

# The Pathophysiology of Hyperventilation Disorders\*

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(*CHEST* 1996; 109:516-34)

CSF=cerebrospinal fluid; PaCO<sub>2</sub>=arterial PCO<sub>2</sub>; PAO<sub>2</sub>=alveolar PCO<sub>2</sub>; PETCO<sub>2</sub>=end-tidal PCO<sub>2</sub>; VA=alveolar ventilation; V̇CO<sub>2</sub>=CO<sub>2</sub> production

**H**yperventilation is breathing in excess of metabolic requirements and is associated with reduction in arterial PCO<sub>2</sub> (PaCO<sub>2</sub>), respiratory alkalosis, and a wide range of symptoms. Many psychosomatic syndromes have been described in the past in which hyperventilation has a variable and uncertain role,<sup>1-6</sup> but the term 'hyperventilation syndrome' was first used in 1938 to describe patients with the somatic symptoms of both hypocapnia and anxiety.<sup>7</sup> This theme has been extended by subsequent authors<sup>8-11</sup> and there have been many reviews,<sup>12-18</sup> but nevertheless, there remains uncertainty and lack of consensus about the boundaries and even existence of this syndrome.<sup>19,20</sup>

Most physicians regard hyperventilation as synonymous with anxiety and thus invariably within the province of the psychiatrists, but anxiety may be absent<sup>21,22</sup> or secondary to hyperventilation.<sup>23</sup> Some diagnose it in the presence of the somatic symptoms of hypocapnia either at rest or induced by voluntary overbreathing without assumptions about etiology.<sup>24</sup> Some regard it as a habit disorder<sup>23</sup> or an abnormality of respiratory control.<sup>25</sup> Many refuse to recognize it as a separate entity or regard it as secondary to organic disease.<sup>26</sup> Hyperventilation is rarely discussed in respiratory textbooks, the symptoms of hypocapnia are rarely recognized in clinical practice, and when they are, they are rarely managed with the same clinical and scientific objectivity as other organic and physiologic disturbances.

These uncertainties reflect the complexity of this subject that falls between psychiatry, clinical medicine, and physiology and is not recognized as a mainstream subject by any of these disciplines. In older studies, techniques to measure PaCO<sub>2</sub> and diagnostic methods

for organic causes of hyperventilation were rudimentary and there is a dearth of data based on modern quantitative criteria. Failure to define patient groups makes it difficult to compare studies. There is uncertainty even at a physiologic level in that control mechanisms during stimulated breathing have been extensively studied but there are few studies at rest and in the hypocapnic range.<sup>27</sup>

In the present context, it is relevant to ask whether this topic should be of interest to a chest physician, and indeed, it is rarely featured in respiratory conferences. At a physiologic level, hyperventilation is a pure respiratory disturbance. It is difficult to give reliable figures for incidence and because of the problems outlined above, most published figures should be treated with caution. Yet, physicians in most specialties, especially in respiratory medicine and emergency medicine, frequently see patients in whom hyperventilation contributes at least in part to the symptoms, and they usually find it difficult to formulate positive diagnostic and management strategies. Disproportionate breathlessness is common in respiratory practice and is often regarded as synonymous with hyperventilation.<sup>28</sup>

In seeking a frame of reference for these difficult disorders, it may be too simplistic to seek a single definition of hyperventilation syndrome. The term is now applied in so many different contexts that its usefulness as a single entity must be questioned. It is certainly incorrect to regard hyperventilation as a simple manifestation of anxiety and there is often a complex interaction among organic respiratory, psychiatric, and physiologic disturbances. At the simplest level, hypocapnia is a clinical laboratory finding indicative of a range of disorders and should be treated in the same way as a raised blood urea or a low blood glucose level. However, it is also useful clinically to recognize a range of syndromes or clinical situations in which hyperventilation is of predominant clinical importance. These often overlap with, but are not necessarily synonymous with, syndromes of disproportionate breathlessness.

The physiologic basis and clinical complexities will now be discussed in more detail. There are still many unknown factors. This will be followed by a description of the symptoms of hypocapnia, the individual disorders that can induce hyperventilation, a range of syn-

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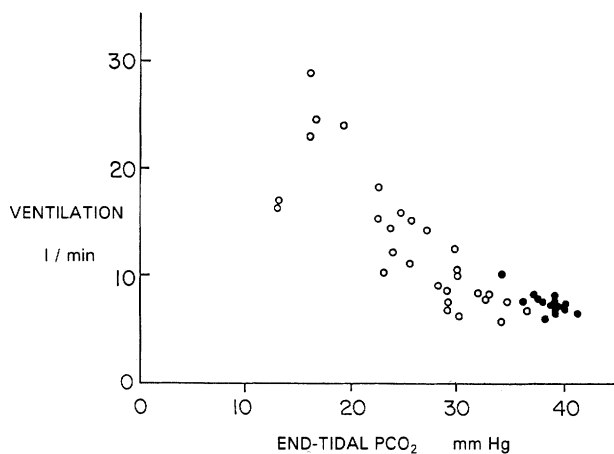


FIGURE 1. Relationship between minute ventilation and  $P_{ET}CO_2$  during resting breathing in 8 normal subjects (closed symbols) and 16 patients with chronic hyperventilation (open symbols, 2 runs per subject). Each symbol is the mean of 40 to 100 breaths (modified from Gardner et al<sup>31</sup>).

dromes in which, in our experience, these factors can combine to induce hyperventilation in clinical practice, and finally a practical scheme for treatment of these patients in a chest clinic.

#### PHYSIOLOGY

Hyperventilation is an abnormality of respiratory control and is defined as breathing in excess of metabolic requirements, *ie*,  $CO_2$  production. In subjects with normal lungs,  $PaCO_2$  is very close to alveolar  $PCO_2$  ( $PACO_2$ ), which in turn can be approximated by end-tidal  $PCO_2$  ( $P_{ET}CO_2$ ). Alveolar ventilation ( $\dot{V}_A$ ),  $CO_2$  production ( $\dot{V}_{CO_2}$ ), and  $PACO_2$  are linked through an equation with the general form of  $\dot{V}_{CO_2} \propto \dot{V}_A * PACO_2 / (P_{barometric} - P_{H_2O})$ , the graphic manifestation of which is the "metabolic hyperbola."<sup>29</sup> An example of this is shown in Figure 1 in which mean minute ventilation is plotted against mean  $P_{ET}CO_2$  for a group of patients with chronic hyperventilation and a matched control group. This relationship is only truly applicable to the steady-state and equivalent relationships have not been derived for the nonsteady-state in which  $CO_2$  production by the tissues may differ from excretion at the lung. This relationship implies that at a constant  $\dot{V}_{CO_2}$  an increase in  $\dot{V}_A$  must be associated with a reciprocal fall of  $PaCO_2$ . Stated another way,  $PaCO_2$  below the normal range (hypocapnia) is invariably associated with a raised  $\dot{V}_A$  and excessive respiratory "drive." Following 15 to 20 min of voluntary hyperventilation to below 20 mm Hg, hypocapnia can be maintained with only an occasional large breath,<sup>30</sup> but even chronic persistent hyperventilation is associated with at least 10% increase in ventilation.<sup>31</sup> It is a fundamental principle in dealing with any hyperventilation-related disorders that the cause or causes of this increased drive should always be sought and documented.

#### $CO_2$ Stores

Hyperventilation washes out  $CO_2$  stores. These are extensive, approximating 120 L. Only about 100 mL of  $CO_2$  is stored in gas pockets, the amount depending on the partial pressure of  $CO_2$  and its physical solution. The remainder is stored in other body compartments but especially in bone, skeletal muscle, and viscera<sup>32</sup> or it is chemically bound as bicarbonate. All tissues have their own  $CO_2$  dissociation curves.  $CO_2$  is easily transferred to and from most body compartments, but bone stores are not easily available.

At the beginning of voluntary hyperventilation, there is a dramatic reduction of  $PACO_2$ .  $CO_2$  elimination at the lungs increases initially but drops within a few minutes and eventually returns to normal as balance is restored between washout from the lungs and tissues.<sup>32-35</sup> There is a 50% change in  $CO_2$  content of the body within 5 min of a change in  $PACO_2$ . There is initially only mobilization of  $CO_2$  from the alveolar gas and blood in the pulmonary veins, left side of the heart, and the first part of the systemic circulation. The peripheral stores are more dependent on the venous  $PCO_2$  and cardiac output. The  $CO_2$  content of blood can be calculated via the  $CO_2$  dissociation curve that is linear between a  $PCO_2$  of 30 and 80 mm Hg, but it is more difficult to estimate changes in other body stores because various organs do not all equilibrate at the same rate.

#### Acid-Base Changes

$PaCO_2$  is linked to arterial hydrogen and bicarbonate ions via the Henderson-Hasselbach equation. After the start of forced breathing, there is a rapid onset of respiratory alkalosis with rise of arterial blood pH, fall of  $H^+$ , and fall of bicarbonate. pH begins to rise within 5 to 20 s, reaches a maximum at 10 to 15 min, and falls to normal within 5 min of the end of forced breathing.<sup>33-35</sup> Arbus et al<sup>36</sup> doubled ventilation in anesthetized patients for up to 90 min. Acid-base adjustments were complete within a few minutes, the relation between  $H^+$  and  $PCO_2$  being described as  $H^+ = 0.74 PCO_2 + 10.4$  with  $H^+$  in nmol/L and  $PaCO_2$  in mm Hg. At a  $PaCO_2$  of 45 mm Hg, significance bands were 40.4 to 46.7 nmol/L for  $H^+$ , 7.39 to 7.33 for pH, 24.2 to 27.9 for  $HCO_3^-$ , and at a  $PaCO_2$  of 15 mm Hg, they were 18.3 to 24.6 nmol/L for  $H^+$ , 7.74 to 7.61 for pH, and 15.3 to 20.5 for  $HCO_3^-$ .

