The Clinical Physiologist

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Ventilatory Failure

Can You Sustain What You Need?

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In Brief

On arrival in the emergency department, a 54-year-old woman in diabetic ketoacidosis was intubated for mechanical ventilation. She was neither hypoxemic nor hypercarbic. Why did she require ventilatory support? What are the contributing mechanisms?

The Clinical Challenge

A 54-year-old woman with insulin-dependent diabetes mellitus was taken to the emergency department because of nausea, vomiting, abdominal pain, and increasingly severe dyspnea. She had no history of lung disease and had never smoked cigarettes. On arrival, the patient was obtunded (Glasgow Coma Scale, 9). Her blood pressure was 80/50, the temperature was 37°C, the heart rate was 133 beats/minute, and the respiratory rate was 32 breaths/minute. Respiratory (abdominal) paradox was present. Her chest was clear to auscultation, and her abdominal examination was normal. A portable chest radiograph was normal. Arterial blood gas measurements performed while the patient received supplemental oxygen at 4 L/minute revealed a pH of 6.84, a Pa_{CO_2} of 24 mm Hg, and a Pa_{O_2} of 210 mm Hg. Blood glucose was 499 mg/dl, serum acetone was present at a dilution of 1:16, and serum bicarbonate was 4 mg/dl. The patient was intubated and placed on mechanical ventilation. Her diabetic ketoacidosis was treated by intravenous volume resuscitation and continuous insulin infusion, and she was admitted to the intensive care unit for further care.

Question

Why did this patient develop acute respiratory failure?

Our patient had profound metabolic acidosis. The acidemia triggered a marked compensatory increase in respiratory drive and minute ventilation that she could not sustain. This was shown by the presence of respiratory paradox, a marker of diaphragm weakness, and an inappropriately high Pa_{CO_2} (her predicted Pa_{CO_2} was 16 mm Hg). Inadequate respiratory compensation for metabolic acidosis resulted in a life-threatening arterial pH. Our patient's respiratory muscle dysfunction may have been caused by hypotension, which reduced oxygen delivery, and her underlying diabetes mellitus, which may have impaired muscle metabolism and energy production. Progressive acidosis probably further compromised muscle function. Mechanical ventilation was employed to improve respiratory compensation for metabolic acidosis and to restore a tolerable arterial pH.

Once ketoacidosis resolved, the patient's ventilatory requirement fell and her respiratory muscle function improved. She was extubated uneventfully after a trial of spontaneous ventilation demonstrated that she could sustain acid–base homeostasis and a normal breathing pattern without the need for ventilatory assistance.

The Science Behind this Patient's Respiratory Failure

Respiratory failure is often classified as hypoxemic (type I) or hypercarbic (type II), based on the clinical context and arterial blood gases. This classification categorizes many, but not all, instances of respiratory system failure. The patient presented here, for example, was neither hypoxemic nor hypercarbic, yet she required ventilatory assistance to sustain adequate minute ventilation.

Table 1. Causes of elevated minute ventilation requirement

1. Increased CO_2 production
a. Vigorous muscle activity
i. High work of breathing
ii. Seizures
b. Infection
c. Inflammation
2. Increased V_D/V_T
a. Elevated physiological dead space
i. All lung diseases
ii. Congestive heart failure
b. Low tidal volume
i. Adult respiratory distress syndrome
ii. Reduced lung or chest wall compliance
iii. Respiratory muscle weakness or fatigue
3. Reduced Pa_{CO_2}
a. Metabolic acidosis
b. Hypoxemia

Definition of abbreviation: V_D/V_T = ratio of physiological dead space to tidal volume.

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The inadequacy of the conventional definition of respiratory failure can be overcome by recognizing that the respiratory system is composed of two vital organs, the lungs and the respiratory pump, either of which can fail. The output of the respiratory pump is ventilation, just as the output of the left ventricle is systemic blood flow. Ventilatory failure is a term that can be used to communicate a failure of the respiratory pump to sustain the required minute ventilation. Ventilatory failure can be compensated by an elevated serum bicarbonate level, or uncompensated. Uncompensated ventilatory failure manifests as an abnormally low arterial pH regardless of whether the arterial P_{CO_2} is low, normal, or high.

