated mechanisms for her disorder are discussed. The importance of close clinical and laboratory observation in similar cases is stressed.

Apnea following passive hyperventilation has been consistently observed1,2 in both man and the experimental animal; however, there are conflicting data concerning posthyperventilation apnea following active voluntary hyperventilation in man.3,4 Haldane and Poulton5 observed apnea vera following hyperpnea and reported their findings in a dramatic clinical presentation before a meeting of the British Physiologic Society. The clinical picture was described as follows: "apnea, then the face gradually becoming leaden, . . . corpse-like appearance . . . characteristic of great anoxemia." The demonstration was so striking that many of those in attendance had to be restrained from applying artificial respiration.

Many of the early observations of posthyperventilation apnea were criticized because the investigators used themselves as the subjects of the experiments.

Fink4 was unable to produce posthyperventilation apnea in an awake group of anesthesiologists. This same group of healthy subjects suffered respiratory cessation following passive hyperventilation. He concluded that nonchemical "cerebral" stimuli were responsible for the maintenance of ventilation in awake hypoxic subjects.

Plum et al.7 suggested that rather than a "cerebral" origin, a "more subtle neurogenic respiratory disturbance" which resulted frequently from brain disease or injury was responsible for prolonged posthyperventilation apnea. The consequences of posthyperventilation apnea may indeed be serious, and death following voluntary hyperventilation has been reported.8

The following case report is an example of a near fatal instance of posthyperventilation apnea.

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*From Tufts University School of Medicine and St. Elizabeth's Hospital of Boston, Boston.
**Associate Professor of Medicine and Director of Respiratory Department.
†Associate Professor of Pediatrics and Chief of Pediatrics.
‡Associate Professor of Neurology and Director of Medicine.

Reprint requests: Dr. MacDonnell, 736 Cambridge Street, Brighton, Massachusetts 02135

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CASE REPORT

This was the first hospitalization of a 14-year-old white girl who was well until five days prior to admission, when she fell while doing a cartwheel on a balance beam in a gymnasium. She struck her jaw and, although stunned, did not lose consciousness. The patient was seen at another hospital where a laceration of her chin was closed with seven sutures. Skull and cervical spine x-ray films were taken and reported as normal. Four days prior to admission, nausea, blurring of vision in the right eye, and a dizzy lightheaded feeling were noted. The patient found it increasingly difficult to open her mouth, and she was seen by another physician. X-ray films of the mandible revealed a fracture and dislocation of the right condylid, resting slightly anterior and inferior to the articular eminence. The mandible was wired. The patient was transferred to St. Elizabeth's Hospital of Boston five days after her injury.

On admission, physical examination revealed a well-nourished, well-developed, attractive girl in no acute distress with her jaw wired. Her temperature was 37°C (98.6°F); she had a regular pulse rate of 89 beats per minute and a respiratory rate of 20/min. A small bluish hematoma approximately 5 to 6 mm in diameter was noted posterior to the pinna of the right ear. There was crusted blood in the right external auditory canal and behind the right tympanic membrane. Visual acuity tested by the Snellen eye chart was 20/100 in the right eye and 20/20 in the left; visual acuity could be improved with the use of a pinhole. Findings from a detailed neurologic examination were within normal limits, as were the findings from the remainder of the physical examination.

LAbORATORY DATA

Laboratory studies disclosed that the following were within normal limits: blood glucose; serum electrolytes; blood urea nitrogen; creatinine; serum calcium; serum phosphorus; complete blood cell count; urinalysis; urine culture; anti-streptolysin O titer; rheumatoid factor; cold agglutinins; electroencephalogram; brain scan; and cerebrospinal fluid (CSF). X-ray films of the chest, cervical spine, and ocular orbits were normal. Tomograms of the right middle ear showed a hairline undisplaced fracture of the tegmen.