In the brain, and probably in other organs, respiratory alkalosis is associated with greatly increased glycolysis with production of lactic and other acids.<sup>37</sup> Renal compensation is probably unimportant in humans and acid-base adaptation is unlikely to make a major contribution to the maintenance of hypocapnia in patients with chronic hyperventilation. In the study of Arbus et al,<sup>36</sup> mean renal excretion of  $HCO_3^-$  during

both the control and hypocapnic period was less than 1 mEq/h with the conclusion that the contribution of renal  $\text{HCO}_3^-$  loss to the reduction in extracellular  $\text{HCO}_3^-$  stores was negligible, one third of this reduction being the result of buffering by hemoglobin and the remainder buffering by the tissues. Renal excretion was little influenced by a variety of premedications, oxygen mixtures, and anesthetics. In more chronic hyperventilation,<sup>38</sup> hypocapnic-induced suppression of renal acid excretion was independent of plasma  $\text{H}^+$  and  $\text{HCO}_3^-$  and was too small to compensate for the direct alkalemic effect of hypocapnia. This was in contrast to studies in dogs<sup>39</sup> in which renal acid secretion by distal tubular exchange with sodium almost completely corrected the arterial pH when  $\text{PaCO}_2$  was reduced to 15 mm Hg by stepwise reduction of inspired oxygen over 4 to 5 days in an environmental chamber.

The unimportance of renal compensation in humans has been confirmed by studies at high altitude. During 8 days stay at altitude by a group of lowlanders, cerebrospinal fluid (CSF)  $\text{HCO}_3^-$  remained 4 to 5 mEq lower than control values after 1 to 2 days at altitude and renal buffer base excretion reduced blood standard bicarbonate only by 1 mEq/L after 1 week.<sup>40</sup> A similar failure of reversal of respiratory alkalosis has been reported in humans over a 5-day stay at 12,000 feet<sup>41</sup> and over a month at a simulated altitude of up to 22,000 feet.<sup>42</sup> CSF compensation is also incomplete, CSF pH in humans showing only 50% compensation at the end of 26 h of voluntary overbreathing to a  $\text{PaCO}_2$  of 31 mm Hg.<sup>43</sup> More complete compensation of pH occurred in long-term residents at an altitude of 3,900 to 4,500 m.<sup>44</sup>

### *Control of Breathing*

Obvious increase in either rate or depth of respiratory movement is not necessarily associated with hypocapnia. For example, a large tidal volume can be associated with a slow respiratory frequency with no change in  $\dot{V}_A$  or  $\text{PaCO}_2$ . In panting, a low tidal volume may be associated with failure to clear the dead-space<sup>45</sup> leading to  $\text{CO}_2$  retention which maintains  $\text{PaCO}_2$  at normal levels despite a clinically dramatic increase in expired ventilation. Such responses have been documented in a patient with a central neuronal lesion,<sup>46</sup> and we have seen a number of demented patients with rapid shallow respiration but a normal  $\text{PaCO}_2$ .

The chemoreceptors will prevent  $\text{PaCO}_2$  from rising much above the resting value but vagal reflexes are probably inactive in hypocapnia<sup>47</sup> and there appear to be few feedback control mechanisms to prevent  $\text{PaCO}_2$  from falling during hyperventilation. However, there remain many uncertainties about control of breathing in the hypocapnia range.<sup>27</sup> At the lower end

of the ubiquitous ventilation vs  $\text{PETCO}_2$  response curve to inspired  $\text{CO}_2$ ,<sup>48</sup> there is a discontinuity or "dog-leg," suggesting reduction or cessation of chemoreceptor activity.<sup>49,50</sup> In normal quiet unstimulated breathing, ventilation is located just on the dog-leg near the junction of the discontinuity with the steeply sloping part of the curve,<sup>51</sup> consistent with a chemoreceptor threshold just below resting. The peripheral chemoreceptor threshold is probably lower than that for the central chemoreceptors.<sup>52,53</sup>

Apnea usually occurs during passive hyperventilation both in animals<sup>54</sup> and in humans during states of altered consciousness and sleep.<sup>55,56</sup> There is more uncertainty in the awake state in humans with descriptions of apnea,<sup>57-59</sup> hyperpnea,<sup>60-62</sup> and normal breathing<sup>55,63,64</sup> following voluntary overbreathing.

We analyzed apneic pauses of greater than 6 s in normal subjects during various rates of recovery of  $\text{PETCO}_2$  following voluntary overbreathing in mild hyperoxia.<sup>65</sup> Immediately after hyperventilation, there was heightened breathing lasting about a minute consistent with afterdischarge.<sup>66</sup> Apneic pauses then occurred intermittently for up to 10 min until  $\text{PETCO}_2$  rose above a threshold, on average 3.4 mm Hg below resting  $\text{PETCO}_2$ , when normal breathing suddenly resumed. The occurrence and length of the pauses were independent of the rate of recovery of  $\text{PETCO}_2$ . These findings suggest that in awake humans, there is no feedback chemical control from the intracranial chemoreceptors when  $\text{PETCO}_2$  is more than about 4 mm Hg below resting, breathing probably being determined by the respiratory centers modified by "feedforward" drives from the cortex and periphery.<sup>27</sup> Similar conclusions were arrived at by de Backer et al<sup>59</sup> who studied the effect on breathing pattern of venous  $\text{CO}_2$  unloading by hemodialysis, and by Cummin et al<sup>62</sup> who found reduction of ventilatory responses to transient pulses of  $\text{CO}_2$  when  $\text{PETCO}_2$  was low following voluntary hyperventilation in normal humans. We could not confirm previous reports that apneas occurred only in subjects familiar with the equipment used to measure breathing,<sup>58</sup> some of our subjects consistently showing few and others many apneas, suggesting that the tendency to apneic pauses is a characteristic of the subject.

Afterdischarge or "poststimulus potentiation" immediately following voluntary overbreathing has been described following a range of stimuli<sup>66</sup> and after voluntary overbreathing at a constant  $\text{PETCO}_2$ .<sup>61</sup> The role of afterdischarge in perpetuation of hypocapnia in patients with hyperventilation remains uncertain.

### SYMPTOMS

Hyperventilation is unlikely to be a problem to a patient unless it results in symptoms, and the way in which these symptoms are induced may hold the key

to understanding why hyperventilation becomes a major problem for some patients. Painful tingling in the hands and feet, numbness and sweating of the hands, and cerebral symptoms following voluntary hyperventilation were first described by Haldane and Poulton.<sup>67</sup> The first cases of spontaneous hyperventilation with dizziness and tingling leading to tetany were described in 1922 by Goldman<sup>68</sup> in patients with cholecystitis, abdominal distention, and hysteria.<sup>68</sup> Many full descriptions of symptoms have since been published<sup>10,24,69</sup> and form the basis for symptom checklists, such as the Nijmegen questionnaire, which are widely used for diagnosis.<sup>70</sup>

Apart from tetany, symptoms are nonspecific for hyperventilation and cogent evidence has been presented that they should not be used as the only basis for diagnosis.<sup>71</sup> They are often used in conjunction with reproduction of symptoms by voluntary hyperventilation,<sup>9,69</sup> but more recent studies suggest that this too may be unreliable as the only basis for diagnosis.<sup>72</sup> For example, voluntary hyperventilation with severe hypocapnia induced the same symptoms as a psychological test that did not result in reduction of PaCO<sub>2</sub>,<sup>73</sup> and mental stress could reproduce reported complaints in the absence of hypocapnia in patients with atypical chest pain.<sup>74</sup> Voluntary hyperventilation in normal subjects for as long as 1 h has been reported to be associated with relatively few symptoms, suggesting that hypocapnia may not be the only explanation for the symptoms in patients with symptomatic hyperventilation.<sup>30</sup>

Symptoms can be discussed in terms of organs or systems, but it is probably most useful to divide them into those due to increase in neuronal excitability, those due to vasoconstriction, especially in the cerebral, coronary, and skin circulations, and those of uncertain etiology. The PaCO<sub>2</sub> at which symptoms occur has been poorly documented in patients, but in normal subjects, light-headedness and paresthesiae occur at a mean P<sub>ET</sub>CO<sub>2</sub> of 20 mm Hg with an outside range of 14 to 29 mm Hg.<sup>75</sup> This study was not able to confirm previous suggestions that symptoms were more dramatic if PCO<sub>2</sub> fell rapidly, and chest pain was not reported.

### Neuronal Excitability

Macefield and Burke<sup>76</sup> studied the neurophysiologic basis of the increase in neuronal excitability. In normal subjects, paresthesiae developed in the hands, face, and trunk when PaCO<sub>2</sub> declined on average by 20 mm Hg, and spontaneous electromyographic activity occurred when PaCO<sub>2</sub> declined by a further 4 mm Hg. As PaCO<sub>2</sub> fell, the size of the compound sensory and muscle potentials evoked by a constant stimulus progressively increased in advance of the onset of symp-

oms. Microneurographic recordings of afferent activity revealed spontaneous bursting activity of cutaneous axons which was perceived as paresthesiae.

