4.5: Compensation

4.5.1: The compensatory response is a rise in the bicarbonate level

This rise has an immediate component (due to a resetting of the physicochemical equilibrium point) which raises the bicarbonate slightly.

Next is a slower component where a further rise in plasma bicarbonate due to enhanced renal retention of bicarbonate. The additional effect on plasma bicarbonate of the renal retention is what converts an "acute" respiratory acidosis into a "chronic" respiratory acidosis.

As can be seen by inspection of the Henderson-Hasselbalch equation (below), an increased [HCO$_3^-$] will counteract the effect (on the pH) of an increased pCO$_2$ because it returns the value of the $\frac{[HCO_3^-]}{0.03pCO_2}$ ratio towards normal.

$$\text{pH} = pK_a + \log \frac{[HCO_3^-]}{0.03pCO_2}$$

4.5.2: Buffering in Acute Respiratory Acidosis

The compensatory response to an acute respiratory acidosis is limited to buffering.

By the law of mass action, the increased arterial pCO$_2$ causes a shift to the right in the following reaction:

$$(CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-)$$
In the blood, this reaction occurs rapidly inside red blood cells because of the presence of carbonic anhydrase. The hydrogen ion produced is buffered by intracellular proteins and by phosphates. Consequently, in the red cell, the buffering is mostly by haemoglobin. This buffering by removal of hydrogen ion, pulls the reaction to the right resulting in an increased bicarbonate production. The bicarbonate exchanges for chloride ion across the erythrocyte membrane and the plasma bicarbonate level rises. In an acute acidosis, there is insufficient time for the kidneys to respond to the increased arterial pCO$_2$ so this is the only cause of the increased plasma bicarbonate in this early phase. The increase in bicarbonate only partially returns the extracellular pH towards normal.

Empirically, the [HCO$_3^-$] rises by 1 mmol/l for every 10mmHg increase in pCO$_2$ above its reference value of 40mmHg. For example, if arterial pCO$_2$ has risen acutely from 40mmHg to 60mmHg (due to decreased alveolar ventilation) then this acute rise of 2 tens (i.e. 60-40=20mmHg rise) results in a rise of plasma bicarbonate by 2 from its reference value of 24mmol/l up to 26 mmol/l. Consequently, we would predict that if this acute respiratory acidosis was the only base disorder present, then plasma bicarbonate would be 26mmol/l.

Though very important for carriage of carbon dioxide in the blood, the bicarbonate system is not itself responsible for any buffering of a respiratory acid-base disorder. This is because a system cannot buffer itself. If HCO$_3^-$ were to react with H$^+$ produced from the dissociation of H$_2$CO$_3$ this would just produce H$_2$CO$_3$ again - reversing the reaction is not 'buffering'.

Ninety-nine percent of the buffering of an acute respiratory acidosis occurs intracellularly. Proteins (especially haemoglobin in red cells) and phosphates are the most important buffers involved. These take up the H$^+$ produced from the dissociation of H$_2$CO$_3$. This intracellular buffering results in a further increase in intracellular [HCO$_3^-$] because it pulls the CO$_2$ hydration reaction to the right. The HCO$_3^-$ that leaves the cell causes the rise in extracellular HCO$_3^-$. The amount of buffering is limited by the concentration of protein as that is low relative to the amount of carbon dioxide requiring buffering.

In summary: Compensation for an acute respiratory acidosis is by intracellular buffering and plasma bicarbonate rises slightly as a result of this buffering. The buffering is predominantly due to intracellular proteins; the bicarbonate system does not contribute to this buffering.

4.5.3: Chronic Respiratory Acidosis: Renal Bicarbonate Retention

With continuation of the acidosis, the kidneys respond by retaining bicarbonate.

If the respiratory acidosis persists then the plasma bicarbonate rises to an even higher level because of renal retention of bicarbonate.

Thus in a chronic respiratory acidosis there are TWO factors present which elevate the plasma bicarbonate:-

- Firstly: The acute physicochemical change and consequent buffering esp by intracellular protein. (Immediate onset - as occurs with an acute respiratory acidosis.)
- Secondly: The renal retention of bicarbonate as renal function is altered by the elevated arterial pCO$_2$ and
additional bicarbonate is added to the blood passing through the kidney. (Slow onset)

Studies have shown that an average 4 mmol/l increase in \([HCO_3^-]\) occurs for every 10mmHg increase in pCO$_2$ from the reference value of 40mmHg. For example, if arterial pCO$_2$ has risen from 40mmHg to 60mmHg (due to decreased alveolar ventilation) and remained elevated for several days, then this chronic rise of "2 tens" (i.e. 60-40=20mmHg rise = 2 rises of 10mmHg) results in a rise of plasma bicarbonate by 8 from its reference value of 24mmol/l up to 32 mmol/l. Consequently, we would predict that if this chronic respiratory acidosis was the only base disorder present, then plasma bicarbonate would be 32mmol/l.