HOSPITAL COURSE

During the initial period of her hospitalization, treatment was supportive. The patient continued to complain of a lightheaded dizzy feeling exaggerated by postural changes. No other changes in her clinical or laboratory status were noted until the 13th day of hospitalization, when the patient was informed that she was to be discharged. On the following day, she suffered her first episode of hyperventilation with a respiratory rate of 40/min, twitching of the angle of the mouth, and carpopedal spasm. Arterial blood gas analysis during the episode disclosed a pH of 7.62, an arterial oxygen pressure (PaO2) of 91 mm Hg, and an arterial carbon dioxide tension (PaCO2) of 20 mm Hg. The blood glucose level was 102 mg/100 ml, the serum sodium level was 141 mEq/L, the serum potassium level was 4.8 mEq/L, and the serum chloride level was 99 mEq/L. During this spell, the patient complained of complete loss of vision lasting for approximately 90 seconds, with return of vision occurring in a circular fashion. The patient was easily agitated, with wide variations in her respiratory rate.

Recent episodes of hyperventilation became almost con-
Figure 1. Wide swings in PaO2, PaCO2, and pH are depicted during various periods of hyperventilation and apnea.

Continuous (representative arterial gas levels are shown in Figure 1). Treatment for these spells was directed towards rebreathing techniques and mild sedation with administration of 5 mg of diazepam (Valium) twice a day. Nonetheless, the following four days were characterized by recurrent episodes of tachypnea and hyperventilation. On the 17th day of hospitalization, an episode of sustained tachypnea and hyperventilation lasting for an hour was followed by a <5-second period of apnea. A psychiatric consultation was obtained; and a diagnosis of traumatic situational reaction of adolescence with secondary anxiety and hyperventilation was entertained, and therapy with chlorpromazine hydrochloride (Thorazine) was instituted.

The clinical situation remained unchanged until the 15th day of hospitalization, when a prolonged episode of posthyperventilation apnea lasting three minutes occurred. During this episode, because of profound hypoxia (Table 1), further observation while anticipating spontaneous resumption of respiration was believed to be unwise.

The patient was intubated and ventilated. The mandibular fracture made the endotracheal tube extremely uncomfortable for the patient; and for this reason a tracheostomy was performed, and the patient was transferred to the respiratory intensive care unit. Addition of dead space to the exhalation port of the tracheostomy tube prevented further apneic spells (with 20 inches of added dead space, arterial gas levels were a pH of 7.36, a PaCO2 of 41 mm Hg, and a PaO2 of 80 mm Hg). Tachypnea persisted. A repeat lumbar puncture was performed, with an opening pressure of 120 mm H2O, a protein level of 31 mg/100 ml, and a glucose level of 74 mg/100 ml with a simultaneous blood glucose level of 96 mg/100 ml; closing pressure was 90 mm H2O, no cells were observed, and the fluid was clear (gas levels appear in Table 2).

During three episodes of apnea, stimulation with administration of doxapram resulted in almost immediate resumption of breathing patterns.

Initial attempts to decrease the added dead space were unsuccessful, and the dosage of chlorpromazine hydrochloride was increased to 25 mg every four hours. A marked improvement, with slowing of the respiratory rate to normal, was accomplished. Monitoring of the patient's EEG revealed that she did not suffer any episodes of posthyperventilation apnea while asleep. These observations were related to the patient, and a psychogenic aspect to her illness was suggested. It was pointed out to the patient that periods of agitation, such as occurred during psychiatric interview and discussion, frequently resulted in recurrent episodes of tachypnea, hyperventilation, and spells of apnea.

The patient was reluctant to admit any emotional component; however, there was a change in her clinical state, and rather than suffering spells of posthyperventilation apnea, she began experiencing typical breath-holding spells which lasted up to 30 seconds without any preceding tachypnea. Subsequently, there was a gradual cessation of tachypnea, breath-holding spells, and posthyperventilation apnea.