Tetany is often thought to be due to fall in serum calcium level, and Kugelberg<sup>77</sup> noted the similarity of hyperventilation-induced tetany to that induced by hypocalcemia. However, as well reviewed by Ames,<sup>10</sup> no change in any aspect of serum calcium level has ever been documented in response to hyperventilation, but there is a rapid and consistent fall in serum phosphorus level<sup>30,36,78,79</sup> that may be due to an insulin-facilitated shift of phosphorus into cells secondary to increased glycolysis.<sup>80</sup> As argued by Magarian,<sup>13</sup> this provides a more likely explanation for the increase in neuronal excitability.

### Blood Flow

Changes in regional blood flow are implicated in many of the symptoms of hypocapnic alkalosis.

*CNS and Cerebral Blood Flow:* Haldane and Poulton described a "peculiar sense of giddiness and abnormality almost resembling the effects of anoxaemia" following voluntary hyperventilation. Giddiness, paresthesiae, loss of consciousness, visual disturbances, headache, ataxia, tremor, and tinnitus,<sup>81</sup> and more alarming symptoms such as hallucination<sup>82</sup> and unilateral somatic symptoms on the left more than the right have been described.<sup>83-85</sup> These are often misdiagnosed as epilepsy, transient ischemic attacks, demyelination, or migraine.<sup>84</sup>

These symptoms probably arise from reduction in cerebral blood flow, described in many studies.<sup>86</sup> This reduction is probably due to change of pH rather than PCO<sub>2</sub><sup>87</sup> and is associated with significant cerebral hypoxia.<sup>88,89</sup> Cerebral blood flow is linearly related to PaCO<sub>2</sub><sup>90</sup> with a 2% decline for each 1 mm Hg decline in PaCO<sub>2</sub>,<sup>91</sup> leveling off below about 22 mm Hg. Flow returns to 90% of normal after 4 h of hyperventilation, with rebound increase after return to normocapnia.<sup>87</sup> The EEG is slowed in one study when jugular venous PO<sub>2</sub> fell to 21 mm Hg.<sup>92</sup> This was more marked in young subjects and was 73% due to reduction in cerebral blood flow and 27% due to the Bohr effect that increased the binding of oxygen to hemoglobin in the presence of alkalosis. It was not prevented by breathing 100% oxygen and was associated with increase in jugular venous potassium level. Anxiety does not cause reduction in cerebral blood flow in the absence of hyperventilation.<sup>89</sup>

*Peripheral Blood Flow and Cardiac Output:* Acute voluntary hyperventilation is associated with reduction in peripheral resistance and mean arterial blood pressure with an increase in heart rate and cardiac output.<sup>93-96</sup> These responses decline after a number of minutes. Hypocapnia and tidal volume have indepen-

dent effects on cardiac output,<sup>97</sup> isocapnic hyperventilation being associated with a smaller increase in cardiac output while hypercapnic hyperpnea is associated with no change initially, but a later increase.<sup>94</sup> In dogs, mechanical hyperventilation induced reduction of cardiac output that was dependent on fluid load.<sup>98</sup>

In skin, most studies show vasoconstriction,<sup>95,99,100</sup> probably leading to the common complaints of cold extremities. In muscle, there is a biphasic response, vasoconstriction due to a direct effect on blood vessels following an initial period of histamine-induced vasodilatation.<sup>95</sup>

*Coronary Blood Flow and Chest Pain:* Coronary blood flow was found to be linearly related to PaCO<sub>2</sub> in dogs, probably due to a direct effect on the coronary vessels as no correlation was found between PaCO<sub>2</sub> and any index of mechanical activity of the heart.<sup>101</sup> This has been confirmed for man in the absence of chest pain, hypocapnia being associated with evidence of myocardial hypoxia but with no change in myocardial oxygen consumption.<sup>102,103</sup> There is probably less effect on pulmonary blood flow.<sup>104</sup>

Hyperventilation is probably an important cause of atypical chest pain<sup>105-109</sup> but the mechanisms are uncertain and not all studies have shown an association.<sup>74</sup> This symptom is particularly important as patients often misattribute such pain to cardiac disease with induction of a vicious circle of increasing anxiety, panic, and further hyperventilation. This subject has been well reviewed by Chambers and Bass.<sup>109</sup>

The pain can take a number of different forms, being either sharp and fleeting with increase in intensity by deep breathing and twisting, a persistent dull ache associated with chest wall tenderness, or a diffuse dull continuous ache not related to chest movement.<sup>110</sup> Overinterpretation of normal somatic sensations,<sup>109</sup> spasm of the chest wall muscles,<sup>105</sup> esophageal reflux and spasm,<sup>111</sup> progressive inspiratory movement of the diaphragm, and air swallowing causing distention of the stomach and thus diaphragm have been suggested, but the latter could not be confirmed in one study.<sup>112</sup>

Hyperventilation may mimic coronary disease by producing ST segment depression<sup>113</sup> and chest pain that may be reproducibly precipitated by exertion.<sup>114,115</sup> In a recent study,<sup>116</sup> we found that 39% of 44 patients with chest pain but without significant ST depression on treadmill exercise had their usual chest pain reproduced during or after 3 min of voluntary hyperventilation at rest. These patients had not only significantly more hyperventilation-related symptoms and respiratory complaints but also shorter breath-holding times, lower mean resting PETCO<sub>2</sub>, higher mean respiratory rates, and higher phobic avoidance scores for agoraphobia than both subjects with normal test results and normal control subjects. PETCO<sub>2</sub> should be routinely measured during treadmill exercise ECG to exclude

false-positive results due to hypocapnia.<sup>115</sup>

Coronary spasm is rare in normal subjects,<sup>117</sup> but hypocapnia can cause total coronary obstruction with associated chest pain and either ST elevation or depression as demonstrated angiographically in patients with preexisting angina.<sup>118-120</sup> Spasm was prevented by a calcium antagonist in these studies. Although coronary arteries narrow in normal subjects in response to hypocapnia,<sup>102</sup> there is little evidence that this narrowing can cause chest pain in the absence of coronary artery disease. Esophageal spasm and reflux is another cause of atypical chest pain and may be linked to coronary artery spasm, hyperventilation, and ECG changes.<sup>111</sup>

Hypocapnia can also induce cardiac arrhythmias, including ventricular fibrillation in animals<sup>121</sup> and atrial arrhythmias in humans,<sup>122</sup> but personal experience suggests that such arrhythmias are very rare unless there is preexisting coronary disease when voluntary hyperventilation should be avoided.

### *Other Systems*

Symptoms can arise from most other systems. In the GI system, epigastric pain, a bloated feeling, and vomiting have been described,<sup>123</sup> but it is uncertain whether these symptoms are due to hypocapnia or to anxiety and misattribution.

### *Breathlessness*

Breathlessness and hyperventilation, especially if chronic, are not necessarily synonymous and one can be present without the other. Hyperventilation due to respiratory disorders is almost invariably associated with breathlessness, but additional psychogenic factors can induce disproportionate breathlessness.<sup>28,124</sup> There are poor criteria for distinguishing psychogenic from organic breathlessness, but "air hunger," described by the patient as difficulty breathing in rather than out or difficulty taking a satisfying breath, may be an important discriminator (see below).<sup>125</sup> Studies of breathlessness are impeded by uncertainty about the basic mechanisms.<sup>126</sup>

### SIGNS

Signs are often unhelpful in detection of hyperventilation. While increase in chest wall movement and rate may be obvious in acute hyperventilation, in chronic hyperventilation this may not be so and resting PETCO<sub>2</sub> can be halved with only about a 10% increase in minute ventilation as shown in Figure 1 for patients with chronic hyperventilation.<sup>31</sup> Patients with hyperventilation often sigh repeatedly (see below), but even in acute hyperventilation as discussed above, dramatic sighing or panting may not necessarily be associated with reduction of PaCO<sub>2</sub>.

*Measurement of PCO<sub>2</sub>*

The gold standard for diagnosis of hyperventilation and respiratory alkalosis is measurement of arterial PCO<sub>2</sub> and blood gas parameters. However, arterial puncture is invasive, may itself induce anxiety and hyperventilation, and will fail to diagnose patients with variable or transient hyperventilation. Alternative measures are less satisfactory.

*End-Tidal PCO<sub>2</sub>:* PETCO<sub>2</sub><sup>127,128</sup> can be measured by capnograph or mass spectrometer from a small sample extracted continuously from a manifold through which the subject breathes to and fro, or by taping a fine catheter a few millimeters inside the entrance of a nostril.<sup>22,128,129</sup> PETCO<sub>2</sub> is equivalent to PaCO<sub>2</sub>. It is equivalent to PaCO<sub>2</sub> in subjects at rest and with normal lungs, but this may not be the case for exercise<sup>130</sup> and in patients with lung disease. Care is required to ensure that a valid end-tidal plateau is obtained and that the analyzer has a sufficiently fast response time.<sup>128,129</sup> Nevertheless, end-tidal measurements will show large changes of PaCO<sub>2</sub> and have the advantage that they can be performed over long periods of time and via a long catheter while the subject is moving about and performing a variety of activities.

