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*Review*

# Hyperventilation Syndrome

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**Abstract.** The hyperventilation syndrome, primary alveolar hyperventilation and respiratory alkalosis accompanied by various signs and symptoms, occurs in about 6–11% of the general patient population. The causes of hyperventilation are: 1) organic and physiologic and, 2) psychogenic (emotional/habit). Hyperventilation syndrome excludes hyperventilation that is compensatory or caused by organic or physiologic factors. Acute or chronic anxiety is usually considered the predominant primary causal factor of the hyperventilation syndrome. The symptoms and signs associated with the hyperventilation syndrome are many and varied and present a composite of the symptoms associated with anxiety and the signs and symptoms caused by the actual physiologic derangements. Unfortunately, the signs and symptoms of the hyperventilation syndrome are indistinguishable from those of anxiety (panic attack, anxiety neurosis, etc.). The diagnosis of the hyperventilation syndrome requires a high index of suspicion and a provocation test consisting of voluntary hyperventilation to reproduce the patient's symptoms. The differential diagnosis includes consideration of those organic, pulmonary, neurologic, cardiac, and gastrointestinal diseases, as well as other psychiatric illnesses, that produce similar symptoms. The treatment involves the four areas of psychotherapy, psychotropic drugs, beta-adrenergic blocking drugs, and behavior therapy.

**Key words:** Hyperventilation syndrome.

## Introduction

"Hyperventilation syndrome" is a clinical term that, although learned early in medical school, is probably never forgotten. Despite the wide spread use of the term "hyperventilation syndrome", it does not appear as a specific or official diagnosis in the current diagnostic classifications of diseases [17, 101]. By definition, hyperventilation means that the time rate of movement of air into and out of the lungs is greater than that rate necessary to maintain the blood carbon dioxide

**Table 1.** Incidence of hyperventilation syndrome

| Type of medical practice | Incidence |
|---|---|
| Ambulatory patients with gastrointestinal complaints, 500 consecutive patients [72] | 5.8% |
| New patients referred for cardiac evaluation [117] | 6.0% |
| Female military dependents, 800 new patients seen over 6 months [94] | 6.3% |
| Patients seen in office practice, 1000 consecutive patients [87] | 10.7% |

tension at the normal value [100]. The hyperventilation syndrome is primary hyperventilation producing respiratory alkalosis associated with a highly variable and impressive array of signs and symptoms. Hyperventilation syndrome, in the usual clinical sense, excludes hyperventilation that is compensatory or caused by organic or physiological factors. Although the symptoms of hyperventilation and respiratory alkalosis may be very similar regardless of the etiology, the term hyperventilation syndrome is usually reserved for hyperventilation and respiratory alkalosis caused by emotional and/or habit factors. Hyperpnea, an abnormal increase in the rate and depth of respiration, can occur with exercise or as a compensatory mechanism in metabolic acidosis, especially diabetic ketoacidosis and renal failure. Although the clinical appearance of hyperpnea can be quite impressive, it may not necessarily produce respiratory alkalosis.

## Incidence

The incidence of the hyperventilation syndrome probably varies from 6–11% (Table 1) depending on the patient population [72, 88, 94, 117]. However, Schimmenti [92] has reported an incidence of 27% among the general female population and the symptoms in 40.2% of patients in a general medical outpatient clinic have been largely attributed to the hyperventilation syndrome [67]. Most studies indicate the hyperventilation syndrome is 2–4 times more common in women [34, 64, 92] than in men and that it occurs predominantly in the third and fourth decades of life [34, 94]. However, Lum has reported an equal sex incidence [66]. Although the majority of cases occur in the third to fourth decade of life, hyperventilation syndrome is also important among the younger and older patients. Among 561 patients with the hyperventilation syndrome, approximately 37% were age 50 years or older and 15% were age 60 years or older [66]. At the other end of the age spectrum, the hyperventilation syndrome can also be a significant problem in children and adolescents and the symptoms in these young patients are quite similar to those in adults [21, 46, 49].

