**Electrolyte quintet**

### Acid-base

Stephen L Gluck

Acid-base disorders are common clinical problems resulting from a wide variety of pathophysiological conditions, including newly recognised acquired and genetic causes. The history and physical examination and measurement of blood and urinary indices allow identification of the underlying cause of these disorders in most cases. Treatment directed at correction of electrolyte abnormalities and the underlying cause for the disorder is essential for preventing the acute and long-term metabolic consequences of acid-base derangements.

#### Acid-base homoeostasis

The extracellular fluid (ECF) contains about 350 mmol of bicarbonate buffer. Every day metabolism produces acid (as H+) to a total of about 70 mmol (1 mmol/kg) as non-volatile sulphuric acid (25 mmol) from aminoacid catabolism, non-metabolised organic acids (40 mmol) and phosphoric and other acids. The kidney reabsorbs all of the filtered bicarbonate (HCO$_3^-$) and generates new bicarbonate in the collecting duct. The proximal tubule reabsorbs some 85% (3800 mmol) daily of filtered HCO$_3^-$, and the thick ascending limb reabsorbs 10% (450 mmol). In the collecting duct, proton secretion titrates the remaining luminal HCO$_3^-$, and buffering of secreted protons by non-bicarbonate buffers in the tubular lumen, mainly phosphate and ammonia, enables the cells to generate new HCO$_3^-$.

The rate of secretion of hydrogen ions (H+, protons) is affected by several factors, including luminal pH, systemic pCO$_2$, mineralocorticoids, and the potential difference across the collecting duct. The renal cortical segment of the collecting duct normally has a potential difference of −30 to −60 mV, arising largely from sodium reabsorption, and this is an important driving force for H+ secretion. The amount of ammonium ion (NH$_4^+$) accumulating in the collecting duct increases as urinary pH becomes more acidic. Urinary ammonia is generated in mitochondria of the proximal tubule by deamination of glutamine. Ammonia production is subject to physiological regulation, adding a mechanism for control of nett acid excretion independent of the rate of distal H+ secretion; the rate of ammonia production per nephron is increased by metabolic acidosis, potassium (K+) depletion, glucocorticoids, loss of functional renal mass, and other factors, and is suppressed by hyperkalaemia. Under normal steady-state conditions, the nett quantity of acid secreted and the consequent renal generation of new bicarbonate equals the rate of metabolic proton generation, preserving H+ balance. When that balance is disturbed the consequence is acidosis or alkalosis.

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### Metabolic acidosis

**Metabolic effects of H+ retention**

In metabolic acidosis non-volatile acid accumulates or HCO$_3^-$ is lost at a rate that induces pathophysiological responses, and this can happen even when the plasma [HCO$_3^-$] is normal. “Non-volatile acid” refers to acids other than carbonic acid or CO$_2$, and I shall use the term acid interchangeably with non-volatile acid unless otherwise stated. Nett retention of H+, which occurs either by increased intake or generation of acid or by loss of HCO$_3^-$, activates three adaptive physiological responses—namely, buffering, increased ventilation, and increased renal reabsorption and generation of HCO$_3^-$. Retained acid is titrated by both extracellular HCO$_3^-$ and “cellular” buffers (mainly bone mineral and skeletal muscle). If the retention of acid is great enough, ventilation is stimulated within minutes, principally by increasing ventilatory volume (Kussmaul respirations). The kidney responds to nett accumulation of acid by increasing HCO$_3^-$ reabsorption in the proximal tubule and thick ascending limb, increasing H+ secretion in the distal tubule and collecting duct, and increasing production of the urinary buffer ammonia, augmenting renal HCO$_3^-$ generation through increased excretion of NH$_4^+$. Under normal conditions, daily NH$_4^+$ excretion is about 30 mmol (0.5 mmol/kg); it can increase to 280 mmol (4 mmol/kg, or 1.5 mmol/mL glomerular filtrate) but that response requires several days.

The normal range for excretion of the tricarboxylic anion citrate is 1–2 mmol (200–400 mg). Citrate excretion is greatly diminished by metabolic acidosis induced by administration of ammonia chloride.

**Evaluation of patient with low plasma [HCO$_3^-$]**

Evaluation of a patient with a low [HCO$_3^-$] should begin with arterial blood gases to exclude primary hyperventilation and with calculation of the serum unmeasured anions, the “anion gap”. The normal anion gap of 12 mmol/L arises primarily from serum albumin so the estimate has to be adjusted for albumin. Indeed the anion gap can be altered by several factors apart from unmeasured anions. However, it does help to distinguish metabolic acidosis due to accumulation of unmeasured acid anions (chiefly organic acids) from metabolic acid due to loss of HCO$_3^-$. 

