Laboratory Monitoring of Mechanical Ventilation

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A patient’s respiratory status and the effectiveness of mechanical ventilation are assessed in many ways. Available methods for determining this information include clinical assessment, pulse oximetry, end tidal carbon dioxide (CO2) monitoring, pressure volume loops, and laboratory tests. This article examines the use of laboratory tests for managing mechanical ventilation. Blood gas analysis is a common test widely used for this purpose, and this is evaluated in detail. Other tests, however, provide valuable insight into the management of patients receiving mechanical ventilation. These include serum electrolytes, thyroid function tests, and adrenal function tests.

Arterial blood gas analysis

Mechanical ventilation controls two basic components of a patient’s physiology: ventilation and oxygenation. Through arterial blood gas analysis, one can determine the patient’s pH, arterial partial pressure of CO2 (P_aCO2), and arterial partial pressure of oxygen (P_aO2). In the most basic terms, the minute ventilation (tidal volume multiplied by respiratory rate) is adjusted to achieve a physiologic appropriate pH and P_aCO2. Both the fraction of inspired oxygen (F_iO2) and mean airway pressure can be adjusted to achieve an acceptable P_aO2. This section reviews the mechanics of blood gas analysis. The use of blood gas analysis for managing specific patient conditions then is explored.
Mechanics

Blood gas analyzers report a range of results, but the only parameters directly measured are the partial pressures of O₂ (PO₂) and CO₂ (PCO₂) and blood pH.

Oxygen electrode

In late 1954, Leland C. Clark, Jr., PhD, designed a blood O₂ electrode, also known as a Clark cell or polarographic electrode [1]. The polarographic O₂ electrode measures the PO₂ in a blood or gas sample. It is composed of a glass-coated platinum cathode and a silver/silver chloride reference electrode, which are immersed in an electrolyte solution of potassium chloride. The necessary reactions occur under a polarizing voltage of 600 to 800 mV, and the total current is limited by the very small exposed area on the platinum cathode. At the anode, electrons are provided by the oxidation reaction of the silver with the chloride ions of the potassium chloride electrolyte solution to give silver chloride and electrons.

\[ \text{Ag}^+ + \text{Cl}^- \rightarrow \text{AgCl} + e^- \]

At the cathode, O₂ combines, by means of a reduction reaction, with the electrons and water, giving rise to hydroxyl ions.

\[ \text{O}_2 + 2\text{H}_2\text{O} + 2e^- \rightarrow \text{H}_2\text{O}_2 + 2\text{OH}^- \]

This equation shows that the number of O₂ molecules available determines the number of electrons that can be taken up at the cathode. The more electrons taken up, the greater the current flow. Thus the current, having been determined by the availability of the O₂ molecules, is directly proportional to the PO₂. A membrane, usually polypropylene, separates the electrode from the blood, preventing deposition of protein but allowing the O₂ tension in the blood to equilibrate with the electrolyte solution. The electrode is kept at a constant temperature of 37°C, and regular checks of the membrane are required to ensure it is not perforated or coated with proteins.

Carbon dioxide electrode

In early 1954 Richard Stow, MD, described his CO₂ electrode, but failed to develop it further. Later that same year, Severinghaus [2] improved upon the Stow-type CO₂ electrode to create the CO₂ electrode in use today. The Severinghaus or CO₂ electrode is a modified pH electrode in contact with sodium bicarbonate solution and separated from the blood specimen by a rubber or Teflon semipermeable membrane. The Severinghaus CO₂ electrode provides a direct method of PCO₂ measurement from the hydrogen ion change associated with the reaction of CO₂ with water.
$\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{HCO}_3^-$

Hydrogen ions are produced in proportion to the PCO$_2$ and are measured by the pH-sensitive glass electrode. CO$_2$, but not hydrogen ions, diffuses from the blood sample across the membrane into the sodium bicarbonate solution, producing hydrogen ions and a change in pH. At the tip of the electrode, CO$_2$ diffuses through the plastic membrane into the mesh impregnated with the bicarbonate solution and combines with the water present, producing the hydrogen ions and bicarbonate. The resulting change of hydrogen ion concentration is measured by the glass electrode. The analyzer then calculates the PCO$_2$.