Recognition of acute ventilatory failure raises two questions:

1. What determines a patient's minute ventilation requirement?
2. What determines how much minute ventilation a patient can sustain?

Let's consider each of these questions.

The Required Minute Ventilation

The fundamental purpose of breathing is gas exchange; to ensure adequate oxygen uptake from the atmosphere to meet peripheral tissue demand and to exhaust the associated carbon dioxide production. Minute ventilation is controlled by many inputs to the respiratory drive center, both central and peripheral, and the resulting partial pressure of carbon dioxide in the arterial blood (Pa_{CO_2}) reflects the final equilibrium of all these inputs balanced against the physiological costs of ventilation. The minute ventilation requirement of a patient in a steady state is given by (1):

$$\dot{V}_E = \dot{V}_{P_{CO_2}} / (1 - V_D/V_T) \cdot Pa_{CO_2} \cdot k, \quad (1)$$

where $\dot{V}_E$ is the minute ventilation (L/min), $\dot{V}_{P_{CO_2}}$ is the CO_2 production (L/min), V_D/V_T is the ratio of physiological dead space to tidal volume, and k is a dimensional constant. Equation 1 demonstrates that a patient's minute ventilation requirement is determined by only three factors (Table 1):

- The rate of CO_2 production ($\dot{V}_{P_{CO_2}}$): Anything that increases CO_2 production, for example, muscular activity or infection, increases the minute ventilation required to keep the Pa_{CO_2} constant.

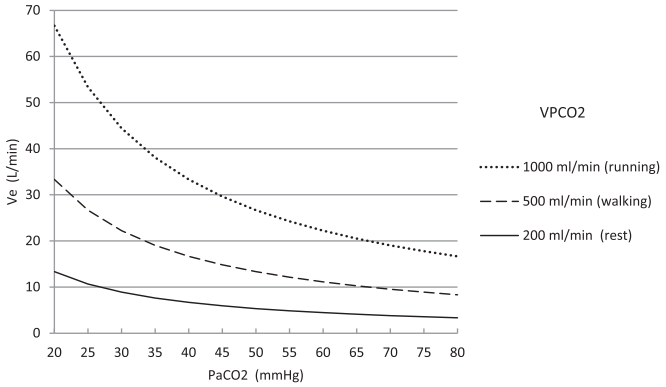

Figure 1. Ventilatory requirement ($\dot{V}_E$) for any given Pa_{CO_2} depends on CO_2 production ($\dot{V}_{P_{CO_2}}$).

- The ratio of dead space to tidal volume (V_D/V_T ratio): Every lung disease, whether it affects primarily the airways, parenchyma, or pulmonary circulation, increases the mismatching of ventilation and perfusion, and this increases the total or physiological dead space volume (2). As V_D becomes a greater proportion of V_T (i.e., V_D/V_T increases), each breath excretes less CO_2, and $\dot{V}_E$ must increase to maintain the same Pa_{CO_2}. The effect is the same when V_D/V_T increases because of a drop in V_T as, for example, with respiratory muscle weakness and during low tidal volume ventilation for adult respiratory distress syndrome. Thus, V_D/V_T is an important measure of how efficiently CO_2 is excreted by the lungs; the higher the ratio, the lower the efficiency, and the greater the required $\dot{V}_E$.
- The Pa_{CO_2} the central drive center demands: A lower Pa_{CO_2} requires a higher minute ventilation, and vice versa. In disease states, metabolic acidosis and significant arterial hypoxemia increase respiratory drive, lower the Pa_{CO_2}, and increase the $\dot{V}_E$ requirement.

The effect of $\dot{V}_{P_{CO_2}}$, V_D/V_T, and Pa_{CO_2} on the required $\dot{V}_E$ is shown in Figures 1 and 2. These factors constitute half of what we need to understand ventilatory failure. The second half concerns question 2 (*see above*). What determines how much minute ventilation a patient can sustain?