## Physiology

Alveolar ventilation per minute ($\dot{V}_A$) is dependent on the tidal volume ($V_T$), dead space per breath ($V_D$), and breathing frequency per minute (f): $\dot{V}_A = (V_T - V_D)f$. An increase in tidal volume or breathing frequency will increase alveolar ventila-

tion. In the absence of significant lung disease, dead space remains relatively constant. Arterial carbon dioxide tension ($P_aCO_2$) and alveolar carbon dioxide tension ($P_ACO_2$) are virtually identical and $P_ACO_2$ is directly proportional to the alveolar $CO_2$ concentration. Hyperventilation, alveolar ventilation in excess of that necessary to maintain the $P_aCO_2$ at the normal value, results in a decrease of the alveolar $CO_2$ concentration, $P_ACO_2$, and $P_aCO_2$ when the carbon dioxide exhaled (produced) per unit time is relatively constant. Primary respiratory alkalosis is a reduction in the physically dissolved fraction of carbon dioxide in the blood and the dissolved $CO_2$ in the arterial blood is directly proportional to the $P_aCO_2$ [19]. A decrease in $P_aCO_2$ can result from primary alveolar hyperventilation. A decrease in $P_aCO_2$ without a change in the bicarbonate ($HCO_3^-$) increases the blood pH producing a primary respiratory alkalosis.

The Bohr effect is the shift in the position of the oxygen dissociation curve by changes in pH, temperature, and $P_aCO_2$. Primary respiratory alkalosis shifts the oxygen dissociation curve to the left and the same oxygen content (or oxygen saturation of hemoglobin) occurs at a lower $P_aO_2$ during alkalosis. In essence, there is a greater affinity of hemoglobin for oxygen and less unloading of oxygen at any given oxygen tension in a tissue capillary.

## Physiologic and Biochemical Consequences

The physiologic consequences of alveolar hyperventilation are real and the symptoms are real. In other words, these symptoms are "not in the patient's mind" but are the direct result of physiologic derangements. These symptoms are then confounded by the symptoms of the anxiety/panic attack. Most of these physiologic changes have been extensively reviewed by Brown [10]. Systemic blood pressure and cardiac output are quite variable but usually either decrease slightly or do not change. There is also a generalized vasoconstriction of the skin blood vessels [10]. Hauge and co-workers have recently described a linear relationship between cerebral blood flow and $P_ACO_2$ [44]. With a decrease in $P_aCO_2$ and respiratory alkalosis, there is vasoconstriction of the cerebral arteries and reduced cerebral blood flow. There is a decrease in cerebral oxygen tension on the basis of both the Bohr effect and the decreased cerebral blood flow [10, 56]. Changes in the electroencephalogram have been reported [91]. Cerebral dysfunction due to diminished cerebral blood flow may be responsible for the dizziness, faintness, visual disturbances, and impaired psychomotor behavior that are commonly described during hyperventilation [4, 66].

The electrocardiogram during hyperventilation will frequently demonstrate abnormalities consisting of inversion of the T-wave and depression of the S-T segment [36, 55, 108, 117]. The specific cause of the electrocardiographic changes is not known but may be related to beta-adrenergic stimulation since propranolol can prevent the T-wave inversions [29].

Tonic rigidity in the muscles of the hands and feet as well as twitching of the facial muscles, pursing of the lips, and tremor and drawing of the fingers occurring with hyperventilation have been noted since the early 1900's [10]. However, it was

not until 1920 that the term tetany was applied to these muscle activities [39]. Although changes in serum calcium have been implicated as a cause of tetany, the fact that hyperventilation tetany is due solely to a reduction in serum calcium ion concentration is debated [10]. As demonstrated in dogs, it may be that hypocalcemia and alkalosis are coparticipants in the development of tetany [18].

One of the most consistent biochemical changes with hyperventilation has been a decrease in the serum inorganic phosphorous [10, 79, 91]. No consistent changes have been noted in serum chloride, potassium, sodium, or magnesium and the calcium (total or ionic) does not change [10, 79, 91, 117]. Although blood lactate increases with hyperventilation [8] and anxiety symptoms can be produced by the infusion of lactate ion [82], the role of the lactate ion in the hyperventilation syndrome is unclear. In animals, a striking increase in brain and cerebrospinal fluid lactate occurs with hyperventilation [83].