$$\text{PCO}_2 = \frac{\text{CO}_2 \text{ concentration}}{100} \times \left( \frac{\text{barometric pressure}}{\text{water vapour pressure}} \right)_{[37^\circ \text{C}]}$$

As with the Clark electrode, the Severinghaus electrode must be maintained at $37^\circ \text{C}$ and calibrated with gases of known PCO$_2$. Additionally, the integrity of the membrane is essential.

**pH electrode**

The pH electrode is an ion-selective electrode dependent on the hydrogen ion-sensitive glass at its tip. A measuring silver/silver chloride electrode is encased in a bulb of special pH-sensitive glass, and it contains a buffer solution that maintains a constant pH. This glass electrode is placed in the blood sample, and a potential difference is generated across the glass that is proportional to the difference in hydrogen ion concentration. The potential is measured between a reference electrode (in contact with the blood by means of a semipermeable membrane) and the measuring electrode. Both electrodes must be kept at $37^\circ \text{C}$, clean and calibrated with buffer solutions of known pH.

When obtaining a sample for blood gas analysis, a heparinized, freshly drawn, bubble-free arterial blood sample is required. Heparin is acidic, and if too much is present in the sample, the measured PCO$_2$ and calculated bicarbonate are reduced. A freshly drawn sample is important, as delay in measurement allows continued metabolism by the erythrocytes, thus reducing pH and PO$_2$ and increasing PCO$_2$. If a delay in analysis is expected, keeping the specimen on ice allows accurate measurement to be postponed for up to 1 hour. A bubble-free sample is necessary, as air bubbles introduce error by causing a fall in PCO$_2$ and an increase in PO$_2$.

**Cases**

Blood gas analysis is a tool used commonly by clinicians for managing mechanical ventilation. Like any clinical tool, the appropriate use and evaluation of blood gas analysis are necessary for the proper management...
of patients receiving mechanical ventilation. The inappropriate interpretation of blood gas results can lead to unnecessarily prolonged mechanical ventilation and ICU care, increased morbidity, and perhaps, increased mortality. This section examines common clinical scenarios in which blood gas analysis is used to determine patient management. The cases examined are of varying levels of complexity, but will provide a general overview of the management of patients receiving mechanical ventilation. Many of the issues explored in this section are described in detail in other sections of this issue, including lung protection strategies in acute respiratory distress syndrome (ARDS) (permissive hypercapnea, positive end-expiratory pressure [PEEP], inverse ratio ventilation, and O₂ toxicity). This section describes these issues in the context of the use of blood gas analysis for managing mechanical ventilation, but not in detail. Before examining specific cases, it is important to know normal values for arterial blood gas analysis. On room air, they are as follows (from the University of Rochester of Rochester Medical Center Laboratory):

1. pH: 7.35 to 7.43
2. PₐCO₂: 36 to 46 mm Hg
3. PₐO₂: 80 to 100 mm Hg
4. Bicarbonate: 19 to 23 mmol/L
5. Base Excess: −3 to +1 mmol/L
6. O₂ saturation: 94% to 100%

Case 1 — the previously healthy patient receiving mechanical ventilation

Previously healthy patients require mechanical ventilation in various situations. Anesthesiologists commonly manage previously healthy patients undergoing mechanical ventilation as part of a general anesthetic. In this case, blood gas analysis usually is not required, as pulse oximetry and end-tidal CO₂ monitoring provide the information needed to adjust the patient’s minute ventilation, inspired O₂ concentration, and mean airway pressure. Depending on the situation, these patients may have an arterial catheter. In this case, blood gas analysis could then be used to adjust these parameters. At times, such a patient may require mechanical ventilation in the ICU for varying periods of time. Examples include patients who suffer large blood losses as a result of trauma, obstetric catastrophes, or other causes. Another example may be marked airway or facial edema in which premature extubation and withdrawal from mechanical ventilation could prove risky. Occasionally surgeons will request several days of paralysis and mechanical ventilation for patients who have undergone complex plastic surgery procedures or those who, for various reasons, have abdominal fascia that was unable to be closed. If such a patient was to arrive in the ICU, initial blood gas analysis may reveal the following values:

pH 7.26, PCO₂ 60 mm Hg, PO₂ 62 mm Hg, and an O₂ saturation of 90%.
Assuming normal values of pH 7.4 and PCO \(_2\) 40, the patient has a pure respiratory acidosis and mild hypoxia. The goal is to achieve a pH and PCO \(_2\) near normal and an O\(_2\) saturation of 92% or better. Recall that there is a 0.08 change in pH for every 10 mm Hg change in PCO \(_2\) from the normal value of 40 mm Hg. Hypercapnea will cause a respiratory acidosis and, thus, a negative change in pH. In this case, the predicted change in pH is determined as follows:

\[
\text{Predicted pH} = 7.4 - (0.08)(\text{PCO}_2 - 40) / 10 \quad \text{torr}
\]

\[
\text{Predicted pH} = 7.4 - (0.08)(60 - 40) / 10
\]

\[
\text{Predicted pH} = 7.4 - 0.16
\]

\[
\text{Predicted pH} = 7.26
\]

The predicted pH is the same as the measured pH, which is consistent with a pure respiratory acidosis. Ventilator adjustments made to improve this patient’s respiratory status would include increasing the minute ventilation (respiratory rate and/or tidal volume), increasing the F\(_1\)O\(_2\) (recognizing the risks associated with O\(_2\) toxicity when O\(_2\) concentrations are greater than 60%), and increasing the mean airway pressure (by increasing the PEEP and/or adjusting the I:E ratio). Assuming the patient weighs 70 kg and is on controlled ventilation with a tidal volume of 400 cc, respiratory rate (RR) = 10, I:E ratio = 1:3, and an F\(_1\)O\(_2\) = 40% with PEEP of 0 cm H\(_2\)O, adjustments may include increasing the tidal volume (V\(_T\)) to 500 cc (maintaining V\(_T\) in the 6 to 8 cc/kg range), increasing the RR to 16, increasing the PEEP to 5 cm H\(_2\)O, changing the I:E ratio to 1:2, and increasing the F\(_1\)O\(_2\) to 50%. In almost all cases, at least 3 to 5 cm H\(_2\)O of PEEP should be used to prevent alveolar collapse. The use of PEEP limits the risk of worsening lung injury and improves oxygenation by decreasing the shunt fraction.

**Case 2—the septic patient**

Sepsis is the cause for many ICU admissions. Early in the disease process, septic patients may be febrile, hypotensive, tachycardic, tachypnic, and are often hypoxic. They are often hypovolemic and have a metabolic acidosis. The tachypnea seen is most often compensatory for a metabolic acidosis. These patients usually are intubated and ventilated to protect their airway and treat respiratory failure. Management also includes aggressive intravenous fluid resuscitation and antibiotics. A typical arterial blood gas (ABG) in such a scenario would be:

pH 7.20, PCO\(_2\) 50 mm Hg, PO\(_2\) 80 mm Hg, and an O\(_2\) saturation of 95%.

This patient has a mixed metabolic and respiratory acidosis. This is evident, because one would expect a patient who has this degree of respiratory acidosis to have a pH of 7.32 if this was a pure respiratory acidosis.
\[ \text{pH} = 7.4 - (0.08)(50 \text{ torr} - 40 \text{ torr})/10 \text{ torr} \]

\[ \text{pH} = 7.4 - 0.08 \]

\[ \text{pH} = 7.32 \]

The measured pH of 7.20 is lower, or more acidic, than the predicted pH, which accounts for the mixed respiratory and metabolic acidosis.