Maximal Sustainable Minute Ventilation

To get at this question, consider a common pulmonary function test, the maximal voluntary ventilation (MVV). This is performed by having the patient breathe as deeply and quickly as possible for 15 seconds and measuring the corresponding ventilation the patient generates. Like all

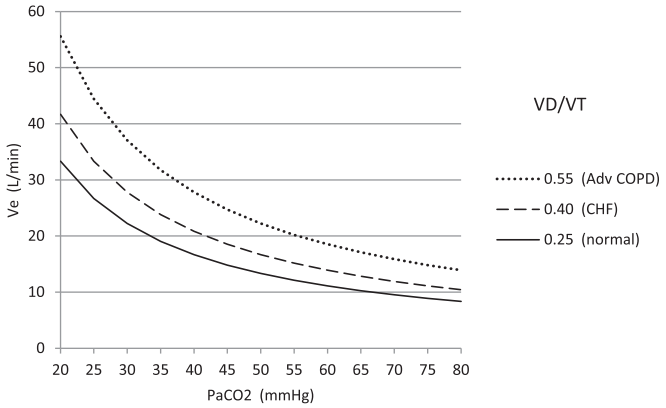

Figure 2. Ventilatory requirement ($\dot{V}_E$) for any given Pa_{CO_2} depends on the ratio of dead space to tidal volume (V_D/V_T). CO_2 production is 500 ml/minute. Adv COPD = advanced chronic obstructive pulmonary disease; CHF = congestive heart failure.

Table 2. Causes of reduced sustainable minute ventilation

1. Increased work of breathing
a. High airway resistance
b. Low lung or chest wall compliance
c. Hyperinflation; Intrinsic positive end-expiratory pressure
d. High $\dot{V}_E$ requirement
2. Respiratory muscle weakness or inefficiency
a. High work of breathing
b. Impaired O_2 delivery
c. Neuromuscular disease
3. Inadequate ventilatory drive
a. Drugs
b. Encephalopathy
c. Seizures
d. Stroke
e. Intracranial hemorrhage

Definition of abbreviation: $\dot{V}_E$ = minute ventilation.

pulmonary function tests, the MVV depends on body size and for an average 70-kg adult male is on the order of 130 L/minute. Obviously, by the nature of the test, the MVV cannot be sustained. Experiments on normal volunteers and trained athletes demonstrate that one can sustain a minute ventilation of 75% of the MVV for only about 15 minutes. By extrapolation, it appears that one can sustain 50% of the MVV for a period of hours, and this is often taken as the definition of the maximal sustainable ventilation (MSV) (3).

Like the required minute ventilation, there are three factors that adversely affect the MSV (Table 2).

- Increased work of breathing: Imagine measuring the MVV in a subject who is breathing through a straw or whose chest has been tightly wrapped with elastic bands. Obviously, both the MVV and the MSV would be reduced. The common factor in this thought experiment is a marked increase in the work of breathing. This is why patients with high airway resistance (e.g., chronic obstructive pulmonary disease and asthma) or reduced respiratory system compliance (e.g., interstitial lung disease, morbid obesity, severe kyphoscoliosis) have an abnormally low MSV.
- Impaired respiratory muscle function: Reduced contractility and pressure generation by the diaphragm and the other respiratory muscles leads to a fall in V_T, which reduces MSV. This can be caused by a large number of diseases that affect the brain, spinal cord, peripheral nerves, neuromuscular junction, or the muscle itself. Clinical examples include multiple sclerosis, spinal cord trauma, Guillain-Barré syndrome, phrenic nerve injury, myasthenia gravis, and muscular dystrophy. Perhaps the most important and frequent example is respiratory muscle fatigue (4).
- Reduced respiratory drive: Diseases that directly impair brainstem function (e.g., hemorrhage or infarction) or its ability to respond to central or peripheral input (e.g., drugs, encephalopathy, seizures) reduce respiratory rate, V_T, and MSV.