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Metabolic acidosis with increased anion gap

Ingested or metabolically generated organic anions have three possible fates (panel 1). The initial addition of the organic acid to plasma results in the titration of HCO₃⁻ to bicarbonate and there is no nett change in plasma HCO₃⁻ concentration. Inadequate renal HCO₃⁻ excretion in disorders ascribable entirely to accumulation of unmeasured anions, the reduction in the serum [HCO₃⁻] matches the anion gap. When this is not the case, a second acid-base disorder (such as hyperchloraemic acidosis or metabolic alkalosis) may be present, although this notion has been challenged. When metabolic alkalosis and acidosis coexist, as in vomiting and ketoacidosis, the plasma [HCO₃⁻] may be normal, and a raised anion gap may be the initial evidence of underlying acid-base disturbances.

Normal anion gap (hyperchloraemic acidosis)

Hyperchloraemic acidosis is a consequence of nett retention of HCl or metabolic equivalent (eg, NH₄Cl and chloride salts of aminoacids) or loss of NaHCO₃, or metabolic equivalent (eg, excretion of salts of organic anions in proportionate excess of chloride, panel 1). In normal plasma, the quotient [HCO₃⁻]/[Cl⁻] is well above 0:25. Loss of bicarbonate may occur from the gastrointestinal tract via diarrhoea or a biliary fistula, for example, or from renal excretion of HCO₃⁻ or its equivalent, or from renal HCO₃⁻ generation insufficient to match acid intake or production.

Renal causes of HCO₃⁻ loss may be distinguished from non-renal causes by measurement of the urinary [NH₄⁺] excretion. In a setting of hyperchloraemic acidosis, a daily urinary [NH₄⁺] excretion of less than 1 mmol/kg is abnormal, indicating that the kidney is a primary cause of the abnormality. If urinary [NH₄⁺] measurement is not readily available it can be estimated from the urinary anion gap (which may be misleading in the presence of large amounts of organic anions), or from the urinary osmolar gap, and the calculations are given in the glossary. If a 24 h urine collection is impracticable, a creatinine measurement on a random urine sample may be used to estimate the total daily excretion of NH₄⁺ (or any other solute). A random urine sample may be used to distinguish among the causes of hyperchloraemic acidosis (panel 2).

Acidosis with abnormal urinary [NH₄⁺]

Gastrointestinal loss of HCO₃⁻ from drainage of gastrointestinal secretions or from diarrhoea produces a hyperchloraemic acidosis if the rate of loss exceeds the capacity for renal HCO₃⁻ generation. Effective bicarbonate loss may also result from ingestion of organic acids with subsequent loss of the sodium or potassium salt in the stool.

Generation of large amounts of organic anion produces a hyperchloraemic acidosis if anion excretion is rapid enough to prevent accumulation of the anion in plasma. Causes include ketoacidosis (as in recovery from diabetic ketoacidosis), hippuric aciduria from the metabolism of ethylene glycol, and ethylene glycol produces calcium oxalate crystalluria.

Panel 1: Fate of ingested or generated organic acids and effect on acid-base status

| Metabolism | nNaHCO₃+HA→NaA+(n-1)NaHCO₃+CO₂+H₂O NaA→NaHCO₃ |
| Nett reaction | HA→CO₂+H₂O |
| Excretion | nNaHCO₃+HA→NaA+(n-1)NaHCO₃+CO₂+H₂O NaA→Urinary excretion |
| Nett reaction | HA+NaHCO₃→(n-1)NaHCO₃ |
| Accumulation | nNaHCO₃+HA→NaA+(n-1)NaHCO₃+CO₂+H₂O |
| Nett reaction | NaHCO₃+HA→NaA+(n-1)NaHCO₃ |

Glossary of equations

Anion gap [Na⁺]+[K⁺]–[Cl⁻]
Total daily \( U_{\text{NH₄⁺}}=U_{\text{NH₄⁺}}+U_{\text{Cl⁻}}\times[(140–\text{age})/50]\times\text{lean body weight} \)
\( * \)For men; multiply by 0:85 for women.

**Urinary unmeasured anion concentration** (sum of urinary K⁺, NH₄⁺, and Na less Cl⁻) estimates sum of urinary sulphate and organic anion concentrations.