## Historical Aspects and Similarities to Other Diagnoses

Although the association of hyperventilation and tetany became established about 1920 [37, 39], the association of various other symptoms with hyperventilation was not noted until several years later. In 1929, White and Hahn [111] described sighing as occurring frequently in young women and "nervous instability" was the commonest condition noted in patients with abnormal sighing. In 1933, Maytum described a neurotic housewife with palpitations, attacks of shortness of breath, and tetany associated with hyperventilation [75]. In 1935, Christie noted that a bizarre spirogram with frequent sighs was indicative of a respiratory neurosis [12]. The term "hyperventilation syndrome" initially appeared in 1937 when the combination of hyperventilation, anxiety symptoms, and physical signs was thoroughly explored [57]. A place in our vocabulary for the term "hyperventilation syndrome" was secured by two subsequent reports [62, 72].

In 1940, Wood [115] discussed Da Costa's syndrome and reviewed the similarities of "the irritable heart of the soldier" (1871), "effort syndrome" (1917), "neurocirculatory asthenia" (1918), and "autonomic imbalance" (1923). Da Costa's syndrome was characterized by a specific group of symptoms which limited the capacity for effort. The main symptoms were breathlessness, palpitations, fatigue, chest pain and dizziness [115]. These symptoms are *indistinguishable* from those of the hyperventilation syndrome or an anxiety disorder. In 1948, Cohen and coworkers discussed nervousness, easy fatigue, shortness of breath, palpitations, spells of faintness, giddiness or apprehension, and poor performance when there was an absence of diagnosable organic disease as the main features of neurocirculatory asthenia (alias effort syndrome or anxiety neurosis) [13]. The authors listed 17 synonyms for this symptom-complex but did not include "hyperventilation syndrome". A review of 173 patients with neurocirculatory asthenia (anxiety neurosis, neurasthenia, effort syndrome) followed for 20 or more years demonstrated similar symptoms [109]. The most common symptoms of anxiety states (anxiety neuroses) are fear, apprehension, palpitations, inattention, dizziness, respiratory distress, sweating, irritability, faintness, chest pains, tremors, fears of death, and a feeling of impending disaster [74, 89]. Including the term hyperventilation syndrome, a list of

41 diagnostic labels synonymous with endogenous anxiety has recently been compiled [93]. Regardless of the label, the symptoms of anxiety, neurocirculatory asthenia, etc., are *indistinguishable* from the symptoms of the hyperventilation syndrome. Therefore, hyperventilation must always be considered as a possible cause for these symptoms.

In psychiatric terminology, Anxiety Disorders is a large group of disorders in which anxiety is either the predominant disturbance or anxiety is experienced if the individual attempts to gain control over the symptoms. Anxiety States (Anxiety Neuroses) is one of three subclassifications of Anxiety Disorders. The hyperventilation syndrome is most congruent with the diagnosis of Panic Disorder, one of three subclassifications of Anxiety States (Anxiety Neuroses) [17]. An essential feature of Panic Disorder is the unpredictable recurrence of panic (anxiety) attacks. The sudden onset of intense apprehension, terror, or fear, often associated with a sense of impending doom, are manifestations of panic attacks. The most common symptoms experienced during a panic attack are dyspnea, palpitations, choking or smothering sensations, chest pain or discomfort, paresthesias, dizziness, vertigo and unsteady feelings, sweating, faintness, feelings of unreality, trembling or shaking, and a fear of dying or loosing control during the attack [17].

## Etiology

The many causes of hyperventilation can be divided into two general categories; 1) organic and physiologic and, 2) psychogenic (emotional/habit). In patients with the hyperventilation syndrome, probably less than 4% have only an organic process as the cause and approximately 65% have only a psychogenic basis as the cause. The remaining patients have various combinations of organic and psychogenic causes [63].

The organic causes of hyperventilation that are sufficient to produce primary respiratory alkalosis include salicylism [90], cirrhosis and hepatic coma [51, 104], encephalitis [43], and the pain and discomfort associated with myocardial infarction, pneumothorax, splenic flexure syndrome, cholecystitis, diabetic neuritis, hiatal hernia, and dissecting aortic aneurysm [3]. Respiratory dyskinesia, a choreatic movement disorder in some patients with degenerative diseases of the basal ganglia, can produce symptomatic hyperventilation and requires differentiation from psychogenic hyperventilation [41]. Patients with pulmonary embolism [38, 70], interstitial lung disease [22], and microscopic tumor emboli to the lungs [50] can present with normal chest roentgenograms and symptomatic hyperventilation, anxiety, and dyspnea. Heat and altitude acclimatization are physiological causes of hyperventilation [31, 61, 114].