Combined Disorders and Vicious Cycles

A few additional aspects of ventilatory failure warrant emphasis. Almost always, patients in ventilatory failure will have both an increased $\dot{V}_E$ requirement and a reduced MSV, and several vicious cycles can be identified. One of the most commonly encountered examples is a patient with ventilatory failure due to an exacerbation of chronic obstructive pulmonary disease (Figure 3). The fundamental derangement is an increase in airflow resistance that increases the physical work of breathing. This in turn increases CO_2 production and therefore increases the required $\dot{V}_E$. However, the increased $\dot{V}_E$ itself further increases the total work of breathing, which thereby further increases the CO_2 production, which of course further increases the $\dot{V}_E$ required. This is a vicious cycle. The increased airflow resistance also disturbs the distribution of ventilation and thereby alters the distribution of ventilation-to-perfusion ratios throughout the lung. This in turn reduces the lung's gas exchange efficiency and is manifest as an increase in the overall V_D/V_T ratio. This further increases the $\dot{V}_E$ required to eliminate the CO_2 production at the Pa_{CO_2} set by the respiratory drive center. In patients with severe airflow obstruction, high $\dot{V}_E$ typically precipitates or worsens dynamic hyperinflation and intrinsic positive end-expiratory pressure. This reduces respiratory muscle efficiency and further increases the work of breathing, which reduces MSV, increases $\dot{V}_{P_{CO_2}}$, and worsens respiratory muscle fatigue. As V_T falls, V_D/V_T rises, which requires a higher $\dot{V}_E$, another vicious cycle.

How can the body interrupt a vicious cycle? One way is for the respiratory drive center to accept a higher Pa_{CO_2}. This of course reduces the $\dot{V}_E$, which otherwise would be required, and lessens the previously discussed vicious cycles. This is a common mechanism in advanced lung disease, but is not always present. Some patients progress to ventilatory failure without increasing their Pa_{CO_2} until the point of collapse. Notice that the operational definition of ventilatory failure as an imbalance between required and sustainable $\dot{V}_E$ does not require an abnormally elevated Pa_{CO_2}. Although hypercarbia is often present, patients with ventilatory failure may have a normal or low Pa_{CO_2}. Ventilatory failure is a clinical diagnosis that is based on all of the clinical information available, not just the Pa_{CO_2}.

Causes and Therapies

When evaluating a patient with ventilatory failure, both the precipitating factor(s) and,

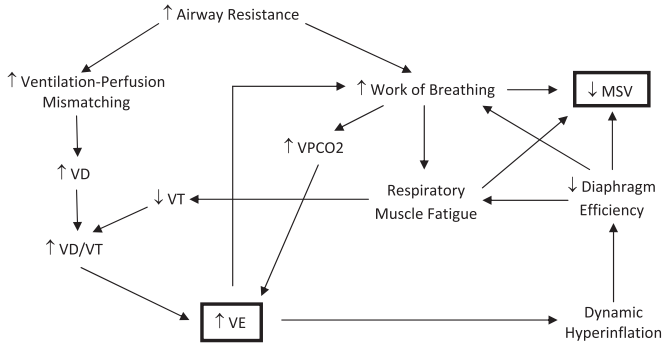

Figure 3. Mechanisms of increased ventilatory requirement ($\dot{V}_E$) and reduced maximal sustainable ventilation (MSV) during a chronic obstructive pulmonary disease exacerbation. These include increased CO_2 production ($\dot{V}_{P_{CO_2}}$), increased dead space volume (V_D), reduced tidal volume (V_T), and an increased ratio of dead space to tidal volume (V_D/V_T).

by extension, appropriate specific therapy can be determined by considering both the causes of a high $\dot{V}_E$ requirement and a reduced MSV (Tables 1 and 2). In most cases, invasive or noninvasive mechanical ventilation will be needed, at least temporarily. Ventilatory support assumes some portion, perhaps a majority, of the patient's work of breathing, thereby increasing the sustainable V_E. At the same time, mechanical ventilation lowers the required $\dot{V}_E$ by reducing respiratory muscle work and CO_2 production, correcting hypoxemia, and increasing tidal volume, which reduces V_D/V_T. Spontaneous ventilation can be resumed once specific therapies have reduced the required $\dot{V}_E$ and/or increased the MSV. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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