The patient was successfully weaned from the dead space and extubated. A gradual reduction and eventual discontinuation of therapy with chlorpromazine hydrochloride was followed by her discharge from the hospital. One and one-half years later, she is well and has resumed her normal activities.

**DISCUSSION**

Hering* originally noted posthyperventilation apnea in 1867. In 1872, his observations were verified by

<table>
<thead>
<tr>
<th>Time</th>
<th>Respiratory Rate</th>
<th>Source</th>
<th>Po2, mm Hg</th>
<th>PaCO2, mm Hg</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>5:10 AM</td>
<td>28/min</td>
<td>Arterial</td>
<td>89</td>
<td>35</td>
<td>7.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Venous</td>
<td>29</td>
<td>40</td>
<td>7.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CSF</td>
<td>...</td>
<td>51</td>
<td>7.32</td>
</tr>
<tr>
<td>6:30 AM</td>
<td>70/min</td>
<td>Arterial</td>
<td>94</td>
<td>33</td>
<td>7.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Venous</td>
<td>35</td>
<td>37</td>
<td>7.39</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CSF</td>
<td>...</td>
<td>38</td>
<td>7.42</td>
</tr>
<tr>
<td>6:45 AM</td>
<td>10-sec apnea</td>
<td>Arterial</td>
<td>43</td>
<td>41</td>
<td>7.38</td>
</tr>
</tbody>
</table>

*Patient was breathing with 15 inches of dead space added to exhalation port of tracheostomy tubing.

**HCO3-, 29.
Ewald, who demonstrated apnea following passive vigorous hyperventilation in dogs. This was then followed by the dramatic demonstration by Haldane and Poulton of the seriousness of posthyperventilation apnea in man before the British Physiologic Society. Vernon, using himself as the subject, reported that after forced breathing for six minutes, ending with four deep inspirations of oxygen, he was able to hold his breath for a period of eight minutes and 13 seconds.

The potential lethal effect of posthyperventilation apnea was reported by Mosso when he hyperventilated nine dogs. After hyperventilation, five of the dogs were left entirely undisturbed to either die apneic or to recover unaided. Two dogs died. The degree of hypoxia observed was striking. At the beginning of their experiment, the arterial oxygen content was 14.8 volumes percent, and the arterial carbon dioxide content was 16.2 volumes percent. At the end of eight minutes of apnea, the arterial oxygen content was zero, and the arterial carbon dioxide content was 21.7 volumes percent. There continue to be conflicting opinions regarding the occurrence and severity of posthyperventilation apnea in the wakeful state.

Posthyperventilation apnea has been reported in awake man and has been found to be quite variable. In subjects breathing enriched oxygen concentrations and hyperventilated to a PaCO2 of 31 mm Hg, posthyperventilation apnea ranged from one breath to 120 seconds, those subjects with the longest periods of apnea being quite sensitive to reduction of the PaCO2 to only 4 to 5 mm Hg below normal.

Others have noted the effect of nonchemical stimuli which may modulate the respiratory effect of carbon dioxide. The role of the central excitatory state and the loss of respiratory movement may have a major impact on the ability to hold breath and the determination of conventional breaking points.

The "black box" model for the control of respiratory activity recognizes a variety of modulating stimuli, including (1) chemical, peripheral, and central chemoreceptors; (2) mechanical (state of inflation of the lung); and (3) cerebral stimulation, both psychogenic and neurogenic.

The exact role of the arterial chemoreceptors in the respiratory scheme is still tentative. It has been suggested that peripheral chemoreceptors acting in response to hypoxia help to determine the set point of the more potent central carbon dioxide, hydrogen ion chemoreceptor. Ablation of peripheral chemoreceptors results in approximately a 15-percent decline in resting ventilation.