**Panel 2: Evaluation of hyperchloraemic acidosis**

<table>
<thead>
<tr>
<th>Urinary solutes</th>
<th>NH₄⁺</th>
<th>Cl⁻</th>
<th>A⁻</th>
<th>Na⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gl tract HCO₃⁻ loss</td>
<td>( \uparrow )</td>
<td>( \downarrow )</td>
<td>( \leftrightarrow )</td>
<td>( \leftrightarrow )</td>
</tr>
<tr>
<td>Generated/ingested organic acids</td>
<td>( \uparrow )</td>
<td>( \leftrightarrow )</td>
<td>( \leftrightarrow )</td>
<td>( \leftrightarrow )</td>
</tr>
<tr>
<td>HCl intake or equivalent *</td>
<td>( \uparrow )</td>
<td>( \leftrightarrow )</td>
<td>( \leftrightarrow )</td>
<td>( \leftrightarrow )</td>
</tr>
<tr>
<td>Inadequate renal HCO₃⁻</td>
<td>( \downarrow )</td>
<td>( \leftrightarrow )</td>
<td>( \leftrightarrow )</td>
<td>( \leftrightarrow )</td>
</tr>
<tr>
<td>Renal HCO₃⁻ loss</td>
<td>( \leftrightarrow )</td>
<td>( \leftrightarrow )</td>
<td>( \leftrightarrow )</td>
<td>( \leftrightarrow )</td>
</tr>
</tbody>
</table>

*NH₄Cl, chloride salts of aminoacids or dilutional acids; \( \leftrightarrow \) designates normal; \( a \) NH₄⁺, >1 mmol/kg daily; \( b \) FE₄, <0:5; \( c \) FE₄, <0:5; \( d \) A=100 mmol/daily; \( e \) FE₄, >1:0; \( f \) FE₄, >1:0; \( g \) NH₄⁺, <1 mmol/kg daily; \( P₃ \times \text{urea} \) FE-fractional excretion of a solute; Urinary unmeasured anion concentration (sum of urinary K⁺, NH₄⁺, and Na less Cl⁻) estimates sum of urinary sulphate and organic anion concentrations.

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toule (glue-sniffing), or D-lactate aciduria in short-bowel syndrome.

Administration of NH₄Cl or chloride salts of aminoacids produces a hyperchloraemic acidosis by metabolism to HCl. Administration of other chloride salts may produce a “dilutional acidosis”, when there is a nett retention of Cl⁻, as in ECF volume depletion and congestive heart failure or with rapid intravenous saline.

Decreased [NH₄⁺]
Abnormalities in the renal regeneration or reabsorption of HCO₃⁻ are the principal causes of hyperchloraemic acidosis with reduced NH₄⁺ excretion. This renal tubular acidosis (RTA) may be distinguished on the basis of the urinary pH in response to changes in the plasma [HCO₃⁻] (figure). The urinary pH is 6 or less at a normal plasma [HCO₃⁻] of 24 mmol/L (point A), and lowering of the plasma [HCO₃⁻] values is often abnormal in distal RTA.

Several subtypes have been identified (panel 3). Patients with a collecting duct that is excessivly permeable to H⁺ (a “gradient” or “permeability” defect), as happens with amphotericin B administration, have a normal urinary pCO₂ in alkaline urine. Patients with an abnormally low rate of H⁺ secretion (“secretory defect”) have a normal pCO₂ as is often abnormal in distal RTA. Several subtypes have been identified (panel 3). Patients with a collecting duct that is excessivly permeable to H⁺ (a “gradient” or “permeability” defect), as happens with amphotericin B administration, have a normal urinary pCO₂ in alkaline urine. Patients with an abnormally low rate of H⁺ secretion (“secretory defect”) have a normal pCO₂ as is often abnormal in distal RTA. Several subtypes have been identified (panel 3). Patients with a collecting duct that is excessivly permeable to H⁺ (a “gradient” or “permeability” defect), as happens with amphotericin B administration, have a normal urinary pCO₂ in alkaline urine. Patients with an abnormally low rate of H⁺ secretion (“secretory defect”) have a normal pCO₂ as is often abnormal in distal RTA.

Renal tubular acidosis

Distal (type 1) RTA
In these disorders H⁺ secretion in the collecting duct or the ability to lower urinary pH is impaired. Patients cannot reduce their urine pH below 5.5, even in the presence of a severe metabolic acidosis. Administration of furosemide reduces urinary pH below 5.5 in normal people but not in patients with type 1 RTA. The urinary pCO₂ (or urine/blood pCO₂ difference) in alkaline urine is another index of H⁺ secretion in the collecting duct that is often abnormal in distal RTA.