Again assume a 70 kg patient, this time with ventilator settings of \( V_T = 400 \text{ cc}, \ RR = 14, \ I:E \text{ ratio} = 1:2, \ F_{I\text{O}_2} = 40\%, \) and \( \text{PEEP} = 5 \text{ cm H}_2\text{O}. \) In this case, the patient has demonstrated good lung compliance with peak inspiratory pressures of 25 cm \( \text{H}_2\text{O}. \) The patient is oxygenating adequately and is on an appropriate level of PEEP. One strategy would be to increase the minute ventilation to correct the pH. This would require increasing the \( V_T \) to 500 to 550 cc and/or increasing the \( \text{RR} \) to achieve a respiratory alkalosis. The problem with this approach is that correcting the pH by hyperventilating the patient does not address the etiology of the metabolic acidosis. The metabolic acidosis is likely caused by excess lactic acid production. Recall that lactic acid is produced during anaerobic metabolism. In sepsis, this usually occurs as a result of end organ hypoperfusion as a consequence of hypovolemia. Some clinicians would elect to administer sodium bicarbonate at this point to correct the metabolic acidosis. This approach, however, fails to address the end organ hypoperfusion. In this case, a more logical strategy would be to correct the respiratory acidosis component of the disorder while correcting the patient’s intravascular volume deficit. The pH then is monitored frequently to assess for resolution of the metabolic component of the acidosis. This helps guide intravenous fluid volume management, the use of inotropes and vasopressors, and the administration of blood products. Although the usual goal is pH correction to the normal value of 7.35 to 7.45, there may be some theoretical benefit to accepting mild acidaemia. Recall that the oxygen–hemoglobin dissociation curve (Fig. 1) is shifted to the right during acidosis.

This allows greater oxygen release from the capillaries to the tissues. Because shock, by definition, is the inadequate delivery of oxygen at a cellular level, initial tolerance of a lower-than-normal pH, by allowing mild-to-moderate \( \text{CO}_2 \) retention (permissive hypercapnea), may be beneficial for \( \text{O}_2 \) delivery.

**Case 3—the septic patient with ARDS**

In the scenario described previously, how would the situation be approached if the patient had ARDS in addition to sepsis? In this scenario, the patient may have the following ABG:

- pH 7.20, \( \text{PCO}_2 \) 50 mm Hg, \( \text{PO}_2 \) 50 mm Hg, and an \( \text{O}_2 \) saturation of 85%.

With ventilator settings of \( F_{I\text{O}_2} = 70\%, \ V_T = 500 \text{ cc}, \ RR = 14, \ I:E \text{ ratio} = 1:2, \) and \( \text{PEEP} = 5 \text{ cm H}_2\text{O}, \) the patient has a peak inspiratory pressure of 55 cm \( \text{H}_2\text{O}. \) In this situation, the patient has several problems. Similar to the
last patient, he has a mixed metabolic and respiratory acidosis. He is also hypoxic, and his lungs are noncompliant.

Compliance = Δ volume/Δ pressure

The patient’s airway pressures are high and a potentially toxic level of inspired oxygen is being administered ($F_{1}O_2 > 60\%$), both of which can lead to further lung injury. One approach to this patient would be to increase the minute ventilation and increase the $F_{1}O_2$. The minute ventilation could be increased by increasing the $V_T$, increasing the RR, or increasing both. Both maneuvers, however, would increase the peak inspiratory pressure and likely would contribute to worsening barotrauma. Increasing the already high $F_{1}O_2$ would increase the potential for the formation of reactive oxygen species and free radicals. Barotrauma and oxygen toxicity can increase the severity of the patient’s ARDS.