When the etiology of the hyperventilation syndrome is psychogenic, acute or chronic anxiety is most often considered the casual factor [80, 77]. In this situation the anxiety is the primary cause of the hyperventilation syndrome. Anxiety, although variously defined [24, 74, 89] is essentially apprehension, tension, or uneasiness that stems from the anticipation of danger, the source of which is unknown [17]. The manifestations of fear and anxiety are the same and include motor tension, autonomic hyperactivity, apprehensive expectation, and vigilence

and scanning [17, 89]. Anxiety is generally distinguished from fear on the basis of lack of a specific object or the source of the anticipated danger is largely unknown. It is important to explore the possibility of a significant event with respect to the very first episode of the hyperventilation syndrome [60]. Not uncommonly the hyperventilation syndrome first occurs in the context of a real or threatened loss (divorce, separation, death), actual physical trauma, or witnessing a particularly frightening event (violent argument, traumatic death, accident). This initial event establishes a set of various internal sensations (feelings, images, sounds, smells) associated with the hyperventilation syndrome. Subsequently, the patient may deny, repress, rationalize, or cover up the actual initial event. However, since the hyperventilation syndrome is anchored to a particular set of internal sensations, any time the internal sensations are accessed, for whatever reason, the hyperventilation syndrome is also accessed.

Although stress (anxiety) will produce some minor degree of hyperventilation in normal subjects, the subjects do not become significantly symptomatic [30, 97]. However, the patients with the hyperventilation syndrome are not "normal" volunteers. In a study of 114 normal subjects and 46 hyperventilation syndrome patients, the normal subjects had a mean $P_ACO_2$ of 40.3 mm Hg compared to 29.1 mm Hg in the hyperventilation syndrome patients during a period of unmanipulated respiration [26]. Compared to normal responses, it is possible to consider the hyperventilation syndrome as part of an exaggerated general stress response pattern or a specific over-responsivity of the respiratory system [30]. Patients with the hyperventilation syndrome seem to over-respond or over-react compared to normal people.

The habit etiology of the hyperventilation syndrome has been largely espoused by Lum who states the primary cause of the hyperventilation syndrome is the bad habit of exaggerated thoracic breathing [66–68]. This bad breathing habit is responsible for the hyperventilation syndrome and the anxiety is a result and not a cause of the hyperventilation syndrome. With the basic bad habit of exaggerated thoracic breathing, any physical or emotional disturbance can initiate an additional increase in ventilation with hypocapnic symptoms precipitating the anxiety. Since Lum feels the major cause is a poor breathing habit, he states that less than 4% of his patients have a primary psychogenic cause of their hyperventilation syndrome [67]. The important fact is that, regardless of the cause of the hyperventilation syndrome, the symptoms of the hyperventilation syndrome result in anxiety and additional hyperventilation and anxiety and the establishment of a vicious cycle.

## Symptoms

The hyperventilation syndrome occurs in an acute (1%) and chronic (99%) form [67, 107]. The acute form of the hyperventilation syndrome is easily recognized because of the dramatic and impressive hyperpnea, tetany, carpopedal spasm, and overt apprehension and anxiety. The chronic form may present with bizarre symptoms referable to any organ system and the breathing pattern may not be grossly abnormal. The chronic form can be easily unappreciated unless it is always considered in the differential diagnosis. Expansion of the concept of the hyper-

**Table 2.** Symptoms of the hyperventilation syndrome

| | |
|---|---|
| General | Cardiovascular |
| Irritability | Palpitations |
| Weakness | Chest pain |
| Exhaustion | Tachycardia |
| Fatigue | Neurologic |
| Respiratory | Headache |
| Sighing and yawning | Faint feeling |
| Shortness of breath | Dizziness |
| Breathlessness | Lightheadedness |
| Air hunger | Numbness and tingling |
| Musculoskeletal | Unsteadiness |
| Arthralgia | Impaired memory/concentration |
| Tremors | Giddiness |
| Myalgia | Visual disturbances |
| Carpopedal spasm | Gastrointestinal |
| Tetany | Belching |
| Psychogenic | Flatulence |
| Apprehension | Dysphagia |
| Anxiety/panic | Dry mouth |
| Nervousness | Bloating |
| Tension | Globus hystericus |
| Sweating | Abdominal distress |
| | Anorexia and/or nausea |

ventilation syndrome beyond the stereotype of the vague and chronically complaining young female is necessary in order to recognize the chronic hyperventilation syndrome in its various and subtle forms [92, 94].