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balance. Ammoniagenesis may be impaired by physiological suppression from hyperkalaemia or glucocorticoid insufficiency. Hyperkalaemia probably suppresses renal ammonia production by inhibiting HCO₃⁻, exit from the proximal tubule cell and raising the cell pH. The type 4 RTA of mineralocorticoid deficiency is a result of hyperkalaemia and suppression of ammonia production. Glucocorticoid is required both for the increase in skeletal muscle protein catabolism and in glutamine synthesis and for the enhanced renal ammoniagenesis observed in metabolic acidosis. Loss of functional renal mass impairs ammoniagenesis by decreasing the number of proximal tubule cells generating ammonia. Type 4 RTA is usually not apparent until 70–80% of nephrons have been lost, but hypercatabolic states in which H⁺ generation increases (eg, fever, severe illness, glucocorticoid administration, and hyperalimentation) may induce overt acidosis. In some renal diseases, such as urinary-tract obstruction, renal ammonia production is suppressed even though there is no loss of renal mass.

**Metabolic alkalosis**

**Mechanisms**

In normal acid-base homoeostasis two factors defend against metabolic alkalosis—the capacity of the kidney to excrete large amounts of HCO₃⁻ and the metabolic production of non-volatile acid. The kidney is highly efficient in excreting infused HCO₃⁻, and administration of Na₂CO₃ causes little or no increase in plasma [HCO₃⁻]. Even if 100% of the filtered HCO₃⁻ is reabsorbed, metabolic acid production consumes 1 mmol HCO₃⁻ daily for every kilogram of body weight. The generation of metabolic alkalosis thus requires both an increase in alkali addition (HCO₃⁻ generation) to the ECF and an impairment in renal HCO₃⁻ excretion.

**Alkali addition**

Alkali addition may occur from sources outside the kidney or from the kidney itself. Extrarenal sources include loss of gastric secretions (which removes HCl) through vomiting or nasogastric suction; redistribution of alkali from intracellular stores to the ECF, as happens in potassium or chloride depletion; and oral or parenteral administration of alkali as, for example, acetate salts of aminoacids in intravenous alimentation, citrate from transfusions, or via absorption of alkali from antacid and oral ion-exchange resins given together, the milk-alkali syndrome, or oral or intravenous HCO₃⁻.

Excessive generation of alkali in the kidney collecting duct occurs in response to sustained elevation of the pCO₂, increased mineralocorticoid activity, increased sodium delivery to the collecting duct, potassium deficiency, and delivery of impermanent anions to the collecting duct. Collecting duct H⁺ secretion is increased in response to hypercapnia, and may persist after return of the pCO₂ to normal. Mineralocorticoids, sodium delivery, and impermanent anions increase collecting-duct acidification by increasing sodium reabsorption and augmenting the lumen-negative potential. Mineralocorticoids also stimulate H⁺ secretion directly. Potassium deficiency stimulates H⁺ secretion in the distal nephron, increases the production of the urinary buffer ammonia, and may stimulate HCO₃⁻ generation by increasing collecting duct expression of an H⁺-K⁺-ATPase that reabsorbs K⁺ in exchange for H⁺ secretion.

**Impaired HCO₃⁻ excretion**

The primary defence against metabolic alkalosis is HCO₃⁻ excretion caused by a decrease in proximal tubule HCO₃⁻ reabsorption. In metabolic alkalosis, factors that can impair ability to excrete HCO₃⁻ include decreased glomerular filtration and stimulation of proximal tubule H₂CO₃ reabsorption (eg, by a raised pCO₂ and hormonal agents such as angiotensin II and norepinephrine, and K⁺ deficiency). K⁺ deficiency appears to act by increasing the inside-negative potential difference of the proximal tubule cells, stimulating cellular HCO₃⁻ exit.

A second renal mechanism in the defence against metabolic alkalosis is HCO₃⁻ secretion by Cl⁻/HCO₃⁻ exchange in the luminal membrane of the cortical collecting duct. In states of chloride depletion, with or without depletion of ECF volume, a reduction of chloride delivery to the collecting duct impairs HCO₃⁻ secretion. Chloride depletion also stimulates release of organic acids from stores. At first this lowers extracellular HCO₃⁻ but because K⁺ is also lost from cellular stores subsequent K⁺ depletion may perpetuate the alkalosis.