A fundamental difficulty with measurement of PaCO<sub>2</sub> is uncertainty about the lower limit of the normal range. Measurements in conscious humans are confounded by cortical influences and additional respiratory stimulation induced by the measuring apparatus.<sup>131</sup> Cortical influences can be reduced by careful control of the laboratory environment,<sup>132</sup> but it is difficult to control for cognitive factors. In our laboratory, we found that mean resting PETCO<sub>2</sub> measured from a nasal catheter in a group of normal subjects was 36.4 mm Hg and 2 SDs below this was 32.2 mm Hg.<sup>31</sup> This value is close to the upper limit for hypocapnic symptom production of 29 mm Hg in normal subjects.<sup>75</sup> Based on these studies, we take 30 mm Hg as a rough lower limit below which we might expect the patient to report symptoms in clinical practice. We suggest, however, that the normal range for this highly labile variable should be determined for each laboratory.

*Transcutaneous PCO<sub>2</sub>:* Recently, transcutaneous PCO<sub>2</sub> measured via a skin electrode and recorded onto an ambulatory system has been used to measure PCO<sub>2</sub> changes over a number of hours under home conditions.<sup>133-135</sup> This system has proved to be useful in determining the association between hyperventilation and panic disorder<sup>135</sup> but has disadvantages. The time constant of response of the electrode to a step change of arterial PCO<sub>2</sub> is minutes, making interpretation of changes difficult, the skin heating necessary to "arterialize" the skin can be tolerated only for a few hours, and the calibration is subject to drift.<sup>133</sup> Future tech-

nical advances may make this technique more useful for routine monitoring.

*Measurement of PCO<sub>2</sub> During Provocation:* Hyperventilation can be induced in many patients by stressors that, in the laboratory, mimic factors that may induce hyperventilation in everyday life. The most widely studied stressor is voluntary overbreathing. This can reproduce symptoms that the patient recognizes and can also be associated with an abnormally slow recovery of PaCO<sub>2</sub> following the cessation of overbreathing, both of which are claimed to be diagnostic of hyperventilation syndrome.<sup>12</sup> In that voluntary overbreathing may mimic everyday activities such as talking, this can be useful for diagnosis, but the exact mechanism and significance of this response remains to be elucidated. In a group of patients with chronic hyperventilation (Fig 2), we reported an apparently distinct subgroup of patients with chronic conditions who were only mildly hypocapnic at rest but who were precipitated into prolonged hyperventilation by either exercise or voluntary overbreathing.<sup>22,31</sup> Patients with no detectable organic or psychiatric disorders who selectively hyperventilate during or immediately after exercise are commonly encountered in practice as described below.

*Hyperventilation Screen:* These studies have provided us with the basis for a test that we perform in selected patients as part of lung function testing. PETCO<sub>2</sub> is measured by capnograph or mass spectrometer via a fine nasal catheter for 5 to 10 min at rest, during and after up to 10 min of exercise at a level appropriate for the patient, and during and after up to 3 min of voluntary overbreathing. We regard PCO<sub>2</sub> over 30 mm Hg at rest, during, and after exercise and at 10 min after overbreathing as normal. This procedure is not diagnostic in isolation but is an aid to clinical assessment. A positive test result suggests either that the patient is overbreathing at rest or responds excessively to provocations and thus may do so at other times. A negative test result is a more powerful indication that the patient is unlikely to be precipitated into hyperventilation by relevant triggers but does not exclude hyperventilation at other times. This test examines only two very limited provocations. Emotionally relevant imagery has been used successfully in some laboratories,<sup>136,137</sup> but it is uncertain whether most operators would have the skill to apply such tests reproducibly.

*Breath-Hold Time*

Breath-hold time is used by many as an indication of a tendency to hyperventilation. However, this is very dependent on the skill of the operator in persuading the patient to continue to the limit, and the normal range of breath-hold times is wide, being dependent on the precise end point, the lung volume at which

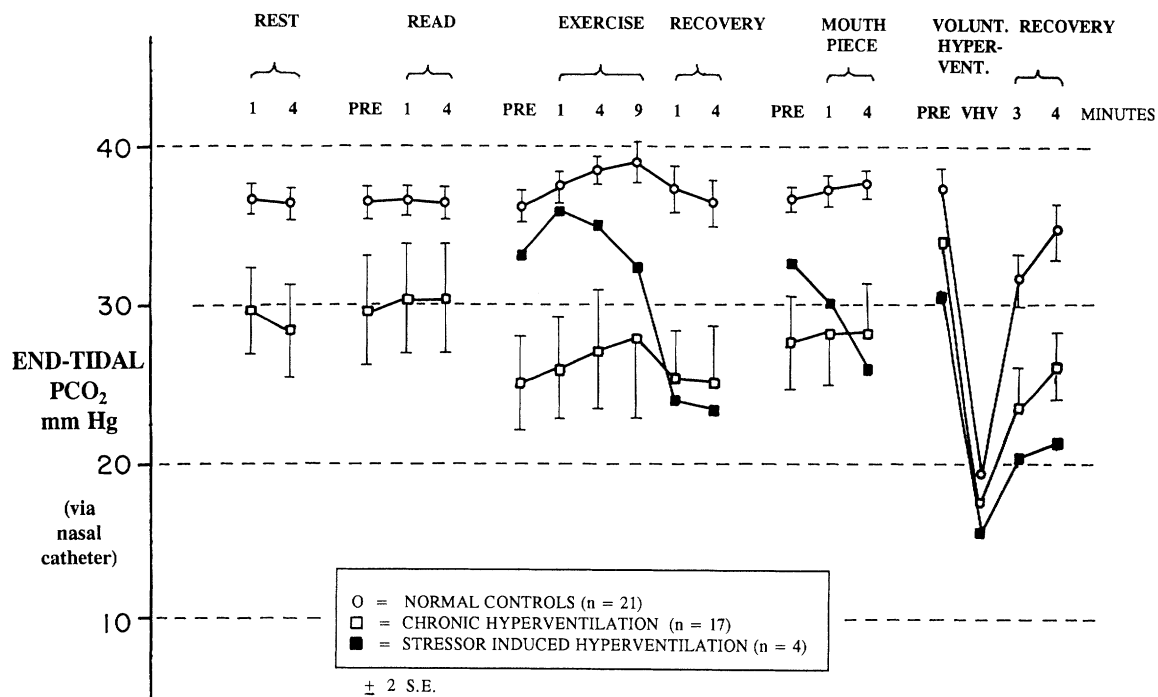


FIGURE 2. Comparison of mean PETCO<sub>2</sub> before (PRE), during, and after various stressors in normal subjects (open circles), patients with chronic hyperventilation (open squares), and patients with hyperventilation induced by either exercise or voluntary hyperventilation (VHV) (closed squares). Bars=2 SE (modified from Gardner et al<sup>31</sup>).

breath-holding is undertaken, whether the glottis is open or closed, and the psychological characteristics of the subject.<sup>138-140</sup> Moreover, patients with breathlessness without hyperventilation may have equal difficulty in breath-holding.

#### Blood Electrolytes

Other changes in plasma constituents are less useful for diagnosis. Serum sodium level falls slightly, both in the arterial and in the jugular venous blood.<sup>36,92</sup> Hyperventilation has been reported to cause both hypokalemia<sup>36,141</sup> and hyperkalemia.<sup>92,142</sup> These variable responses of plasma K<sup>+</sup> may reflect different experimental techniques and differences in the anionic composition of plasma, in plasma osmolality, and in the level of adrenal and pancreatic hormones.<sup>143</sup> During prolonged hypocapnia, there is transient early increase in renal potassium excretion with return to control levels by 24 h despite sustained arterial hypokalemia, suggesting decrease in the set point for renal regulation of plasma K<sup>+</sup>, possibly involving shift of K<sup>+</sup> from the extracellular to the intracellular space.<sup>38,143</sup>

#### ETIOLOGY

Factors that can induce hyperventilation will be discussed individually, although such a division is artificial and a number of factors often combine to induce symptomatic hypocapnia. These factors are shown in Figure 3 and can be classified as psychogenic, organic,

and physiologic. It is useful to distinguish those that can initiate hyperventilation from those that sustain it.

