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talis should be monitored by ECG during the infusion since administration of calcium may produce fatal arrhythmias if the infusion is given rapidly. In severe hypocalcemia a continuous intravenous infusion of calcium

gluconate may be necessary. Between 15 and 20 mg of elemental  $\text{Ca}^{2+}$  per kilogram of body weight can be given in 4 to 8 h as needed. Other available calcium salt preparations are shown in Table 32-5.

TABLE 32-5 • Calcium preparations for clinical use

Compound	Dosage	Content	Indications	Mechanisms	Complications
Calcium carbonate*	1-2 g three times daily	260 mg elemental calcium per 650-mg tablet	Mild hypocalcemia Osteomalacia Osteoporosis Renal osteodystrophy	Converted in stomach to soluble calcium salt by HCl; ineffective in patients with achlorhydria	Hypercalcemia after long-term therapy, particularly if vitamin D given concurrently
Calcium chloride	5-10 ml of 10% solution given slowly IV (rarely given orally because of irritation of GI tract)	360 mg per 10-ml ampule	Severe hypocalcemia	Rapidly increases $\text{Ca}^{2+}$	Irritant to veins and subcutaneous tissue if extravasated Hypercalcemia during long-term therapy, particularly if given with vitamin D
Calcium gluceptate (glucoheptate)	5-10 ml solution, IV. In newborn infants, 0.5 ml after every 100 ml in exchange transfusion; 2 to 5 mg IM in gluteal region	220 mg/ml or 80 mg/ml of calcium per 5-ml container	Severe hypocalcemia Exchange transfusion	Increases $\text{Ca}^{2+}$	Transient tingling and metallic taste after IV infusion Enhanced digitalis effect in the heart, precipitating arrhythmia
Calcium gluconate	20 ml of 10% solution injected slowly, followed by slow infusion of 30-40 ml of 10% solution in 500 ml or 1 liter of 5% glucose or 0.9% NaCl over a 4-h period Children should receive 500 mg/kg body weight daily in divided doses Adults, 15g daily in divided doses	90 mg elemental calcium per 10-ml ampule 90 mg elemental calcium per 1-g tablets	Severe hypocalcemia, IV Mild hypocalcemia, oral	As above	As above
Calcium lactate	Adults, 1.5-3.0 g 3x daily with meals Children should receive 500 mg/kg body weight orally in divided doses	60 mg elemental calcium per 300-mg tablet	Mild hypocalcemia and maintenance therapy	As above	As above

\* Calcium should not be mixed with any solution containing bicarbonate because of the possibility of precipitation.

TABLE 32-6 • Dose requirements of vitamin D and metabolites

	Daily dose for hypoparathyroidism, $\mu\text{g}$	Time to achieve normocalcemia, weeks	Maximal effect, weeks*	Duration of effect after cessation, weeks
Vitamin D <sub>2</sub> (ergocalciferol)	750-3000	4-8	4-10	6-18
DHT	250-1000	1-2	2-4	0.5-1
25-OH-D <sub>3</sub>	50-200	2-4	4-20	0.5-1
1 $\alpha$ ,25-(OH) <sub>2</sub> D <sub>3</sub>	0.5-2.0	0.5-1	4-12	0.5-1

\* Earliest times for maximal effect uncertain.

SOURCE: Adapted from Martinez-Maldonado M, Garcia A, chap 3: Hypo- and hypercalcemia, in Martinez-Maldonado M (ed), *Handbook of Renal Therapeutics*. New York, Plenum, 1983.

### Chronic

Long-term treatment of hypocalcemia is required most commonly in hypoparathyroidism or in chronic vitamin D deficiency states. The initial treatment includes oral administration of 2 to 4 g of elemental calcium per day. The addition of a vitamin D preparation is necessary in most cases, particularly when serum calcium has been less than 7.5 mg/dl before treatment is initiated. The optimal dose of vitamin D varies according to the preparation used (Table 32-6) and the condition requiring treatment.<sup>189,337</sup>

In hypoparathyroidism 25-OH-D<sub>3</sub> can maintain serum calcium within a narrower range than vitamin D<sub>3</sub> or dihydrotachysterol (DHT).<sup>345</sup> Exogenous 25-OH-D<sub>3</sub> can also be advantageous in conditions associated with external losses of 25-OH-D<sub>3</sub> such as hepatobiliary disease, intestinal bypass surgery,<sup>415</sup> or nephrotic syndrome. Neonatal hypocalcemia has also been shown to respond to 25-OH-D<sub>3</sub>.<sup>64,147</sup> 1 $\alpha$ ,25-dihydroxycholecalciferol can be useful when 1 $\alpha$  hydroxylase activity is low or absent such as in renal disease, vitamin D-dependent rickets, or pseudohypoparathyroidism.