**Evaluation of patient with metabolic alkalosis**

Assessment of ECF volume, urinary electrolytes, and transtubular K⁺ gradient (TTKG, an index of K⁺ secretion) allow the underlying causes of metabolic alkalosis to be distinguished (panel 4). Common settings are conditions associated with primary increase in mineralocorticoid activity or with ECF depletion.

**Increased mineralocorticoid activity**

Mineralocorticoid (or mineralocorticoid-like) activity increases in primary hyperaldosteronism, Cushing’s syndrome, and congenital adrenal hyperplasia with 11β and 17β hydroxylase defects, and by ingestion of

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**Panel 4: Evaluation of metabolic alkalosis**

<table>
<thead>
<tr>
<th>Condition</th>
<th>ECF</th>
<th>U [Cl⁻]</th>
<th>U [Na⁺]</th>
<th>TTKG</th>
<th>U pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary increase in mineralocorticoid activity; pseudohyperaldosteronism syndromes</td>
<td>↑*</td>
<td>&gt;20</td>
<td>&gt;20</td>
<td>&gt;2</td>
<td>&lt;6</td>
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<tr>
<td>External alkali intake in renal failure</td>
<td>↑</td>
<td>&gt;20</td>
<td>&gt;20</td>
<td>..</td>
<td>&gt;6</td>
</tr>
<tr>
<td>External alkali intake in oedematous states</td>
<td>↑</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>..</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Post-hypercapnia (active)</td>
<td>↑</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>&gt;2</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Diuretics (active)</td>
<td>↑</td>
<td>&lt;20</td>
<td>&gt;20</td>
<td>&lt;6</td>
<td>&lt;8</td>
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<tr>
<td>Bartter’s syndrome</td>
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<td>&gt;20</td>
<td>&gt;20</td>
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<tr>
<td>Gastrocystoplasty</td>
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<td>&gt;20</td>
<td>&gt;20</td>
<td>&gt;6</td>
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<td>Magnesium deficiency</td>
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<td>&gt;20</td>
<td>&gt;20</td>
<td>&gt;6</td>
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<tr>
<td>Nasogastric suction and vomiting (active)</td>
<td>↑</td>
<td>&lt;20</td>
<td>&gt;20</td>
<td>&gt;6</td>
<td>&lt;8</td>
</tr>
<tr>
<td>Chloride diarrhoea</td>
<td>↓</td>
<td>&gt;20</td>
<td>&gt;20</td>
<td>&lt;2</td>
<td>..</td>
</tr>
<tr>
<td>Impermeable anion excretion</td>
<td>↑</td>
<td>&lt;20</td>
<td>&gt;20</td>
<td>&gt;2</td>
<td>5–6</td>
</tr>
<tr>
<td>Diuretics (prior), nasogastric suction and vomiting (prior)</td>
<td>↑</td>
<td>&lt;20</td>
<td>&lt;20</td>
<td>&lt;2</td>
<td>&lt;6</td>
</tr>
</tbody>
</table>

*Without oedema and hypertension present. †May be increased in oedematous states such as congestive heart failure.
compounds with mineralocorticoid activity. Primary mineralocorticoid excess produces alkalosis by inducing K⁺ deficiency and stimulating distal nephron Na⁺ reabsorption and H⁺ secretion. Not all patients with primary hyperaldosteronism have hypokalaemia, and the plasma-aldosterone/renin quotient may be used as a screening test in patients without renal insufficiency. Glucocorticoids in the physiological range do not have mineralocorticoid activity because of selective metabolism in collecting duct epithelial cells by 11β-hydroxysteroid dehydrogenase (11β-HSDH). When the capacity of that metabolic system is exceeded, as in Cushing’s syndrome or with steroid therapy, glucocorticoids do also exert significant mineralocorticoid activity. The drug carbamazepine, a mineralocorticoid (the active compound in liquorice) have mineralocorticoid-like properties and act by inhibiting renal 11β-HSDH.

Simple volume depletion raises angiotensin II and mineralocorticoid levels but seldom causes metabolic alkalosis because renal HCO₃⁻ generation is not increased. Distal flow rates and sodium delivery, two of the major factors affecting K⁺ secretion, will both decrease but the distal nephron undergoes an adaptive response that sustains K⁺ secretion. Nor does volume depletion increase the non-bicarbonate buffer required to generate more HCO₃⁻. Although angiotensin II does stimulate proximal ammoniagenesis this is probably counterbalanced by increased proximal tubule reabsorption. Isolated K⁺ deficiency produces little or no metabolic alkalosis because hypokalaemia inhibits aldosterone secretion.