#### Psychogenic

**Anxiety:** Although anxiety was a key component in the original description of hyperventilation syndrome and is usually thought by general physicians to be the main etiologic factor, the relationship of hyperventilation and anxiety is not simple. A clinical association with stress does not necessarily imply an etiologic association or the absence of organic etiologic factors. Chronic hyperventilation is often not associated with formal psychiatric morbidity apart from a mild phobic state in some subjects<sup>21,22,31</sup> and anxiety may be secondary to hyperventilation rather than a primary initiating factor.<sup>15</sup> The reporting of psychogenic abnormalities depends on the referral source, patients from general medical clinics being less likely to report psychiatric symptoms than those already in the psychiatric environment.<sup>144</sup>

Anxiety, suppressed anger, and guilt can be associated with both mild hyperventilation and abnormalities of breathing pattern.<sup>125,145-147</sup> Tobin et al,<sup>147</sup> using a respiratory inductive plethysmograph, reported clusters of both shallow and slow deep breathing with increased sigh rate in anxious patients, but hyperventilation was rare. These abnormal patterns were masked by breathing on a mouthpiece. A higher respiratory rate, smaller tidal volume, and shorter breath-hold

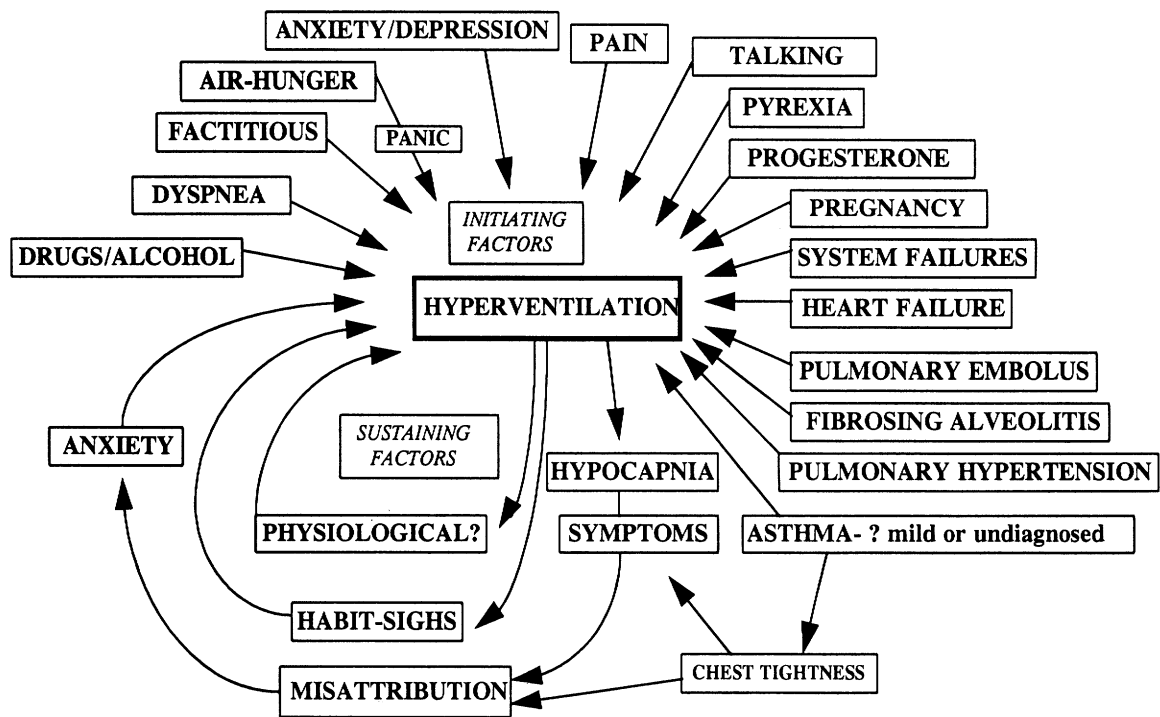


FIGURE 3. The interaction of factors initiating (top and right) and sustaining (bottom left) hyperventilation. A possible model for acute/subacute hyperventilation.

times have been reported in anxious patients with somatic symptoms,<sup>6</sup> and larger changes of heart and respiratory rates and in  $PCO_2$  have been reported in normal subjects subjected to the stress of an anticipated electric shock.<sup>148</sup> Such changes were not found in normal subjects waiting for an examination in whom there were only very small changes of heart rate and  $PACO_2$ .<sup>149</sup> Endogenous nonretarded depression is associated with hyperventilation<sup>150</sup> and phobic patients have a high prevalence of breathing difficulties.<sup>151,152</sup>

The predisposition to overbreathe in response to stress may be dependent on biologic vulnerability, personality, and cognitive variables,<sup>144</sup> as well as individual interpretation of the hyperventilation-induced somatic symptoms that may actually be pleasurable in some subjects.<sup>153</sup> Anxious patients who hyperventilate may be more prone to develop future conditioned anxiety responses.<sup>144</sup> Hyperventilation may induce, as well as be induced by, anxiety.

**Panic:** Recent research has focused on the issue of panic disorder. Panic disorder consists of a broad range of symptoms, including dyspnea, extreme fear, tachycardia, and palpitations and may take a number of different forms, some of which can be reproduced only in a laboratory by the inhalation of high concentrations of  $CO_2$  or by the infusion of lactate.<sup>154</sup> The mechanisms of panic are uncertain. The large number of pharmacologic and physiologic factors, including both  $CO_2$  inhalation and hyperventilation that can induce panic in the laboratory,<sup>155,156</sup> suggests that it may be

due to the cognitive misinterpretation (or misattribution) of somatic symptoms to a life-threatening illness such as a myocardial infarction or a stroke,<sup>156,157</sup> but it can also occur during sleep and when misattribution is unlikely.<sup>155,158</sup> Klein<sup>159</sup> proposes that physiologic misinterpretation by a suffocation monitor misfires an evolved suffocation alarm system,<sup>159</sup> but the neurophysiologic basis for this is unclear. Organic disease may present with panic and hyperventilation, and there is a report in the literature of pulmonary hypertension presenting in this way in association with depression and suicidal ideation.<sup>160</sup>

There is a complex relationship among anxiety, hyperventilation, and panic, well reviewed by Bass et al.<sup>144</sup> The association of panic with hyperventilation is controversial but it appears that there are certain circumstances under which both hyperventilation can induce panic and panic can cause hyperventilation.<sup>135,144</sup> The role of misattribution in the etiology of hyperventilation in the absence of panic is also uncertain,<sup>144,159</sup> but this was a constant feature of many of the original descriptions of hyperventilation syndrome. For example, in a carefully documented description of the clinical features of patients with spontaneous hyperventilation, Ames<sup>10</sup> described misattribution by both patient and attending physicians to epilepsy, hypoglycemia, thyrotoxicosis, peripheral vascular disease, poliomyelitis, and organic cardiac disease. Such misdiagnoses are still being made<sup>160,161</sup> and can lead to a vicious circle of increasing anxiety and hyperventilation



(see below).

**Sighing and Air Hunger:** Sighing is a common finding in these patients and, when excessive, should probably be classified as a psychogenic symptom. The rate of sighing in normal subjects varies from 9 to 10/h<sup>162</sup> to 4/min.<sup>147</sup> Tobin et al,<sup>147</sup> using a respiratory inductive plethysmograph, found an increased rate of up to 25 sighs per minute in anxious patients. Increased numbers of sighs have been reported in patients with hyperventilation,<sup>163</sup> associated with either air hunger<sup>125</sup> or habit. Air hunger or a sensation of inability to take a satisfying breath was a common feature of many of the older descriptions of hyperventilation syndrome.<sup>10</sup> In normal subjects after 15 min of sustained hyperventilation, hypocapnia can be maintained with only an occasional large breath<sup>30</sup> and this may be one of the causes of continuation of overbreathing in patients with chronic hyperventilation in whom air hunger is common.<sup>31</sup>

The mechanism of air hunger is uncertain but it is probably an isolated neurotic symptom. In our experience, some cases may be initiated by very mild undiagnosed asthma. It is of interest that raised PaCO<sub>2</sub> is capable of inducing a sensation of air hunger in the absence of chest wall movement,<sup>164</sup> but it is not known if a change of PaCO<sub>2</sub> can be similarly sensed in hypocapnic range. Even in the absence of air hunger, in our experience, it is very common for a patient, when faced with any unexplained symptoms, to take large breaths in order to "get more oxygen in" and Lum<sup>23</sup> has described habit as a major etiologic factor in his patients with chronic hyperventilation.

Our view about the interaction of panic, hyperventilation, and air hunger is that air hunger is the primary initiating factor. We have seen many patients in whom this is reported as an isolated symptom associated with varying degrees of panic that the patient can usually control without assistance. Only in extreme cases does the panic in turn lead to clinically significant hyperventilation, but the tendency to take large breaths to counter the air hunger often induces a background of chronic hypocapnia that makes induction of hypocapnic symptoms with a vicious circle of increasing panic and hyperventilation more likely.

**Factitious:** Factitious hyperventilation leads to bizarre clinical syndromes that often require considerable time to investigate. Covert observation of the patient can be helpful as can prolonged and overnight recording of PETCO<sub>2</sub>.

### Organic

There is a multifactorial etiology in most cases in which hyperventilation contributes to the presenting symptoms, and attempts to attribute hyperventilation to a single cause are probably unrealistic.<sup>9</sup> Many respiratory and other organic disorders are associated with

documented hyperventilation. An exhaustive list will not be attempted herein, but the conditions of relevance to a chest physician will be emphasized.

**Respiratory Disease:** The best known example is asthma in which PaCO<sub>2</sub> can fall below 25 mm Hg in association with only mild or moderate reduction of FEV<sub>1</sub>.<sup>26,165,166</sup> The mechanism is uncertain. In acute asthma, ventilation and respiratory rate are increased more than can be induced by methacholine challenge in the laboratory.<sup>167</sup> Inspiratory muscle activity is increased, not all related to either increased chemical drive<sup>168</sup> or to bronchoconstriction as the increased drive in moderately severe asthma is not reversed immediately by metaproterenol.<sup>169</sup> In patients with mild asthma, antigen challenge produces significant reduction of PETCO<sub>2</sub> during the early response but in the delayed response with comparable reduction of FEV<sub>1</sub>, there was only small and variable reduction of PETCO<sub>2</sub> that was not reversed by salbutamol.<sup>170</sup> Stimulation of vagal afferents may be at least partly involved as histamine and antigen challenge in dogs stimulates breathing via vagal afferent pathways rather than via bronchoconstriction *per se*.<sup>171,172</sup> The reduction of PaCO<sub>2</sub> in asthma is quantitatively consistent with the response expected from hypoxic stimulation of the peripheral chemoreceptors,<sup>173</sup> but supplemental oxygen does not necessarily restore ventilation to normal.<sup>166,167</sup> Hyperinflation may be a prerequisite for hyperventilation in asthma and is associated with tonic inspiratory electromyographic activity during expiration.<sup>174</sup>

In practice, we believe that asthma, especially if mild, previously undiagnosed and atypical in presentation can contribute to symptomatic hyperventilation or be the sole etiologic factor in a significant proportion of patients.<sup>175</sup> In our clinical experience, patients in whom asthma has not been diagnosed previously suffer from intermittent dyspnea and chest tightness that is often misinterpreted as a heart attack or other catastrophic abnormality, rapidly leading to a vicious circle of increasing anxiety, panic, and hyperventilation with all of its associated symptoms (Fig 3).