An alternative approach to this case would be to accept the respiratory acidosis and use permissive hypercapnea as a lung protective strategy. Increasing the mean airway pressure by increasing the PEEP or decreasing the I:E ratio from 1:2 to 1:1.5 or 1:1 usually will result in improved
oxygenation by means of alveolar recruitment (inflating collapsed alveoli). A combination of both strategies could be used, as this may allow decreasing the \( F_1O_2 \) to a less-than-toxic level. Increasing the PEEP not only improves oxygenation, but also may improve lung compliance. Improving lung compliance decreases the difference between peak pressure and PEEP (\( \Delta P \)). It is the \( \Delta P \), not the peak pressure, which is the primary determinant of shear forces, and high shear forces lead to further injury of the lung. The improved compliance leads to less pressure needed to properly inflate the lung, reducing barotrauma.

Another lung protection strategy is to accept low-normal oxygen saturations. Specifically, accepting an oxygen saturation of about 92% (with a PO\(_2\) in the 60 mm Hg range) can minimize the F\(_1O_2\) required. It is important to remember that the primary determinant of \( O_2 \) delivery is hemoglobin \( O_2 \) saturation. There is little improvement in oxygen delivery by increasing the oxygen saturation to 96% or 98% from 92%. By increasing the F\(_1O_2\) to levels greater than 60%, however, there is a much greater potential for lung injury because of \( O_2 \) toxicity.

In summary, a sound approach to ventilator management for this patient with both sepsis and systemic inflammatory response syndrome (SIRS) would include increasing the PEEP, decreasing the I:E ratio, accepting a mild-to-moderate respiratory acidosis, and accepting an \( O_2 \) saturation of approximately 92%. This would minimize the potential for further lung injury while providing adequate oxygen delivery and adequate removal of CO\(_2\). As with the prior patient, addressing the patient’s metabolic acidosis with an appropriate fluid resuscitation would be necessary. The initial approach (increasing the minute ventilation and inspired oxygen concentration) could have led to worsening lung injury, resulting in worsening lung compliance and worsening hypoxia.

**Case 4—weaning the previously healthy patient from mechanical ventilation**

A common problem faced in the ICU is weaning patients from mechanical ventilation. Inappropriate use or incorrect analysis of ABG data can lead to unnecessarily prolonged periods of mechanical ventilation and ICU stay. In weaning patients, critical care physicians typically use weaning modes of ventilation such as pressure support or continuous positive airway pressure and, decreasing the amount of support a patient receives as he or she improves. In addition to mechanical ventilation, these patients also commonly receive some degree of sedation to tolerate endotracheal intubation, mechanical ventilation, and wound pain. A fairly common ABG for this type of patient on a weaning mode of ventilation such as pressure support (PS) with settings of PS of 12 cm H\(_2\)O, F\(_1O_2\) = 40% and PEEP of 5 cm H\(_2\)O would be as follows:

\[
pH \, 7.36, \, PCO_2 \, 50 \, mm \, Hg, \, PO_2 \, 95 \, mm \, Hg, \, and \, an \, O_2 \, saturation \, of \, 96%.
\]
This ABG is consistent with a respiratory acidosis with metabolic compensation. Approaches to a patient who has these ABG results may be to increase his or her pressure support or switch to a controlled mode of ventilation. It is important to make decisions such as these based on the patient’s clinical condition and vital signs, however. If such a patient had a RR of 16 with good tidal volumes and appeared comfortable, the etiology for his or her respiratory acidosis likely would be mild respiratory depression caused by sedation. Placing this patient on increased pressure support is unnecessary and would only increase both the time requiring mechanical ventilation and the potential for associated morbidity such as ventilator-associated pneumonia and decubitus ulcers. A better approach would be to continue the patient’s weaning by decreasing pressure support or making no ventilator setting changes and simply observing his or her ongoing clinical course.