The signs and symptoms (Table 2) associated with the hyperventilation syndrome are many and varied and represent a composite of those signs and symptoms caused by the actual physiologic derangements associated with hyperventilation and the vast array of symptoms associated with the anxiety [20, 63, 66, 67, 77, 88, 94, 107]. Surprisingly, in a group of 250 patients with the hyperventilation syndrome, 52% presented with symptoms referable to the cardiovascular system, 23% referable to the neurological system, and only 6% referable to the respiratory system [64]. However, the frequency of various symptoms and symptom-complexes is highly variable [88, 94, 117]. The major difficulty is that these symptoms are essentially *indistinguishable* from the symptoms that occur in many psychiatric disorders, particularly anxiety disorders, hypochondriasis, hysterical personality disorder, and borderline personality disorder [5, 17, 53, 74, 89].

The chest pain associated with the hyperventilation syndrome is frequently a prominent symptom and must be distinguished from angina pectoris due to coronary artery disease [23]. In 20 patients [117] and 50 patients [94] with the hyperventilation syndrome, chest pain was present in 100% and 42% respectively. In patients with anxiety neuroses, chest pain occurred in 85% of the patients versus 9.8% in a control group [109].

The chest pain can be described as sharp, stabbing, aching, gnawing, burning, tight, shooting, and twisting [23]. Wheatley [108] described three distinct types of

chest pain occurring in the hyperventilation syndrome; 1) sharp, fleeting, periodic, and usually in the hypochondrium or left anterior chest, 2) a persistent, localized, aching discomfort, usually under the left breast, and 3) a diffuse, dull-aching, heavy-pressure sensation over the entire precordium or substernum. Typically there is no constant relationship with exertion and the duration of the pain may vary from minutes to hours. Although most of this pain does not originate in the myocardium, hyperventilation can impair the coronary circulation. Primary respiratory alkalosis can interfere with the myocardial oxygen supply by a combination of coronary artery vasoconstriction and increased oxygen affinity of the blood (Bohr effect) in the coronary capillaries [78]. Additionally, the coronary artery spasm of Prinzmetal's variant form of angina can occur with a decrease in hydrogen ions (hyperventilation) at the cellular level [116].

Dyspnea, a word frequently used as synonymous with breathlessness, is a totally subjective sensation. Dyspnea can be considered difficult, bothersome, or uncomfortable breathing that is perceived as a subjective sensation with the modification of the sensation by the interaction of an individual's genetic content and the sum of life experiences. The symptom of breathlessness occurs in 50–90% of patients with anxiety neurosis or the hyperventilation syndrome [72, 94, 109, 117]. The breathlessness is rarely related to exertion [1]. Sighing, overbreathing, or an increased respiratory rate is often present in patients with the hyperventilation syndrome but is frequently not recognized nor appreciated by the patient [1, 12, 15, 21, 34, 77, 111]. Breathlessness may also occur in depression where it is noticeable during rest with particular difficulty during inspiration [11].

Tetany is actually quite unusual and only rarely do patients present with the classic clinical picture of paresthesias, tachypnea, and tetany [68, 77].

The various symptoms associated with anxiety can also be a manifestation of the abuse or withdrawal from frequently abused substances. The abuse and abrupt discontinuation of various drugs [85], including amitriptyline [32], opiates [35], and imipramine [96] can result in anxiety and panic attacks. Caffeinism (excess caffeine from the abuse of coffee, tea, colas, and over-the-counter and prescription drugs) can cause various symptoms and signs, including persistent anxiety, cardiac palpitations, irritability, agitation, tachypnea, tremulousness, and muscle twitchings that are entirely consistent with the signs and symptoms of the hyperventilation syndrome [40, 69, 87]. Caffeine abstinence and withdrawal can also result in increased anxiety and muscle tension, headache, nervousness, and irritability [40, 100]. Caffeine related anxiety may be sufficient to initiate panic attacks or the hyperventilation syndrome.

A careful and complete history, physical examination, and evaluation is necessary before deciding that a patient's symptoms and signs are due to hyperventilation syndrome caused by psychogenic factors.