In the clinical conditions that produce metabolic alkalosis, mineralocorticoid excess is accompanied by continued sodium delivery to the distal nephron, by potassium depletion, or both. Diuretics maintain high distal nephron flow rates and sodium delivery concomitantly with high aldosterone levels, which sustain a large potential difference in the distal nephron, promoting K⁺ excretion and H⁺ secretion. Bartter’s and Gitelman’s syndromes arise from genetic defects in salt transporters in the thick ascending limb and distal tubule, respectively; they are the physiological equivalents of regular high-dose loop or thiazide diuretics.

Nasogastric suction generates alkali by removing HCl; the Na₂CO₃ generated is partly excreted until the corresponding alterations in alveolar ventilation, resulting in loss of K⁺ and Cl⁻, inducing alkalosis. Impaired anions stimulate distal H⁺ secretion and K⁺ losses by increasing the potential difference of the collecting duct.

Respiratory acid-base disorders

Under normal conditions, the blood pCO₂ is maintained at 39–41 mm Hg by alveolar ventilation under the control of respiratory centres in the pons and medulla oblongata. Changes in the production of CO₂ are accompanied by corresponding alterations in alveolar ventilation, resulting in little or no change in pCO₂. Ventilation is regulated by brainstem chemoreceptors for pCO₂, PO₂, and pH, by neural impulses from arterial chemoreceptors and lung-stretch receptors, and by impulses from the cerebral cortex. Respiratory acidosis or alkalosis arise from a primary increase or decrease in blood pCO₂. They may coexist with other primary acid-base disorders.

Acute hypercapnia has many causes, including airway obstruction, respiratory-centre depression (as from drugs or brainstem injury), neuromuscular weakness (drugs, myasthenia, Guillain-Barré), restrictive pulmonary disease (pneumothorax, severe pneumonia), inadequate mechanical ventilation, and severe circulatory impairment. Within minutes of an acute rise in pCO₂, there is a small increase in the plasma [HCO₃⁻] (about 1 mmol/L for every 10 mm Hg), due largely to intracellular buffering of carbonic acid protons and cellular loss of the bicarbonate in exchange for chloride. The increase in [HCO₃⁻] is not accompanied by an increase in renal bicarbonate secretion, indicating an adaptive increase in bicarbonate reabsorption. Hyperphosphataemia usually occurs in acute hypercapnia. Patients manifest anxiety and shortness of breath, which may progress to delirium, encephalopathy, myoclonus, and seizures in severe hypercapnia. Treatment should be directed toward increasing ventilation, by mechanical ventilation if necessary, and correcting the underlying cause.

Sustained hypercapnia, or chronic respiratory acidosis, can be caused by disorders such as chronic obstructive lung disease, respiratory centre disorders (eg, obesity-hypoventilation syndrome), neuromuscular disorders (eg, amyotrophic lateral sclerosis), and restrictive defects (intestinal fibrosis, thorax deformities). The pCO₂ of the CSF changes rapidly to match the arterial blood pCO₂. Hypercapnia that persists for more than a few hours induces an increase in CSF [HCO₃⁻] that reaches a maximum by 24 h and partly restores the CSF pH. Prolonged hypercapnia also stimulates renal net acid secretion, causing the blood [HCO₃⁻] concentration to increase to a new steady state after 3–5 days (figure). Caution must be exercised in reducing the pCO₂ in these patients. Sudden correction of hypercapnia (eg, by mechanical ventilation) alkalinises the CSF which may cause seizures, and induces an acute systemic metabolic alkalosis that can persist for days.

The causes of acute hypocapnia include hypoxia, anxiety, pain, sepsis, hepatic failure, CNS disorders (such as stroke and infections), pulmonary disorders (eg, infections and interstitial lung disease), drugs (salicylate intoxication), and pregnancy can produce a chronic respiratory alkalosis. Sustained hypcapnia produces a corresponding reduction in CSF pCO₂ and a fall in the CSF [HCO₃⁻], correcting the pH toward normal. Within minutes to hours of sustained hypcapnia, there is an inhibition of proximal tubule bicarbonate reabsorption.
and a subsequent bicarbonaturia. A new steady state is reached in 2–3 days, with a reduced plasma [HCO₃⁻] concentration (figure). The [HCO₃⁻] may require several days to return to normal after correction of chronic hypocapnia, resulting transiently in a hyperchloremic metabolic acidosis.

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