Ergocalciferol (vitamin D<sub>2</sub>) and DHT have also been used in the treatment of chronic hypocalcemia. The doses of vitamin D<sub>2</sub> or DHT required are generally higher than with the vitamin D<sub>3</sub> derivatives, but treatment with D<sub>2</sub> is less expensive than with the calciferol derivatives.

When hypomagnesemia is the cause, magnesium can be replaced by the administration of MgSO<sub>4</sub> · 7H<sub>2</sub>O either intramuscularly or intravenously. Because of the painful effects of intramuscular medication, a continuous intravenous infusion of 48 meq/24 h may be preferable (see Chap. 34 for further details of treatment of hypomagnesemia).

Hypercalciuria usually ensues when serum calcium returns to normal. This increases the risk of nephrolithiasis and nephrocalcinosis. Treatment with a low-salt diet and thiazide diuretics may help to diminish hypercalciuria and avoid its consequences.

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of serum magnesium levels are obviously required. The patient's response to therapy dictates the quantity of additional doses.

## HYPERMAGNESEMIA AND MAGNESIUM TOXICITY

Since large loads of magnesium can easily be eliminated in the urine when renal function is normal, it is unusual to encounter hypermagnesemia in the absence of azotemia. Some of the conditions in which hypermagnesemia have been noted include (1) acute and chronic renal failure, (2) adrenal insufficiency, (3) magnesium therapy for eclampsia (the hypermagnesemia also affecting the infant), and (4) during the administration of pharmacologic doses of magnesium and use of magnesium-containing oral purgatives, rectal enemas, or antacids, especially in patients with impaired renal function. Absolute magnesium excretion falls as the GFR declines; this may result in hypermagnesemia. As long as the patient remains on a normal diet, the serum levels of magnesium will stabilize at approximately 2.5 meq/liter. However, when patients with chronic renal failure are treated with magnesium-containing antacids, the plasma level can reach 4 to 6 meq/liter, a value often associated with signs and symptoms of toxicity.

Elderly subjects are more likely to develop magnesium toxicity, because renal function declines with age and magnesium-containing antacids or vitamins are commonly consumed by this group.

The principal sources of magnesium in medications can be classified as antacids, laxatives, and urologic irrigation solutions. Table 34-5 lists the most commonly used prescriptions associated with magnesium toxicity in patients with reduced renal function.

### Signs and symptoms

The signs and symptoms of hypermagnesemia reflect the ion's action on the nervous and cardiovascular systems. Deep tendon reflexes are usually lost when blood magnesium concentration exceeds 6 meq/liter. Respiratory paralysis, narcosis, hypotension, and a prolonged P-R interval with abnormal cardiac conduction may occur as blood levels of magnesium approach 10 meq/liter, and complete heart block may occur at levels approaching 15 meq/liter.

Several reports have suggested a relationship between the blood levels of magnesium and symptoms. However, there seems to be a great deal of individual variability. While some patients have reported drowsiness and altered levels of consciousness at levels of 5 meq/liter, others reported normal mental and CNS responses during

mild hypermagnesemia.<sup>129,154,158</sup> The most common clinical signs and symptoms described in patients whose blood magnesium increased to 4 meq/liter were drowsiness, lethargy, and diaphoresis.

### Treatment

Discontinuation of the patient's exposure to magnesium, coupled with the intravenous administration of calcium compounds, is the initial step in treating symptomatic hypermagnesemia. The administration of 5 to 10 meq (100 to 200 mg) of elemental calcium may be adequate to reverse the manifestations of hypermagnesemia, but greater amounts may be required. Peritoneal dialysis or hemodialysis may be needed to lower the concentration of blood magnesium in patients with severe hypermagnesemia.

## MAGNESIUM METABOLISM IN RENAL FAILURE

Renal failure may be associated with disturbances in several aspects of magnesium metabolism. These include the renal handling of magnesium, its concentration in blood, tissue content, intestinal absorption, and overall balance.