In these patients, results of standard lung function tests are often normal or are difficult to interpret due to anxiety, panic, or dyspnea. Often, a month of treatment with high-dose inhaled steroids and bronchodilators is required as a clinical trial. Wheeze in these patients can also be due to bronchoconstriction induced by hyperventilation<sup>176,177</sup> probably due to increased inhalation of cold air.<sup>178</sup> This can further confuse the interpretation of lung function and bronchial provocation tests.

There is also documented evidence of hypocapnia in patients with chronic bronchitis,<sup>179</sup> emphysema, fibrosing alveolitis, and pneumonia.<sup>166</sup> In patients with interstitial lung disease, PaCO<sub>2</sub> has been reported as raised,<sup>180</sup> normal,<sup>181,182</sup> or reduced with a range from

30 to 40 mm Hg associated with no change in CO<sub>2</sub> production.<sup>183</sup> Both increase in tidal volume with decrease in frequency<sup>184</sup> and rapid shallow breathing<sup>180</sup> increasing with severity of disease<sup>183</sup> have been described, the latter response mimicking elastic loading, suggesting involvement of mechanoreceptors. In one report, awake abnormalities were not carried over in sleep,<sup>180</sup> but others have reported hypocapnia during sleep as being diagnostic of an organic etiology.<sup>185</sup> In asthma, the most profound hyperventilation occurs with relatively mild disease<sup>165,175</sup> and the same may apply to early interstitial lung disease but data are lacking. Tachypnea occurs in patients with pneumonia<sup>166</sup> and in animal models was found to be dependent both on intact vagal afferent fibers<sup>186</sup> and other factors, possibly chest wall afferents.<sup>187</sup> Hypoxic chemoreceptor drive may also contribute to respiratory drive in these patients.<sup>182</sup> Heart failure can cause hyperventilation, but CO<sub>2</sub> retention is also common.<sup>188</sup>

Pulmonary embolus is a potent cause of hyperventilation and hypocapnia, and is usually associated with hypoxia.<sup>189</sup> A ventilation perfusion scan will not only exclude pulmonary embolic disease, but a normal scan allows more confident exclusion of other lung disorders. Pulmonary hypertension can present with dyspnea, hyperventilation, depression, and panic disorder.<sup>160</sup>

*CNS Disorders:* Lee et al<sup>190</sup> documented tachypnea or Cheyne-Stokes breathing associated with hypocapnia in patients with acute bilateral pontine infarctions, but hypoxia may have contributed to respiratory stimulation. Hyperventilation has been reported as the first sign of an extensive pontine tumor<sup>191</sup> and in association with an astrocytoma of the medulla, pons, and midbrain.<sup>192</sup> The hyperventilation in these cases continued during sleep and was resistant to most treatment strategies but responded partially to morphine.<sup>192</sup> Plum and Leigh<sup>193</sup> have more recently argued that primary neurogenic hyperventilation is extremely rare, if it exists at all. They document the requirements for such a diagnosis as including a low PaCO<sub>2</sub>, high PaO<sub>2</sub> with commensurably elevated arterial blood pH, a high CSF pH with absence of cells, persistence of respiratory changes during sleep, and exclusion of metabolic causes such as salicylate overdose. They argue that in most cases in the literature, hyperventilation with an apparent central origin has resulted from irritants in the CSF or associated pulmonary congestion with stimulation of C-fibers.

*Pain and Other Organic Disorders:* Hyperventilation is induced by pain,<sup>194</sup> probably due to stimulation of group 3 and 4 afferents nerve fibers.<sup>195</sup> This may explain the association between hyperventilation and chest pain, and yet patients with chest pain due to coronary artery disease had a surprising absence of hyperventilation when genuine angina was induced by

exercise testing.<sup>115</sup> Chest pain is rare in normal subjects during voluntary overbreathing.<sup>75</sup> Hyperventilation is associated with pain of abdominal origin, and indeed, the first description of spontaneous hyperventilation was in patients with cholecystitis and gastric abnormalities.<sup>68</sup> Hyperventilation is also used in anesthesia to increase the pain threshold.<sup>196</sup>

The association of hyperventilation with mitral valve prolapse, well reviewed by Tavel,<sup>17</sup> remains to be proved. Hyperventilation can be a predominant symptom in overdose of drugs such as aspirin,<sup>197</sup> major system failures,<sup>198</sup> and may contribute to habituation to alcohol. The symptoms of hypocapnia can mimic those of both diabetic ketoacidosis<sup>161</sup> and hypoglycemia.<sup>199</sup> These conditions have all been missed in emergency departments in patients too readily labeled as having hyperventilation syndrome. It is commonly assumed that thyrotoxicosis is associated with hyperventilation. Although these patients complain of dyspnea due to respiratory muscle weakness<sup>200</sup> and the slope of the CO<sub>2</sub> response curve is increased,<sup>201</sup> there is little evidence for hypocapnia in the literature.

### *Physiologic*

There are a variety of physiologic conditions that can induce hyperventilation. While these alone rarely cause symptomatic hypocapnia, they often combine with other factors to reduce PaCO<sub>2</sub> below the average level of 20 mm Hg at which symptoms occur.<sup>75</sup>

The most important is the effect of progesterone in women that reduces PaCO<sub>2</sub> by up to 8 mm Hg in the second half of the menstrual cycle and even lower in pregnancy.<sup>202</sup> Progesterone combines with estrogen to increase ventilation by an action both centrally and on the carotid body.<sup>203</sup> This makes women more vulnerable to symptomatic hyperventilation premenstrually and probably explains the higher incidence of these disorders in women.

Hyperventilation is induced by speech<sup>204</sup> and in our experience, acute attacks are sometimes precipitated following prolonged conversations. Bunn and Mead<sup>204</sup> studied seven subjects reading aloud. In six subjects, there was a 6 to 21% increase in minute ventilation from spontaneous levels due to increase in flow during phonation and quick nonphonated expirations, usually at the end of a phrase. The lowest PETCO<sub>2</sub> recorded was 29 mm Hg and this was followed by apnea lasting up to 18 s immediately after reading.

Hyperventilation and respiratory alkalosis due to hypoxic stimulation of the peripheral chemoreceptors is a well-known adaptation to altitude,<sup>40</sup> but there is no information (to our knowledge) about the incidence of symptomatic hyperventilation at altitude. Pyrexia can stimulate breathing due to a direct effect on the carotid bodies.<sup>205</sup>

It is uncertain whether abnormalities of control of

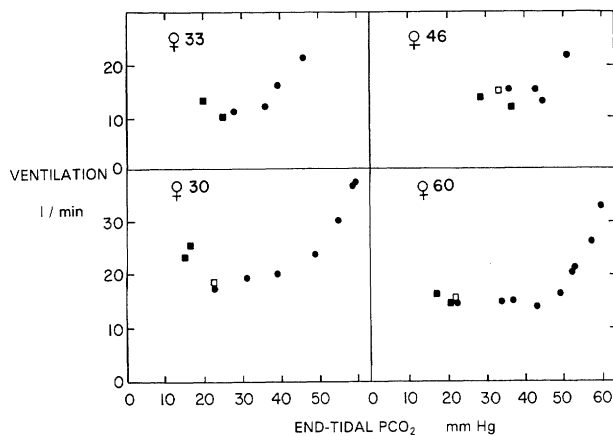


FIGURE 4. Mean responses (closed circles) to increasing levels of steady-state (6 to 8 min) CO<sub>2</sub> inhalation in four patients with chronic hyperventilation. Closed and open squares are resting value before and after the CO<sub>2</sub> inhalation, respectively. Each symbol is the mean of 30 to 40 breaths at the end of each steady state.

breathing can contribute to initiation or perpetuation of hyperventilation. In our patients with chronic hyperventilation,<sup>31</sup> we found no physiologic or therapeutic maneuver, including CO<sub>2</sub> inhalation for up to 1 h, which would permanently reverse the hypocapnia suggesting some form of physiologic resetting. One hour of CO<sub>2</sub> inhalation may be insufficient to reverse acid-base adaptation, but resetting of chemoreceptor sensitivity could not be implicated in our patients with chronic conditions, as it has been shown repeatedly that they have no ventilatory response to inhaled CO<sub>2</sub> until near-normal resting levels of PETCO<sub>2</sub> are reached.<sup>25,50</sup> This is illustrated in Figure 4 that shows the ventilatory response to steady-state CO<sub>2</sub> inhalation in four of our patients with chronic hyperventilation. Folgering and Colla<sup>25</sup> have described an increase of ventilation in these patients at low levels of PETCO<sub>2</sub> and have suggested the possibility of maintenance of hyperventilation by positive feedback in extreme hypocapnia.<sup>25</sup> The mechanism for this is uncertain, but an initial fall of ventilation between the resting and first inhaled CO<sub>2</sub> value as CO<sub>2</sub> was increased can be seen in some of the patients in Figure 4. This also accords with our clinical experience in occasional patients who, below a PETCO<sub>2</sub> of about 15 mm Hg, appear to develop a vicious circle of increasingly violent hyperventilation with progressively falling PETCO<sub>2</sub>, which can be reversed only with the greatest of difficulty.

