

## Blunted Response to Hypercapnia: Synonymous With Depressed Respiratory Drive?

The pathophysiology of failure to wean from mechanical ventilation consists of depressed central respiratory drive, impaired respiratory mechanics, respiratory muscle weakness, increased load, impaired gas exchange, and compromised cardiovascular performance. Among patients with weaning failure, depressed central respiratory drive occurs in only a small portion (approximately 10%),<sup>1</sup> whereas most patients demonstrate augmented drive with the development of progressive ventilatory failure.<sup>2</sup>

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SEE THE ORIGINAL STUDY ON PAGE 1012

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To assess central respiratory controller output, the pressure generated during the first 0.1 second of an airway occlusion ( $P_{0.1}$ ) that coincides with the onset of inspiratory effort has been widely used. Its measurement is noninvasive, and it has the advantage of being independent of respiratory-system resistance, compliance, and Hering-Breuer inflation reflex,<sup>3</sup> and automatic acquisition of  $P_{0.1}$  is available on intensive-care-unit ventilators.<sup>4</sup> However, the interpretation of  $P_{0.1}$  as an index of respiratory-center drive can be challenging, particularly when the connecting nerves from the respiratory controller to the respiratory muscles are disrupted, the respiratory muscles are weak, or the  $P_{0.1}$  measurement is not obtained at resting end-expiratory lung volume.<sup>3</sup>

At volumes higher than resting end-expiratory lung volume (dynamic hyperinflation), a phase lag between pressure generation and flow occurs, due to a prolonged time constant and absence of an end-expiratory pause. Under this condition the negative pleural-pressure swing occurs early, that is, during late exhalation, before flow reverses to inspiration; but  $P_{0.1}$  cannot be measured until flow becomes zero. The measured  $P_{0.1}$  value can be equal to, higher than, or lower than the rate of pressure generation in the beginning of inspiratory effort, depending on the shape of the airway pressure waveform.<sup>3</sup>

At volumes lower than resting end-expiratory lung volume that are attributable to expiratory muscle activation, the  $P_{0.1}$  generated at zero flow can result partly from the negative elastic recoil pressure produced by relaxation of the expiratory muscles. When lung volume is below its resting volume, observations of healthy subjects rebreathing carbon dioxide showed that the means of generating

pressure at onset of inspiration are unimportant as long as the relationship between  $P_{0.1}$  and ventilation remains stable.<sup>3</sup>

Another consideration is that  $P_{0.1}$  measured at the mouth can be underestimated, in comparison to that measured from esophageal pressure. This occurs because the time constant of the airways, which consists of airways resistance and mouth-cavity-walls compliance, is prolonged. In intubated patients this latter consideration is irrelevant because endotracheal-tube placement circumvents the problem.<sup>3</sup>

Despite its limitations, when interpreted critically,  $P_{0.1}$  remains a reliable index of respiratory-center drive. Together with ventilation, its measurement is incorporated with  $\text{CO}_2$  rebreathing to assess respiratory-center chemosensitivity. The original Read rebreathing method requires the subject to rebreathe a mixture of  $\text{CO}_2$  and hyperoxic gas to achieve equilibrium of end-tidal, arterial, and mixed venous  $\text{CO}_2$  tension, such that changes in end-tidal  $\text{CO}_2$  represent those in arterial and mixed venous blood, and, most importantly, in brain tissue as a stimulus for changes in central chemoreceptor output.<sup>5</sup> Under this condition,  $\text{CO}_2$  stimulus is independent of the dependent variable, ventilation. The slopes of the ventilatory (change in minute volume [ $\Delta\dot{V}_E$ ] divided by  $\Delta P_{\text{CO}_2}$ ) and  $P_{0.1}$  responses to hypercapnia ( $\Delta P_{0.1}/\Delta P_{\text{CO}_2}$ ) are calculated as estimates of central respiratory drive. As with resting  $P_{0.1}$ , using  $\text{CO}_2$  rebreathing to assess central respiratory drive has several limitations:

1. Abnormal respiratory system resistance and compliance preclude ventilatory response to hypercapnia, and leaves only  $P_{0.1}$  response to  $\text{CO}_2$  as a means to estimate central respiratory drive.