The renal response is underway by 6 to 12 hours with a maximal effect reached by 3 to 4 days. This maximal effect is not sufficient to return plasma pH to normal, but because of the additional renal contribution, the pH is returned towards normal much more than occurs in an acute respiratory acidosis.

The response occurs because increased arterial pCO$_2$ increases intracellular pCO$_2$ in proximal tubular cells and this causes increased H$^+$ secretion from the PCT cells into the tubular lumen. This results in:

- increased HCO$_3^-$ production which crosses the basolateral membrane and enters the circulation (so plasma [HCO$_3^-$] increases.)
- increased Na$^+$ reabsorption in exchange for H$^+$ and less in exchange for Cl$^-$ (so plasma [Cl$^-$] falls)
- increased 'NH$_3$' production to 'buffer' the H$^+$ in the tubular lumen (so urinary excretion of NH$_4$Cl increases)

4.5.4: 'Maximal compensation' versus 'full compensation'?

The increase in plasma [HCO$_3^-$] results in an increase in amount of bicarbonate filtered in the kidney and this amount increases as plasma bicarbonate continues to increase. Eventually a new steady state is reached which is referred to as maximal compensation.

This level of compensation has long been believed to be less than that required to return the plasma pH to normal. That is the actual compensation ('maximal compensation') is less than 'full compensation'. If the pH was found to actually be within the normal range, the interpretation of this was that there was a co-existing metabolic alkalosis (e.g. due to use of diuretics or corticosteroids) or there had been transient hyperventilation from the stress of arterial puncture.

A recent study$^1$ examined the actual maximal response in a group of patients with stable chronic hypercapnic respiratory failure without a clinical condition or medications those could cause a metabolic alkalosis. The majority of these patients had pH values in the normal range as the compensation was greater than that predicted by the classic 4 for 10 rule. They found that bicarbonate increased by 5.1 mmols/l for every 10mmHg pCO$_2$ rise.

Consequently, a diagnosis of mild metabolic alkalosis should not be made in patients with stable chronic respiratory acidosis with pH values in the normal range unless there is other evidence (e.g. use of thiazide or loop diuretics, or corticosteroids) consistent with the diagnosis.

In summary, the compensation for hypercapnia is:

https://med.libretexts.org/Bookshelves/Anatomy_and_Physiology/Book%3A_Acid-base_pHysiology_(Brandis)/Chapter_4%3A…

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• Acute: Buffering only and predominantly intracellular (99%)
• Chronic: Renal retention of bicarbonate (in addition to buffering)

Summary notes about the compensation terms

**Maximal compensation** refers to the actual maximal amount of compensation that is typically seen in a patient with a simple acid-base disorder.

**Full compensation** refers to the amount of compensation that would correct the pH all the way back to within the normal range.

The general rule for all acid-base disorders is that the body's compensatory response is almost never sufficient to return the plasma pH to normal. If the pH is normal then it suggests that a second, compensating acid-base disorder is present. Contrary to this 'classic' teaching, a recent paper suggests that in many patients with chronic stable hypercapnia, compensation may be sufficient to return pH to within the normal range.

4.5.5: Differing time courses of compensation and correction

The situation may be complicated because of the differing time courses of compensation & correction. Consider a couple of typical situations which sometimes cause confusion in interpretation:

**Scenario 1**

Correction of a chronic respiratory acidosis can occur more rapidly than correction of the renal compensation so it is possible that the blood gases in an individual patient may appear to show 'full compensation' if the alveolar ventilation has increased and before the kidneys have had time to adjust. The stimulation of being in the Emergency Room may result in such a situation and the snapshot provided by a single set of gases may reveal such a situation. (Remember this when the junior doctor alights upon such a set of results and says, "But I thought you said that compensation never ‘fully’ returns the pH to normal but this is what has happened here?")

**Scenario 2**

If a patient with chronic respiratory acidosis is intubated and ventilated, the arterial pCO$_2$ can be rapidly corrected (by adjusting the ventilator parameters). This can occur quite rapidly, but the elevated bicarbonate takes longer longer than this to fall. The situation can be more complicated because some such patients have additional factors which inhibit the ready excretion of the elevated bicarbonate, as occurs in 'post-hypercapnic metabolic alkalosis'.

References

1. Martinu T, Menzies D, and Dial S. *Re-evaluation of acid-base prediction rules in patients with chronic respiratory acidosis.* Can Respir J 2003 Sep; 10(6) 311-5. PubMed *[See also the accompanying editorial]*