It is often suggested that hyperventilation is the result of "bad breathing," imbalance between the action of the diaphragm and chest wall muscles, poor posture, or other abnormalities of respiratory pattern.<sup>206</sup> Excessive use of the upper chest in relation to the diaphragm has been described in these patients<sup>23</sup> but could not be confirmed by systematic measurement of rib cage motion.<sup>147</sup>

*Initiating and Sustaining Etiologic Factors:* It is

helpful clinically to differentiate etiologic processes that may initiate hyperventilation from those that sustain it once it has become established (Fig 3). Most of the etiologic factors described above can have both roles, but factors that are probably most potent in sustaining hyperventilation include misattribution and panic, sighing as part of a habit disorder, and some form of physiologic resetting as discussed above.

#### HYPERVENTILATION—CLINICAL PRESENTATIONS

The clinical finding of a low arterial or PETCO<sub>2</sub> will provide a diagnosis of hyperventilation, but this may not be associated with symptoms of hypocapnia, or such symptoms may be of minor importance compared with the symptoms of the disorder causing the hyperventilation. In these cases, a diagnosis of hyperventilation is of little clinical relevance. In other situations, the symptoms of hyperventilation are pivotal to the patient's clinical presentation. In our view, it is not clinically useful automatically to label a patient with hypocapnia as having hyperventilation syndrome. This term no longer has a universally agreed meaning, is not helpful in a disorder that is usually complex and multifactorial, and can be dangerous in the emergency department context. In all cases, the cause or causes of the increased respiratory drive causing the hyperventilation should be sought, with distinction made between initiating and sustaining factors.

Nevertheless, there are a number of clinical situations in which one or more of the above etiologic factors combine to produce recognizable clinical patterns. It is clinically useful to distinguish these groupings because of implications for treatment and prognosis. The following schemes are tentative and reflect our personal views. Many etiologic factors remain to be clarified, and there is considerable overlap between categories described. They are described in order of increasing etiologic complexity with syndromes with a single etiologic factor being described first followed by syndromes in which there is a complex interaction of a number of factors.

#### Single Etiologic Factors

*Chronic Anxiety:* Patients with chronic anxiety states can present with symptomatic hyperventilation in the absence of panic, misattribution, or other organic or physiologic factors. In our experience, patients with pure anxiety without other complicating factors are uncommon, and are within the province of the psychiatrists.

*Organic Disorder:* Hyperventilation can occasionally be the main presenting complaint in patients with a single organic disorder such as asthma in the absence of psychogenic or physiologic factors. These patients are invariably mislabeled as being in an anxiety state or having hyperventilation syndrome; this can have di-

sastrous consequences and these patients should be treated by a chest physician. We have described such a presentation in a patient with a history of childhood chest discomfort but no previous diagnosis of asthma who presented with tetany in a physician's office, subsequently often woke with tetany associated with mild early morning "dipping" of the peak flow, hyperventilated in response to histamine, responded to asthma inhalers, and in whom the hyperventilation recurred with every subsequent exacerbation of asthma.<sup>175</sup> It is not known why some patients have this excessive ventilatory response to mild asthma. Pulmonary hypertension has been described as presenting with hyperventilation<sup>160</sup> and, as described above, pulmonary embolism and major system failures may present in this way.

*Air Hunger:* While air hunger can be a component of most categories of hyperventilation, patients can also present with this as the only complaint. This can be a most distressing symptom, and, as described above, in some patients can lead to episodic panic and acute hyperventilation. There is little in the literature about the pathophysiology of air hunger but it is probably of psychogenic origin. While it can be intractable to manage, our experience suggests that occasional patients respond dramatically to asthma treatment in the absence of other clinical features of asthma, and it is worth giving all patients a trial of at least 1 month of inhaled steroids and bronchodilators. Antidepressive medication can also sometimes be helpful, and a combined approach from a chest physician and psychiatrist is usually indicated. There is often spontaneous resolution over 6 to 12 months with reassurance alone.

### *Multiple Etiologic Factors*

*Acute/Subacute Hyperventilation:* We use this term to describe patients with a multifactorial etiology with symptoms extending over a time span of up to about 2 years.<sup>207</sup> It is justifiable to distinguish this group from those with chronic hyperventilation as these patients are eminently amenable to treatment by a chest physician if the condition is recognized early and managed with a positive and informed strategy. These patients have usually attended a range of clinics before their condition is recognized. The scheme illustrated in Figure 3 is similar to descriptions in the older literature<sup>7-10,15,23</sup> and proposes that a number of the etiologic factors as described above combine to induce hypocapnia. At a certain point in time, PaCO<sub>2</sub> falls below about 20 mm Hg<sup>75</sup> with a sudden onset of alarming symptoms of hypocapnia that often include chest pain, paresthesiae, and altered consciousness. The patient panics and takes large breaths to relieve symptoms, with resulting worsening of the hyperventilation and hypocapnic symptoms that are misattributed

by both patient and attending physician to serious disease such as a heart attack, epilepsy, or a stroke. The patient is often admitted to a coronary or other acute medical unit but the underlying basis for the attack is not recognized and cardiologic and neurologic investigations fail to reveal a diagnosis. The patient is discharged from the hospital, often on a regimen of cardiac drugs, with heightened anxiety and fear of further attacks. As the precipitating factors have not been recognized or treated, this sequence recurs, the patient has increasingly unrewarding visits to a variety of medical and psychiatric clinics, and rapidly descends into chronic invalidism, hyperventilation often being perpetuated by a combination of sighs, misattribution, and possibly physiologic resetting by mechanisms yet to be defined.<sup>31</sup> This sequence can destroy the life of an otherwise fit young person within months, and rapid recognition and positive management are essential.

Some of the possible initiating factors in this sequence are illustrated in a recent study in which we investigated a group of patients presenting sequentially to the emergency department, labeled on clinical grounds by the physician as having acute hyperventilation.<sup>208</sup> The most usual presenting complaints were dyspnea, paresthesiae, chest tightness, and panic. These symptoms were misattributed to life-threatening conditions and especially heart attack and stroke in 87% and this was probably the main reason for presentation of the patient to hospital. About three quarters of the patients had evidence of asthma, both previously diagnosed and undiagnosed, about half had evidence of chronic anxiety, and about a fifth reported involvement with drugs and alcohol. Only the asthmatics had evidence of hyperventilation when studied some weeks after the presenting attack, although a history of previous acute episodes of hyperventilation was reported by most patients. This study illustrates the multifactorial basis of the etiology, the importance of misattribution in these patients, and the danger of using the blanket label of hyperventilation syndrome.

There are other reports in the literature of potentially life-threatening diseases such as diabetic ketoacidosis<sup>161</sup> and hypoglycemia<sup>199</sup> being mislabeled as hyperventilation and anxiety states in the emergency department. In this situation, not only is the term hyperventilation syndrome of dubious value clinically, but its use can be dangerous in that it distracts from seeking the true causes of the increased respiratory drive. To our knowledge, there have been no studies of the efficacy of the traditional breathing from a paper bag, and indeed this can be lethal in the presence of preexisting hypoxia due to lung disease.<sup>209</sup> Such misdiagnosis can be avoided by insisting that arterial blood gas analysis and chest radiography be performed in all cases of hyperventilation. Even with a normal chest radiograph, a psychogenic etiology should not be

considered as the sole diagnosis unless the PaO<sub>2</sub> is raised proportionately to the reduction in PaCO<sub>2</sub>.

These patients can usually be treated by a chest physician. There are no good treatment studies, but in our experience, the sequence of events can be reconstructed from a careful history with specific questioning about attribution, and the patient's decline can be reversed over weeks or months by explanation, demonstration of the effects of hypocapnia, and continual reassurance, combined with adequate investigations to exclude the feared disorders and treatment of initiating factors such as asthma. Panic can usually be controlled by the patient once the nature of the above sequence is understood, but may occasionally require psychiatric referral that may also be required for underlying depression. Relaxation and breathing exercises (see below) administered by a physiotherapist help some patients to control breathing during panic but are usually not required.

*Chronic Hyperventilation:* This is probably closest to the original descriptions of hyperventilation syndrome,<sup>7-10,15,23</sup> but elements of the subacute group can also be found in these older descriptions. It would be tempting to assume that chronic hyperventilation is the end result of subacute hyperventilation after many years of management neglect, but clinical experience suggests that it may be a distinct group with hyperventilation maintained by unknown etiologic factors.