2. The range of normal values in healthy awake subjects is wide, for  $\Delta\dot{V}_E/\Delta P_{\text{CO}_2}$  it is 0.47–6.23 L/min/mm Hg.<sup>6</sup> To date, no study with a large number of subjects has described the range of normal values for  $\Delta P_{0.1}/\Delta P_{\text{CO}_2}$ . However, in one study in anesthetized healthy subjects, in which the anesthetic agent had no effect on central respiratory drive, the range of  $\Delta P_{0.1}/\Delta P_{\text{CO}_2}$  was 0.17–0.62 cm  $\text{H}_2\text{O}$ /mm Hg.<sup>7</sup>

3. Both ventilatory and  $P_{0.1}$  responses to hypercapnia exhibit wide variability. In healthy subjects the coefficients of variation for ventilatory and  $P_{0.1}$  responses to

hypercapnia are 56% and 66%, respectively.<sup>8</sup> This variability is all the more enormous in patients recovering from acute respiratory failure, in whom the coefficient of variation for  $\Delta\dot{V}_E/\Delta P_{CO_2}$  is 81%, and that for  $\Delta P_{0.1}/\Delta P_{CO_2}$  is 76%.<sup>2</sup>

In this issue of the Journal, Raurich et al<sup>9</sup> report on a large number of patients recovering from acute respiratory failure of various etiologies (with the exception of chronic obstructive pulmonary disease and neuromuscular disease) and who were ready to wean. In the patients who failed to wean, both ventilatory and  $P_{0.1}$  responses to hypercapnia were lower than in the patients who weaned successfully. Do their findings indicate that patients who fail to wean had depressed central respiratory drive?

Raurich et al<sup>9</sup> excluded patients with chronic obstructive pulmonary disease and neuromuscular disease. Nonetheless, in patients without airflow limitation, intrinsic positive end-expiratory pressure (PEEPi) increased 5-fold with  $CO_2$  rebreathing during a modest level of pressure-support ventilation.<sup>10</sup> During a weaning trial of patients with diverse etiologies, Laghi et al<sup>11</sup> found that patients who failed to wean had higher respiratory-system resistance, lower dynamic compliance, and higher PEEPi than patients who weaned successfully. In addition, many of the patients who failed to wean had diaphragm muscle weakness, as assessed via twitch pressure produced by phrenic-nerve stimulation, which is a measure of diaphragm muscle function uninfluenced by voluntary effort. The absence of information on PEEPi or diaphragm muscle function hampers the interpretation of the blunted  $CO_2$  response in the patients who failed to wean.

Raurich et al<sup>9</sup> also found that both ventilatory and  $P_{0.1}$  responses to hypercapnia, and the ratio of hypercapnia-test  $P_{0.1}$  to resting  $P_{0.1}$  were not useful as predictors of weaning outcome. The latter finding contrasts with those of Montgomery et al,<sup>12</sup> who found, in a small number of patients with diverse etiologies, that the ratio of hypercapnia-test  $P_{0.1}$  to resting  $P_{0.1}$  separated patients who failed to wean from those who weaned successfully. It is difficult to compare these 2 studies, because they did not use similar  $CO_2$  rebreathing methods or conditions. The patients of Raurich et al<sup>9</sup> rebreathed  $CO_2$  via added dead space, without initial  $CO_2$  gas mixture, during pressure-support ventilation, whereas those of Montgomery et al<sup>12</sup> rebreathed  $CO_2$  via a bag filled with a mixture of  $CO_2$  and oxygen, without

ventilatory support. The large sample size in the study by Raurich et al<sup>9</sup> is commendable; however, it is interesting to note that the ratio of respiratory frequency to tidal volume ( $f/V_T$ ) measured at baseline had an area under the receiver-operating-characteristic curve that was similar to that of the ratio of hypercapnia-test  $P_{0.1}$  to resting  $P_{0.1}$ , which suggests that a test as simple as  $f/V_T$  provides information similar to that obtained with  $CO_2$  rebreathing.

Among patients who fail to wean it is likely that only a small proportion of these failures are caused by a depressed respiratory-center drive, whereas the majority are caused by impaired respiratory system mechanics and diaphragm muscle weakness.

**Catherine S Sassoon MD**

Pulmonary and Critical Care Section  
Department of Medicine  
Veterans Affairs Long Beach Healthcare System  
Long Beach, California

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Correspondence: Catherine S Sassoon MD, Pulmonary and Critical Care Section, Veterans Affairs Long Beach Healthcare System, 5901 East 7th Street, 11/111P, Long Beach CA 90822. E-mail: csassoon@uci.edu.