Case 5—weaning the patient with pre-existing lung disease from mechanical ventilation

This scenario is similar to Case 4. In this case, however, the patient had chronic obstructive pulmonary disease (COPD) with a PCO$_2$ = 60 mm Hg and PO$_2$ = 60 mm Hg on 21% O$_2$ (room air) before perforating his or her bowel. This injury required surgical intervention, resulting in prolonged mechanical intervention and several weeks of ICU care. Before the perforation (ie, in the patient’s baseline condition), the patient would be expected to have a bicarbonate level of 32 mmol/L.

\[
\text{Bicarbonate correction} = 4 \text{ mmol/L for each 10 torr change in PCO}_2 \\
+ \text{“normal bicarbonate level”}
\]

\[
\text{Bicarbonate correction} = (4 \text{ mmol/L})(60 \text{ torr} - 40 \text{ torr})/10 \\
+ 24 \text{ mmol/L}
\]

\[
\text{Bicarbonate correction} = 8 \text{ mmol/L} + 24 \text{ mmol/L}
\]

\[
\text{Bicarbonate correction} = 32 \text{ mmol/L}
\]

The pH is calculated using the Henderson-Hasselbach equation as follows:

\[
\text{pH} = 6.1 + \log([\text{HCO}_3^-]/[(.03)(\text{PCO}_2)])
\]

\[
\text{pH} = 7.35
\]

This patient’s lung disease will not be corrected by his or her ICU stay, and, if anything, it may worsen. In this case, the ABG during weaning may be:

pH 7.32, PCO$_2$ 65, PO$_2$ 78, HCO$_3$ 34 on F$_1$O$_2$ of 40%.

This patient has baseline lung disease and CO$_2$ retention. This patient has metabolic compensation for his or her chronic respiratory acidosis that is worse than baseline because of a combination of sedative medications and
deconditioning caused by prolonged ventilatory support. If the patient appeared comfortable with no clinical evidence of respiratory insufficiency, there would be no indication to increase ventilatory support. Furthermore, efforts to correct the patient’s bicarbonate to normal (eg, by administering acetazolamide) would make weaning more difficult or impossible by forcing the patient to produce an unobtainable minute ventilation to correct his or her pH. One caveat of this approach is that most patients do not arrive in the ICU with baseline ABGs, especially with emergent admissions. In this case, a best guess of the patient’s baseline ABG based on the patient’s history is made.

Other laboratory tests

As previously mentioned, arterial blood gas analysis is the primary modality for monitoring respiratory status. There are other clinically useful laboratory tests, however. Venous blood gas analysis is useful for ventilator management if arterial blood samples are not easily available and there is an alternate way to measure a patient’s oxygenation. Monitoring serum electrolytes also gives information about respiratory issues. Finally, if patients are failing to wean from the ventilator, checking adrenal and thyroid function may identify relatively easy-to-treat etiologies for persistent respiratory failure.

Venous blood gas

In the ICU, access to arterial blood usually is accomplished through the use of an arterial catheter. As a patient’s clinical status improves, the risks associated with an arterial line such as infection and vascular injury often outweigh the benefits. Without an arterial catheter, obtaining an arterial blood sample would require a skin puncture, which is uncomfortable, and, after a prolonged ICU course, could prove difficult. Most patients admitted to an ICU for a prolonged period of time, however, have a central venous catheter. The information obtained from a venous blood gas (VBG), specifically the pH and the PCO$_2$, can be very useful. Because a VBG provides little information about a patient’s arterial blood oxygenation, the patient’s O$_2$ saturation must be available from an alternate source such as a pulse oximeter. Normal values for venous pH and PCO$_2$ at the University of Rochester Medical Center are pH: 7.32 to 7.42 and P$_v$CO$_2$: 40 mm Hg to 50 mm Hg.

Kelly and colleagues [3] compared arterial and venous samples on 246 patients admitted to the emergency department and found that the difference in pH values ranged from −0.16 to +0.06 units, with the average being −0.04 units. The P$_v$CO$_2$ will vary somewhat depending on the sample site, determined by the metabolic activity of the area of venous drainage. It is for this reason that a mixed venous sample will give the most reliable PCO$_2$ for the whole body. A mixed venous sample is obtained from the
pulmonary artery and represents a mixing of all of the blood returning to the heart. A normal mixed venous PCO\(_2\) is 46 mm Hg. Clearly, needing a pulmonary artery catheter adds risk to the patient. In general, the PCO\(_2\) should be about 4 to 8 mm Hg higher than the arterial PCO\(_2\). An example using the VBG is described in the following section.