## Diagnosis

Diagnosis of the hyperventilation syndrome is relatively easy if the physician maintains a high index of clinical suspicion. Patients with the chronic hyperventilation syndrome may experience recurring acute exacerbations that resemble the acute

**Table 3.** Subtle clues to presence of hyperventilation syndrome

| |
|---|
| Patient commonly young |
| Many vague and unrelated minor complaints |
| Concerns about a life threatening illness |
| Has visited numerous physicians |
| Usually feels "nervous" |
| "Nervousness" common in family |
| Marital and sexual problems |
| Complaints have "baffled" previous physicians |
| Use of various "tranquilizers" or "nerve pills" |
| No relation of symptoms to exertion |
| Occasional sighing or yawning |
| Cold and moist hands |
| Tachycardia, tachypnea, and tremor |

form of the hyperventilation syndrome. There are a variety of subtle clues (Table 3) to the chronic hyperventilation syndrome that include the patient's curious lack of awareness of the overbreathing, the absent correlation of acute exacerbations with physical exertion, and the frequent sighing, heaving, and overbreathing that can be seen while eliciting the history.

It will be obvious to the clinician when an individual is acutely hyperventilating with tachypnea and large tidal volumes. The changes in the arterial $CO_2$ content and tension are greatest during the first 30 to 60 seconds of acute hyperventilation and the $P_aCO_2$ can decrease to half the normal value after less than 30 s of hyperventilation [20, 63]. During the first 20–30 min of voluntary hyperventilation, considerable effort is required to maintain a low alveolar $CO_2$ concentration. However, once hypocapnia has developed, the markedly reduced arterial blood carbon dioxide tension ($P_aCO_2$) can be maintained with very little effort with only an occasional deep breath (sigh) superimposed on the normal spontaneous respiratory rhythm [79, 91]. A single deep expiration and inspiration can reduce the $P_aCO_2$ by 7–16 mm Hg [25]. This is particularly important since the unwary physician may not be able to clinically detect hyperventilation in the patient with chronic hyperventilation, i.e., possibly as many as 99% of the patients with the hyperventilation syndrome [15, 66].

When the hyperventilation syndrome is suspected as a cause of the patient's signs and symptoms, the diagnosis is easily confirmed by observation of the effects of voluntary hyperventilation (the hyperventilation provocation test) [15]. The patient is instructed to breathe deeply and rapidly and, in the majority of instances, a two or three minute period of vigorous hyperventilation is sufficient [95]. Ninety seconds of 20 to 30 deep respirations per minute may even be sufficient to evoke the patient's symptoms [94]. If the patient's symptoms are not reproduced, the voluntary hyperventilation should be discontinued after four–five minutes or when the patient complains of dizziness [73]. Once symptoms are produced, the acute event can be terminated by rebreathing into a bag. The physician can directly observe the effects during hyperventilation and can also question the patient about symptoms after an adequate amount of hyperventilation. With sufficient hyperventilation, everybody will eventually develop various symptoms. The purpose of the

hyperventilation provocation test is to precipitate and reduplicate the symptoms that underlie the reason for consulting a physician. The reproduction and termination of a typical attack can also provoke the disclosure of highly emotionally charged material.

There is essentially no risk of voluntary hyperventilation in the healthy person [15, 113]. It should not be done in patients with pulmonary insufficiency and an elevated arterial carbon dioxide tension since apnea and death can result [6, 113]. Although voluntary hyperventilation has been done without difficulty in patients with cardiac disease [113], it should probably not be performed in patients with Prinzmetal's variant form of angina or in patients with coronary artery disease [78, 116]. In individuals with atypical chest pain, whose pain may be due to myocardial ischemia or represent a hyperventilation syndrome symptom, the hyperventilation provocation test can be done with electrocardiographic monitoring. Since cerebral blood flow is markedly reduced with hyperventilation [106], the hyperventilation test should be omitted in patients with cerebrovascular disease. Hyperventilation can activate petit mal epilepsy and evoke clinical psychomotor seizures [76] and, in patients with sickle cell disease, can cause cerebral thrombosis and cerebellar infarction [2, 84]. Voluntary hyperventilation should be avoided in patients with significant anemia.

Folgering and Colla [26] described a group of tests to diagnose the hyperventilation syndrome that included a $CO_2$ response curve, a hyperventilation provocation test, end-tidal alveolar carbon dioxide tension, blood gas values, and finger blood flow. They concluded that none of the tests were specific for the patients diagnosed clinically as the hyperventilation syndrome.