### RENAL HANDLING OF MAGNESIUM IN RENAL FAILURE

The daily urinary excretion of magnesium is usually reduced in patients with advanced renal failure.<sup>123,129,157,169</sup> In 50 patients with creatinine clearance of 1 to 30 ml/min studied in our laboratory, the urinary excretion of magnesium per 24 h ranged between 12 and 133 mg with a mean of  $57 \pm 31$  (SD) mg. Only two-thirds of the patients had significant reduction in their excretory rates; the other one-third had either normal or increased excretion of magnesium.<sup>123</sup> In patients with uremia and salt wasting, such as those with chronic interstitial nephritis, the 24-h urinary excretion of magnesium may be normal or high,<sup>123</sup> and renal magnesium wasting has been reported in few such patients.<sup>129</sup>

The fraction of filtered magnesium excreted (fractional excretion) increases as renal failure progresses<sup>40,78,123,124,157</sup>; the increment is more marked when the GFR is less than 10 ml/min. It is important to consider the changes in the fractional excretion of magnesium in terms of the renal handling of sodium, since in tubular reabsorption these two ions are interrelated.<sup>30,51,104</sup> Indeed, there is a positive and significant correlation between the fractional excretion of magnesium and that of sodium in patients with GFRs below

VOLUME III

# EMERGENCY MEDICINE

## Concepts and Clinical Practice

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tored setting via a large-bore peripheral venous catheter or a central venous access.<sup>23,32</sup>

Burning at the infusion site is the most common side effect of IV potassium administration. Slowing the rate of infusion will usually decrease venous irritation. The most important potential risk of intravenous potassium administration is acute hyperkalemia, which is most likely in patients with renal insufficiency. Thus particular caution should be used in these individuals. If dysrhythmias (e.g., frequent premature ventricular contractions [PVCs], heart block, tachycardia, and widening of the QRS complex) develop, the potassium infusion should be discontinued immediately.

Oral potassium is preferred for mild hypokalemia. Several oral preparations are available in liquid or tablet form. Although liquid preparations are typically better absorbed, matrix tablets are often better tolerated. Hypokalemia can be effectively corrected with oral supplements, and large amounts of orally administered potassium can be given to increase serum levels rapidly.

Potassium can be given as the chloride salt in most patients. Potassium phosphate, rather than potassium chloride, may be given if there is associated hypophosphatemia (e.g., in diabetic ketoacidosis). Patients with distal RTA should be treated with potassium bicarbonate, potassium citrate, or potassium gluconate, which provide both potassium and base equivalents. The hypokalemia of proximal RTA may be better treated with potassium chloride because the administered base cannot be reabsorbed well proximally and can obligate potassium loss when it reaches the distal tubule.

## Hyperkalemia

### Etiology

**General.** Hyperkalemia has been estimated to occur in 1% to 2% of hospitalized patients.<sup>24</sup> Hyperkalemia may be the result of (1) increased intake or enhanced potassium absorption, (2) impaired potassium excretion, or (3) shifts of potassium out of cells into the serum (Box 145-6).

**Pseudohyperkalemia.** When faced with a report of a high serum potassium level, the EP should first consider the possibility of laboratory error. Hemolysis during phlebotomy, as may occur when blood is obtained with a small needle or sampled in a high-vacuum tube, releases potassium into the sample and causes a spuriously high potassium level to be measured.<sup>23</sup> Laboratory technicians usually note the presence of pink serum, indicating hemolysis. Pseudohyperkalemia may also occur when potassium is released from platelets in patients with severe thrombocytosis or from leukocytes in patients with extreme leukocytosis.<sup>33</sup>

**Increased Intake.** Hyperkalemia rarely results from increased potassium intake. This is more common when potassium supplements are inadvertently taken by patients with renal insufficiency or in those taking a potassium-sparing diuretic or an ACE inhibitor.<sup>33</sup> Parenteral medications such as penicillin and carbenicillin, as well as transfused blood, also contain significant amounts of potassium and may precipitate hyperkalemia.

**Impaired Excretion.** Renal insufficiency (i.e., decreased GFR), defects in tubular potassium secretion, or hypoaldosteronism can cause hyperkalemia. As GFR decreases to approximately 5 to 15 ml/min, excretion of the normal daily potassium load is impaired. Defects in tubular potassium