**Serum electrolytes**

Serum electrolytes, particularly serum bicarbonate, are also of use in monitoring ventilation. Patients recovering from sepsis or SIRS often will have significant edema. If these patients also have concomitant lung disease, they may require significant diuresis in order the successfully wean from the ventilator. Unfortunately, a forced diuresis can lead to a significant metabolic alkalosis. It is important to determine whether a patient is alkalemic for two reasons. First, because of the shift of the O\(_2\)-hemoglobin dissociation curve seen with alkalemia, O\(_2\) will be bound more tightly to hemoglobin, making O\(_2\) delivery to the tissues more difficult (see Fig. 1). This may result in tissue hypoxia. Second, failure to recognize that this is a metabolic compensation for a respiratory acidosis could result in the wrong therapy. This situation could be determined by obtaining the blood pH by means of a VBG. An acidotic pH would indicate a respiratory acidosis with metabolic compensation, and no pharmacologic correction of the bicarbonate would be necessary. An alkalemic pH, however, would indicate a contraction alkalosis that should be treated. In this case, the metabolic alkalosis is treated commonly with a carbonic anhydrase inhibitor such as acetazolamide.

**Serum cortisol level**

Adrenal insufficiency is relatively common in critically ill patients, with one study reporting an incidence as high as 36% [4]. The adrenal insufficiency usually represents relative dysfunction of the adrenals as opposed to true adrenal failure. Nevertheless, it can cause significant problems for affected patients, including respiratory failure and vasopressor-resistant hypotension and shock.

Huang and Lin [5] performed a prospective, randomized, placebo-controlled double-blinded study on 93 patients requiring mechanical ventilation in a tertiary care teaching hospital. They started with 472 patients and excluded those successfully extubated within 72 hours, those with hemodynamic instability, those already receiving steroids, and those with a severe neurologic injury. Out of the 93 remaining patients, 70 met the criteria for adrenal insufficiency and were randomized to receive either stress-dose steroids or placebo. They then compared three groups: patients with adequate adrenal reserve, patients with inadequate adrenal reserve receiving steroid replacement, and patients with inadequate adrenal reserve but receiving
no replacement (placebo group). Successful ventilator weaning was significantly higher in the adequate adrenal function (88.4%) and stress-dose treatment (91.4%) groups than in the placebo group (68.8%).

Despite these results, the diagnosis and treatment of adrenal insufficiency in the ICU are somewhat controversial. Most would agree that a morning cortisol level less than 25 μg/dL and failure to elicit at a 9 μg/dL rise in cortisol level in response to high-dose cosyntropin stimulation represents adrenal insufficiency. Some would argue that these criteria are too strict and may exclude patients with treatable adrenal insufficiency. Nonetheless, using these criteria, most patients with adrenal insufficiency should be identified. Huang’s study provides good evidence that treating these patients can improve the chances of success of weaning them from mechanical ventilation.

**Thyroid function tests**

In the ICU, hypothyroidism can result in respiratory failure, congestive heart failure, central nervous system (CNS) dysfunction, and hyponatremia. For patients who have hypothyroidism on mechanical ventilation, respiratory failure may be attributed to decreased hypoxic and hypercapnic ventilatory drive. Respiratory muscles also are noted to be weak. For patients not yet intubated and requiring mechanical ventilation, an enlarged tongue and obstructive sleep apnea can contribute to respiratory failure. Rarely, a large goiter can cause upper airway obstruction and subsequent respiratory compromise [6]. Other contributing factors include alveolar hypoventilation and pleural effusion.