Honda et al demonstrated that a chemoreceptor’s discharge in a cat can be halted even in the presence of severe hypoxia if the levels of arterial carbon dioxide and hydrogen ion are forced far enough below normal by vigorous hyperventilation. This phenomenon may explain the lack of respiratory response to the profound hypoxia experienced by our patient and in those instances described by Haldane and Priestley and by Vernon. Indeed, if there is no peripheral response to hypoxia, its central effect, which is one of respiratory depression, may worsen the clinical situation.

Episodes of apnea were prevented in our patient by the addition of dead space to her tracheostomy tubing or by enriching her inspired gas with carbon dioxide. She also responded to carbon dioxide inhalation by increasing her respiratory rate and minute ventilation. Infusion of doxapram produced a resumption of ventilation. These responses all indicated a central respiratory apparatus capable of physiologic response.

Plum et al have described substantial periods of posthyperventilation apnea in patients with relatively fixed neurologic defects following traumatic brain injuries. This abnormality of the respiratory system could be reproduced with repeated testing.

We were unable to demonstrate any fixed neurologic defects, in spite of meticulous clinical and laboratory testing. Moreover, no episodes were recorded during sleep, and when a psychogenic origin was suggested to the patient, his pattern of episodes converted into typical breathholding spells.

It is, of course, impossible to completely eliminate a minute, as yet ill-defined, posttraumatic disruption of the respiratory control system, which could account for the severe degree of hyperventilation and posthyperventilation apnea occurring in this patient. An unusual psychic conversion reaction seems a more likely explanation of the entire picture. In either case, the potential danger of such a situation should be emphasized.

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Acquired Continuous Murmur Associated with Acute Pulmonary Thromboembolism*

Richard L. ZuWallack, M.D.;** Joseph P. Liss, M.D.;† and Bimal Lahiri, M.D., F.C.C.P.*

Two cases of a continuous murmur following an acute pulmonary embolic episode are presented, and eight previously reported cases with an acquired postembolic continuous murmur (found in a review of the literature) are discussed. This finding is common in both chronic and acute pulmonary embolism and is suggestive of significant embolic obstruction. Although the continuous murmur is an unusual sign in patients with pulmonary embolism, its auscultation is often quite distinctive, and its appearance may lead to more definitive diagnostic studies when the presentation or associated clinical findings are nonspecific.

The physical findings in patients with pulmonary thromboembolism without infarction are usually nonspecific in nature and are often not very helpful in establishing the diagnosis. A relatively unusual finding, an acquired continuous murmur, has received some attention in the American literature since 1959.1-3 Interestingly, the cases reported up to this time show the continuous murmur associated with chronic symptoms and often with histories suggestive of recurrent pulmo-

*From the Cardiopulmonary Section, Department of Medicine, St. Francis Hospital, Hartford, Conn.
**Senior Fellow, Section of Pulmonary Diseases.
†Assistant Professor of Medicine, University of Connecticut Health Center, and Chief, Exercise Laboratory.
‡Assistant Professor of Medicine, University of Connecticut Health Center, and Associate Director, Section of Pulmonary Diseases.
Reprint requests: Dr. ZuWallack, Section of Pulmonary Diseases, St. Francis Hospital, Hartford 06105

Figure 1. Phonocardiogram (case 1) showing mid and late systolic (SM) and early diastolic murmur (DM). S1, First heart sound; and S2, second heart sound.

Figure 2. Pulmonary angiogram (case 1) showing saddle embolism in right main pulmonary artery.

nary emboli. We report two cases of acute pulmonary thromboembolic disease with both systolic and early diastolic murmurs.

Case 1

A 20-year-old white woman was admitted to St. Francis Hospital on July 9, 1974 with a two-day history of pain in the left side of the chest and cough. Other than a three-month history of using an oral contraceptive, the remainder of her history was noncontributory. On examination, her respiratory rate was 16/min, her pulse was 76 beats per minute, and her temperature was 38.2°C (100.8°F). There was evidence of a pleural effusion on the left. A grade 2-3/6 midsystolic