### BOX 145-6 Causes of Hyperkalemia

- I. Pseudohyperkalemia
  - A. Hemolysis of sample
  - B. Thrombocytosis
  - C. Leukocytosis
  - D. Laboratory error
- II. Increased potassium intake and absorption
  - A. Potassium supplements (oral and parenteral)
  - B. Dietary—salt substitutes
  - C. Stored blood
  - D. Potassium-containing medications
- III. Impaired renal excretion
  - A. Acute renal failure
  - B. Chronic renal failure
  - C. Tubular defect in potassium secretion
    1. Renal allograft
    2. Analgesic nephropathy
    3. Sickle cell disease
    4. Obstructive uropathy
    5. Interstitial nephritis
    6. Chronic pyelonephritis
    7. K-sparing diuretics
    8. Miscellaneous (lead, systemic lupus erythematosus, pseudohypoaldosteronism)
  - D. Hypoaldosteronism
    1. Primary (Addison's disease)
    2. Secondary
      - a. Hyporeninemic hypoaldosteronism (type IV RTA)
      - b. Congenital adrenal hyperplasia
      - c. Drug-induced
        - i. Nonsteroidal antiinflammatory medications
        - ii. ACE inhibitors
        - iii. Heparin
        - iv. Cyclosporine
- IV. Transcellular shifts
  - A. Acidosis
  - B. Hypertonicity
  - C. Insulin deficiency
  - D. Drugs
    1. Beta blockers
    2. Digitalis toxicity
    3. Succinylcholine
  - E. Exercise
  - F. Hyperkalemic periodic paralysis
- V. Cellular injury
  - A. Rhabdomyolysis
  - B. Severe intravascular hemolysis
  - C. Acute tumor lysis syndrome
  - D. Burns and crush injuries

excretion are associated with a number of conditions. Hypoaldosteronism may be the result of causes as varied as type IV RTA, Addison's disease, nonsteroidal antiinflammatory drugs (NSAIDs), and ACE inhibitors.<sup>33,34</sup>

**Transcellular Shifts.** Transcellular potassium shifts (e.g., acute acidosis,  $\alpha$ -receptor stimulation, or  $\beta$ -receptor antagonists)

ism) are another major cause of hyperkalemia. Periodic paralysis is an inherited disorder characterized by hyperkalemia caused by cellular efflux of potassium associated with stressors such as exercise, infection, and diet. Drugs may also be the cause of transcellular potassium shifts. Digitalis poisons the Na<sup>+</sup>/K<sup>+</sup> ATPase pump, with resultant hyperkalemia in severe cases. Succinylcholine causes transient potassium efflux because of depolarization of the muscle cell membrane.<sup>24,33</sup> High-dose trimethoprim-sulfamethoxazole has also been implicated in hyperkalemia, especially with concomitant renal insufficiency.<sup>36,37</sup>

**Cellular Injury.** Life-threatening hyperkalemia may result when large amounts of potassium are released from damaged cells. Rhabdomyolysis, tumor cell necrosis, and hemolysis are important causes.<sup>23</sup> Acute renal failure that may be associated with these conditions impairs potassium excretion, further exacerbating endogenous hyperkalemia.

**Clinical Features.** Cardiovascular and neurologic dysfunction are the primary manifestations of hyperkalemia.<sup>33,38</sup> Patients may have a variety of dysrhythmias, including second- and third-degree heart block, wide-complex tachycardia, ventricular fibrillation, or even asystole. The electrocardiogram (EKG) can provide valuable clues to the presence of hyperkalemia. As potassium levels rise, peaked T waves are the first characteristic manifestation. Further rises are associated with progressive EKG changes including loss of the P waves and widening and slurring of QRS complex. Eventually the tracing assumes a sine wave appearance, followed by ventricular fibrillation or asystole.<sup>31</sup> Concomitant alkalosis, hypernatremia, or hypercalcemia antagonizes the membrane effects of hyperkalemia and may delay or diminish the characteristic EKG findings.

Neuromuscular signs and symptoms of hyperkalemia include muscle cramps, weakness, paralysis, paresthesias, tetany, and focal neurologic deficits, but these are rarely specific enough to suggest the diagnosis in themselves.<sup>29,30</sup>

#### Management

**Monitor.** All patients with suspected hyperkalemia should be on a cardiac monitor with attention paid to the morphology of the T waves and QRS complex. Peaked T waves, loss of the P waves, slurring of the QRS, and second- or third-degree heart block all suggest hyperkalemia and are indications for immediate therapy.<sup>33</sup>

**Calcium.** Treatment of the hyperkalemic patient is directed toward antagonism of the membrane effects of hyperkalemia, promotion of transcellular potassium shifts, and removal of potassium from the body. Immediate antagonism of potassium at the cardiac membrane is achieved with IV administration of calcium chloride or gluconate. This is indicated in patients with unstable dysrhythmia or hypotension. Several ampules of calcium (10 ml of 10% solution) may be required.<sup>23,30,33</sup> Because of the brief duration of action (approximately 20 to 40 minutes), other measures should also be instituted promptly.<sup>33</sup>

**Sodium Bicarbonate.** Sodium bicarbonate infusion promotes a shift of potassium into cells. One ampule (44 mEq) should be given by slow IV push over 5 to 15 minutes. The duration of action is approximately 2 hours.<sup>23</sup> Sodium bicarbonate should be used with caution when hypertonicity, volume overload, or alkalosis pose a risk to the patient. Bicarbonate therapy is less efficacious than insulin or al-

buterol and may be relegated to third-line treatment behind calcium and insulin or glucose.<sup>39,40</sup>

**Glucose and Insulin.** Cellular uptake of potassium can also be induced with a regimen of intravenous glucose and insulin. Regular insulin (10 to 20 U) may be given by bolus infusion. Dextrose should be administered to euglycemic and diabetic patients with blood glucose below 250 to prevent hypoglycemia. This combination takes longer to produce an effect (30 minutes) but lasts 4 to 6 hours.<sup>33</sup> Rapid infusion of hypertonic glucose solution may transiently exacerbate hyperkalemia by its osmotic effect on cells.