Our own study of chronic hyperventilation<sup>22,31</sup> in many ways reflects the characteristics previously described by Lum,<sup>23</sup> Ames,<sup>10</sup> and others. Our patients presented with unimpressive symptoms, often atypical chest pain, fatigue, mild dyspnea or exercise intolerance, or even bizarre symptoms such as face pain. Air hunger was common, suggesting a psychogenic etiology, but there was no psychiatric morbidity detectable on formal testing in 50% of patients, the other 50% providing evidence of a mild phobic state. PETCO<sub>2</sub> was either chronically low at rest and throughout all provocation or was only mildly reduced at rest but was precipitated into prolonged reduction by either exercise or voluntary overbreathing. Figure 2 shows that the PETCO<sub>2</sub> in these patients responded to a range of stressors in the same way as a normal control group but was reset to a value constantly about 10 mm Hg lower. The hypocapnia could not be permanently reversed by any physiologic or therapeutic maneuver, including prolonged CO<sub>2</sub> inhalation for times of up to 1 h. PETCO<sub>2</sub> gradually increased by up to 20 mm Hg to reach near normal after 3 to 4 h of sleep, again suggestive of a psychogenic etiology, but fell back to the previous evening's low value when the subjects woke. This increase during sleep was far greater than is observed in normal subjects. Chest wall movements were not obviously increased, minute ventilation being only increased by about 10% (Fig 1) due to a variable

combination of increase in tidal volume and frequency. Steady-state CO<sub>2</sub> inhalation showed a marked dogleg in the CO<sub>2</sub> response curve (Fig 4), suggesting that maintenance of chronic hypocapnia did not involve resetting of the CO<sub>2</sub> response curve.<sup>50</sup> These patients have proved to be resistant to all known treatments.

There may be overlap of chronic hyperventilation with other syndromes with a similar chronic presentation. Rosen et al<sup>210</sup> have emphasized the similarity of chronic fatigue syndrome to the older "effort syndrome"<sup>2</sup> and have suggested, on the basis of excessive hyperventilation in response to the "think test," that chronic hyperventilation may be an important etiologic factor in chronic fatigue syndrome. However, we found that a group of patients with well-documented chronic fatigue syndrome were mostly not hypocapnic at rest and did not hyperventilate excessively in response to either exercise or voluntary hyperventilation.<sup>211</sup> We accept that we studied only two of many possible forms of provocation but believe that our results are inconsistent with a major etiologic role for hyperventilation in chronic fatigue syndrome. There is probably also some overlap with chronic somatization syndrome.

*Disproportionate Breathlessness:* Disproportionate breathlessness in the absence of detectable organic or psychogenic disease should be regarded as a separate syndrome in that the symptoms of hyperventilation, if present, are unlikely to be of major importance to the patient and rarely require specific treatment. The breathlessness usually occurs during or immediately after exercise. These patients are probably synonymous with our subgroup of patients with chronic hyperventilation who were only precipitated into overbreathing during or after exercise<sup>22,31</sup> (Fig 2). The etiology of the breathlessness in these patients is obscure as indeed are the fundamental mechanisms of breathlessness in normal subjects,<sup>126</sup> but, in our experience, there is often no evidence of a psychogenic etiology. Bronchospasm immediately after exercise has been documented in some of these patients in the absence of a history of asthma.<sup>212</sup> In our experience, such bronchospasm is resistant to asthma medication.

Howell<sup>28</sup> has reviewed this subject. Burns and Howell<sup>124</sup> found that disproportionately breathless patients without lung disease, in comparison with a group of patients with lung disease, tended to be younger, had more variable breathlessness which was poorly correlated with exercise, had more symptoms suggestive of hyperventilation but were not necessarily hypocapnic when tested, often feared they were going to die during an attack, and had difficulty breathing in rather than out. Three quarters of their patients were either anxious or depressed, the remainder having "premorbid hysterical personalities" with strong perfectionist traits. They reported significantly more bereavement, separation, marital disharmony,

and other stressful life events in the previous 3 years. As yet, we have few effective treatment strategies in this group, but reassurance and antidepressives may have a role.

#### CLINICAL MANAGEMENT

A positive clinical strategy with a stepwise approach to assessment is required. It is helpful to categorize patients according to the groupings described above, and simplistic labeling of patients as having hyperventilation syndrome should be avoided. These patients are very time consuming, and a detailed initial history and assessment with multiple follow-ups are usually required. In our experience, joint management by a chest physician and a liaison psychiatrist in a chest clinic offers the best approach to the treatment of these complex patients. The steps in management are as follows.

##### *Assessment of Presenting Complaints*

Organic causes for the presenting symptoms should be excluded as a necessary first step to reassuring both patient and referring physician that potentially life-threatening disorders that may contribute to misattribution are not present, and that hyperventilation contributes to the presenting symptoms. Many of these investigations will have already been done, but cerebral symptoms may require CT or MRI scan of the brain, and chest pain often requires full cardiologic investigations, including even coronary angiography to reassure that significant coronary artery disease is not present.

##### *Diagnosis of Hyperventilation*

The next stage is to prove the presence of hyperventilation which may be continually present or may be unmasked by provocation. Often the patient, friends, or attending physicians will provide a clear history of hyperventilation but, as discussed above, increased chest movement is not necessarily associated with hypocapnia. All of our patients undergo a hyperventilation screen as described above that is performed by our lung function technicians. This can be interpreted only as part of overall clinical assessment. Overnight measurement of  $PETCO_2$  is also useful.

##### *Assessment of Causes of Hyperventilation*

The next stage is to seek the causes of the hyperventilation and to attempt to classify the patient into one of the groupings described above. The history and especially the events surrounding the initial episode should be carefully elicited. Clinical examination, chest radiography, and routine blood tests are required in all patients. Lung function tests, home peak flow monitoring, and occasionally bronchial challenge testing may be required to detect asthma and the other res-

piratory disorders, but lung function tests are often difficult to perform or results are normal, and a positive clinical response to a trial of asthma inhaled medication and especially inhaled steroids can be the quickest way to confirm or exclude mild asthma. A ventilation/perfusion scan will detect pulmonary embolus and a normal scan makes significant airway or lung disease unlikely. Fine-cut CT scan of the lung and BAL are occasionally useful to detect early interstitial lung disease that can be present with a normal chest radiograph. An echocardiogram or direct measurement of pulmonary artery or right heart pressures will exclude pulmonary hypertension.

##### *Treatment*

The final stage involves treatment of the factors contributing to excessive respiratory "drive" or as a last resort, amelioration of symptoms by treatment of the hyperventilation *per se*. Many aspects of treatment have been discussed above. Lack of a universally accepted diagnostic process or definition for these disorders is reflected in the paucity of well-controlled treatment studies. In our experience, patients with single etiologies, acute/subacute hyperventilation, and short histories are most amenable to treatment, but recovery often requires many months, the patient gradually returning to a normal life, whether or not the hyperventilation persists. Patients with chronic hyperventilation, disproportionate breathlessness, and those in whom no clear etiologic factors can be elucidated are the most resistant to treatment.

These patients often have a long history of alarming symptoms for which no one has been able to offer an explanation, and they have been labeled as having anxiety states or being malingerers. Considerable time is required in taking a history to determine probable etiologic factors, to exclude feared disorders, to persuade the patient that hyperventilation may have a role in their symptoms, and to eliminate habits such as persistent sighing. Disorders such as mild asthma contributing to excessive respiratory drive require aggressive treatment, but additional extensive explanation and reassurance, given with confidence and authority by a trained physician, is one of the keystones to successful management.

Many regimens have been developed for treatment of hyperventilation *per se*, summarized in a recent book edited by Timmons and Ley<sup>206</sup> and critically reviewed by Garssen and Rijken.<sup>213</sup> In some patients, and especially those verging on panic, a regimen involving breathing exercises and diaphragmatic retraining may be of benefit.<sup>23</sup> Some believe that the effect of such training is nonspecific, but a recent study showed that guided breathing retraining improved cardiac symptoms and physiologic variables in a group of patients with hyperventilation.<sup>214</sup> However, other

controlled studies suggest that these techniques have only limited effectiveness.<sup>215,216</sup> Our clinical view is that these techniques should not be offered to all patients. They can be helpful when no cause for the hyperventilation can be found and in selected patients who require techniques for relaxation and for self-control of breathing in mild panic. In other patients, they can be positively harmful in inducing excessive introspection about the respiratory act.

In acute hyperventilation, rebreathing from a paper bag is widely prescribed but its mode of action and efficacy has not been formally determined and may involve distraction as much as accumulation of CO<sub>2</sub>. As described above, it can be dangerous in the emergency situation in hypoxic patients with undiagnosed lung disease.

Drugs have only a limited role in symptomatic treatment of hyperventilation.<sup>213</sup> Beta-blockers are useful to remove sympathetically mediated symptoms such as palpitations, trembling, and sweating<sup>217</sup> but must not be used if there is any suspicion of asthma. Benzodiazepines reduce subjective complaints<sup>218</sup> but a lasting effect has not been demonstrated and addictive potential limits long-term use. Monoamine oxidase inhibitors may have a place in patients with panic anxiety and multiple autonomic symptoms,<sup>219</sup> as may tricyclic antidepressives.<sup>220</sup> Clomipramine and imipramine may help to normalize Pco<sub>2</sub> in panic.<sup>221</sup>

In summary, we believe that the treatment of these difficult patients is firmly within the remit of the chest physician. Clinical and physiologic assessment in combination with psychiatric support can supply a prompt, positive, and informed approach leading to a clear treatment strategy that is vital to prevent the rapid descent into iatrogenic chronic invalidism and somatization which is all too commonly the fate of these otherwise fit and often young patients.

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