Martinez and colleagues [7] studied three patients who had confirmed hypothyroidism and respiratory failure and found that all three had diaphragmatic dysfunction corrected with adequate hormone replacement. Datta and Scalise [8] performed a retrospective study on 173 patients admitted to a regional weaning facility for failure to wean from mechanical ventilation. Of those 173 patients, 140 had screening thyroid-stimulating hormone (TSH) levels obtained on admission. Seventeen patients (12%) were found to have elevated TSH levels, and low serum tri-iodothyronine (T3) and/or low thyroxine (T4) levels confirmed the diagnosis of hypothyroidism in four (3%) patients. With the addition of thyroid replacement therapy, three patients were weaned from mechanical ventilation successfully. The fourth patient died from unrelated causes. The authors concluded that hypothyroidism is an uncommon cause of failure to wean from mechanical ventilation, but because it is an easily treatable cause, it should be considered in all patients who fail to wean from mechanical ventilation.

Laboratory tests used to make the diagnosis of hypothyroidism include T4 and TSH levels as noted previously and the free thyroxine level (FT4). Classically, decreased T4 and FT4 levels with an elevated TSH level are seen in primary hypothyroidism, and decreased T4 and FT4 levels with a low or normal TSH level are seen in secondary hypothyroidism. Making
the diagnosis of secondary hypothyroidism, however, can be difficult. Many severely ill patients are found to have low serum T4 concentrations with normal or low TSH concentrations, and the FT4 concentration may be low, normal, or high. In these cases, most patients have nonthyroidal illness (euthyroid sick syndrome) and should have follow-up thyroid function tests after recovery from their acute illness. If there is other evidence of pituitary or hypothalamic disease, the diagnosis of secondary hypothyroidism should be considered [6].

**Phosphate level**

Phosphate is the most abundant intracellular anion. It is necessary for ATP production, and it is a component of DNA, RNA, and 2,3-diphosphoglycerate (2,3-DPG). The normal serum phosphate range is 2.5 to 4.5 mg/dL (0.81 to 1.45 mmol/L) in adults. Hypophosphatemia is defined as mild (2 to 2.5 mg/dL or 0.65 to 0.81 mmol/L), moderate (1 to 2 mg/dL or 0.32 to 0.65 mmol/L), or severe (<1 mg/dL or 0.32 mmol/L) [9]. Mild hypophosphatemia has nonspecific manifestations such as myalgias, weakness, and anorexia. Severe hypophosphatemia may cause tetany, seizures, coma, rhabdomyolysis, and ventricular tachycardia [10]. Severe hypophosphatemia is also a clear cause for acute respiratory failure. Less clear is whether moderate or mild hypophosphatemia can contribute to respiratory failure and inability to wean from the ventilator. Respiratory insufficiency and failure to wean likely can be attributed to weakness caused by insufficient ATP production. Furthermore, inadequate 2,3-DPG production can hinder respiratory function by shifting the O₂-hemoglobin dissociation curve to the left (see Fig. 1). It should be noted that serum phosphate levels may not reflect phosphate content in respiratory muscles accurately. Fiaccadori and colleagues [11] demonstrated significant phosphorus depletion in the respiratory muscles of COPD patients when compared with patients with normal lung function. No correlation with serum phosphorus levels was demonstrable in these patients, however.

When confronted with a patient with an unclear etiology for his or her respiratory failure, it is logical to rule out hypophosphatemia as a cause. Although it is unclear how relevant a mild or moderate serum phosphorus level may be, it is reasonable to correct deficiencies regardless of severity, especially if the etiology for the respiratory failure is unclear.

**Summary**

Laboratory analysis is clearly necessary for the effective management of most patients receiving mechanical ventilation in the ICU. Blood gas analysis, using either arterial or venous samples, is the mainstay of management. Serum bicarbonate levels noted on serum electrolyte analysis are often useful in ventilator management. When patients have persistent, unexplained
respiratory failure, however, it is also prudent to check adrenal function, thyroid function, and phosphate levels.

References