The use of arterial blood gas analysis for the diagnosis of the hyperventilation syndrome can be confusing. The finding of a decreased $P_aCO_2$ and an elevated arterial pH may only reflect the acute hyperventilation in response to the discomfort and apprehension associated with an arterial needle puncture. A low $P_aCO_2$ with a near normal pH can indicate chronic alveolar hyperventilation and the associated renal compensation that has returned the arterial pH to near normal values. After an episode of voluntary or involuntary hyperventilation, the $P_aO_2$ can be significantly decreased while the $P_aCO_2$ may be decreased or in the low normal range [16, 86]. In an individual with chest pain and dyspnea, this blood gas abnormality could easily be confused with a pulmonary embolus. In patients with relatively normal lungs, the end-tidal carbon dioxide concentration can be monitered at the nose or mouth and used to calculate the $P_ACO_2$ that is essentially the same as $P_aCO_2$ [14]. A persistently low $P_ACO_2$ is consistent with alveolar hyperventilation. An arterial pH would be necessary to exclude metabolic acidosis with compensatory hyperventilation. Regardless of actually demonstrating alveolar hyperventilation, it is important to reduplicate the patient's symptomatology with voluntary hyperventilation to substantiate the diagnosis of the hyperventilation syndrome.

In essence, it is important to always consider the hyperventilation syndrome as a possible cause of symptoms but it is equally important to consider the other organic and physiologic causes of hyperventilation mentioned previously. The differential diagnosis includes consideration of those organic, cardiac, pulmonary, neurologic, and gastrointestinal diseases, as well as other psychiatric illnesses, that produce similar symptoms (Table 4).

**Table 4.** Some diseases, illnesses, or processes simulating the signs and symptoms of hyperventilation syndrome

| Functional | Organic |
|---|---|
| Aerophagia | Angina pectoris |
| Anxiety disorder | Asthma |
| Anxiety neurosis | Caffeinism or drug withdrawal |
| Borderline personality | Cholecystitis |
| Da Costa's syndrome | Cirrhosis and hepatic coma |
| Depression | Encephalitis |
| Effort syndrome | Hiatal hernia |
| Globus hystericus | Hypersensitive xiphoid |
| Hysterical personality | Interstitial lung disease |
| Neurasthenia | Peptic ulcer disease |
| Neurocirculatory asthenia | Pneumothorax |
| Panic disorder | Pulmonary emboli |
| | Splenic flexure syndrome |

## Treatment

Treatment of the hyperventilation syndrome is often stated to be just simply reduplicating the characteristic symptom complex by requesting the patient to voluntarily hyperventilate. In theory, the patient is alarmed by the appearance of the troublesome signs and symptoms and impressed by the rapid relief obtained by breathing into a bag. An emotional catharasis should occur from the patient and, with some additional explanation by the physician, about 70% of the patients are apparently "cured" [63, 64]. It is doubtful that this type of simplistic therapy is really of value. Although reassurance and periodic breath-holding or rebreathing into a bag can terminate the symptoms of an acute hyperventilation episode, it is not adequate therapy [21, 88]. Rebreathing into a bag can seem physiologically rational to the physician but it can seem frightening, absurd, or even claustrophobic to most patients with the hyperventilation syndrome [81]. Explanations to the patient such as "it is all in your mind", "it is nothing to worry about", or "just slow down your breathing" are not therapeutically beneficial. Additionally, treatments with amonium chloride, the inhalation of oxygen-carbon dioxide gas, and an acid-ash diet [88] are no longer appropriate.

The contemporary treatment of the hyperventilation syndrome involves four major areas; 1) psychotherapy, 2) psychotropic drugs, 3) beta-adrenergic blocking drugs, and 4) behavior therapy. None of these four areas of treatment have been proven superior. The physician should maintain sufficient flexibility to change treatment if beneficial results are lacking. Personally, I consider behavior therapy as the area with the least potential.

Psychotherapy includes a variety of techniques including hypnosis, symptom prescription, reframing, and other forms of therapy to decrease anxiety and provide the patient with additional response choices [60]. Hypnotherapy, especially auto-hypnosis, may be an important therapeutic modality in the patient with the hyperventilation syndrome [47, 112]. Symptom prescription, such as having the

patient practice hyperventilation daily until the attacks cease [15], can be helpful. Since the difficulties are frequently sexually related, marital therapy and sex counseling are indicated. The physician may have insufficient time and skill for this therapy and the patient can be referred to an individual with a major interest and training in psychotherapy and psychosomatic medicine.

The use of psychotropic drugs in the treatment of the hyperventilation syndrome (panic disorder) is not well defined. Pharmacologic treatment of panic disorder is usually accomplished with an antidepressant such as the tricyclic imipramine [89, 93]. Once it has been determined that the patient has the hyperventilation syndrome, and other psychiatric and medical conditions have been excluded, consideration of a trial of imipramine is reasonable. Imipramine effectively blocks the recurrence of panic attacks [42, 65]. The initial imipramine dose of 25 mg/d at bedtime can be increased by 25 mg every other night until there is improvement or a dose of 150 mg/d at bedtime is reached. Beneficial effects of the drug appear in 3 to 14 d. Discontinue the imipramine if there is no improvement after 14 d of 150 mg daily or if there are various side effects that include sedation, orthostatic hypotension, dizziness, nausea, vomiting, constipation, and dry mouth. The imipramine can be gradually discontinued when a patient has been without panic attacks for 6–12 months [7, 42, 58, 59, 65]. In six patients suffering from the hyperventilation syndrome, treatment with clomipramine, a tricyclic antidepressant not currently available in the United States, resulted in all six of the patients feeling well 18 months after starting a nine month treatment program [48]. Anxiolytic drugs are often unsuccessful or only temporarily successful in the treatment of panic disorder [89]. Emotional support and sincere concern are also a part of the treatment program that utilizes psychotrophic agents.

Beta-adrenergic blockade has been utilized as therapy for the hyperventilation syndrome [27, 28, 49], panic attacks [42], anxiety [52, 98], and stage fright [9]. This therapy is based on the premise that the symptoms of the hyperventilation syndrome are caused by sympathetic stimulation. Beta-adrenergic blockade with propranolol has been demonstrated to largely block the increase in minute ventilation produced by the intravenous infusion of norepinephrine or isoproteronol [45, 54]. Additionally, hyperventilation induced T-wave inversion on the electrocardiogram can also be blocked with propranolol [29]. The symptomatic improvement with beta-adrenergic blockade therapy in the hyperventilation syndrome is consistent with the finding of increased urine epinephrine levels in patients with the hyperventilation syndrome [27] and increased arterial epinephrine levels after hyperventilation in control subjects [102].

In children (mean age 10.6 years) who continued with the hyperventilation syndrome despite six months of general supportive therapy, 13 of 14 patients treated with 30 mg propranolol daily had all symptoms of the hyperventilation cease during the first week of therapy [49]. Specific $beta_1$-adrenergic blockade with metoprolol has also been found useful in the therapy of the hyperventilation syndrome [27, 28]. Metoprolol is useful therapy to increase alveolar $CO_2$ and ameliorate hypocapnia but seems to have no effect on the subjective complaints [28].

A trail of propranolol, 40–80 mg or more daily [52, 98, 99] for several weeks, can be considered. However, a drug such as propranolol that blocks both $beta_1$ and

$beta_2$-adrenergic receptors should not be used in patients with bronchospastic lung disease [71]. It is preferable to initiate a trial with metoprolol, a cardioselective beta-adrenergic blocking drug, using 200 mg daily [27, 28].

Behavior therapy, including the techniques of systematic desensitization, relaxation, and biofeedback, focuses on changing maladaptive patterns by modifying the conditions that reinforce the pathological behavior. Systematic desensitization can be used effectively in treating patients with the hyperventilation syndrome [105]. When biofeedback is compared to breathing exercises (breathe slowly and not too deeply) for the treatment of the hyperventilation syndrome, both methods raise end tidal $PCO_2$ at the conclusion of therapy and at three months follow-up [103]. However, a larger reduction in complaints occurs at the conclusion of therapy in the biofeedback treated patients but the benefit is not maintained [103].

Lum states that a bad breathing habit consisting of exaggerated thoracic breathing and a basic respiratory pattern of overbreathing is the primary cause of the hyperventilation syndrome [66, 67]. Treatment of the bad breathing habit consists of breathing awareness, relaxation, and breathing training to convert patients to a slow diaphragmatic type of breathing. Lum claims that 75% of the patients are completely free of all symptoms after 12 months of therapy [68]. Others agree with this type of therapy but indicate the therapy is best performed by behavior therapy specialists. It has also been pointed out that there are no published controlled studies and there is little established proof of this particular therapy [33].

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