**Beta-2 Agonists.** The known effect of  $\beta_2$ -agonists to cause movement of potassium into cells may also be harnessed to lower the serum potassium level acutely. Treatment with nebulized albuterol (5 to 20 mg) lowers the serum potassium level for at least 2 hours.<sup>41,42</sup>

**Exchange Resins.** Definitive treatment for hyperkalemia remains the removal of potassium from the body. The use of exchange resins (e.g., sodium polystyrenesulfonate, Kayexalate) and hemodialysis are two such options. Given orally or rectally, Kayexalate can remove approximately 1.0 mEq of potassium for each gram of Kayexalate given. Twenty grams of Kayexalate in a 70% sorbitol, given orally, produces effects in 1 to 2 hours. Rectal enemas of 50 gm of Kayexalate, retained for 30 minutes, work in approximately 30 minutes. Kayexalate should be used with caution in patients with poor cardiovascular reserve because there is a potential to exacerbate volume overload.<sup>23</sup>

**Dialysis.** Hemodialysis corrects hyperkalemia rapidly, and consultation with a nephrologist is indicated in the unstable hyperkalemic patient with newly diagnosed or chronic renal failure. Hyperkalemia resulting from severe rhabdomyolysis is difficult to treat with the usual measures and also mandates consultation for emergent dialysis. Dialysis removes potassium from the blood only, and subsequent shifts of intracellular potassium may cause rebound hyperkalemia. Even during CPR, dialysis can be effective in treating hyperkalemia-induced cardiac arrest.<sup>43</sup>

**General.** Treatment of any underlying causative disorder should be initiated at the same time as therapy for hyperkalemia. This may include the treatment of rhabdomyolysis with fluids and bicarbonate; treatment of Addison's disease with corticosteroids, IV fluids, and glucose; treatment of digitalis toxicity with digoxin-binding antibodies; or discontinuation of drugs that may have precipitated hyperkalemia.

Patients with hyperkalemia should be admitted to a monitored bed, with care provided by a clinician skilled in the treatment of electrolyte disorders.

## CALCIUM

### Physiology

Hundreds of enzymatic reactions are mediated by changes in intracellular calcium. Cellular growth and reproduction, membrane integrity, receptor activation, neurotransmission, glandular secretion, enzyme activation, muscle contraction, cardiac contractility, platelet aggregation, and immune function all depend on the precise regulation of free calcium. There is also evidence that cellular injury, and ultimately cell death, are mediated by changes in free intracellular calcium.<sup>44</sup>

The adult human body contains approximately 1,200 gm of calcium, more than 99% of which is found in the mineral component of bone. The remaining 1% is distributed in three different plasma fractions. Approximately 50% is bound to serum proteins, primarily albumin; 10% is complexed with serum anions (phosphate, bicarbonate, citrate, lactate); and 40% is in the free ionized state. Ionized calcium is the physiologically active form, and concentrations are tightly regulated by the endocrine system.<sup>45,46</sup>

Dietary calcium is absorbed in the proximal intestine through both active and passive processes. Absorption is enhanced by the action of vitamin D. In the kidneys, 99% of the filtered load of calcium is reabsorbed. Approximately 90% of calcium reabsorption occurs passively in the proximal tubule and loop of Henle. The remaining 10% occurs in the distal tubule under the control of parathyroid hormone (PTH). A fall in free serum calcium stimulates the release of PTH, which in turn increases reabsorption.<sup>47</sup> PTH also mediates the hydroxylation of vitamin D to its active form, 1,25-dihydroxycholecalciferol (1,25-DHCC).

The skeleton acts as a calcium pool that buffers acute changes in serum concentration. When the serum calcium falls, PTH stimulates an increase in bone turnover and the release of calcium into the serum. A rise in serum calcium suppresses PTH production and causes the release of calcitonin. Calcitonin decreases osteoclastic activity and enhances skeletal deposition of calcium.

The serum calcium level reflects the net outcome of several processes. On one hand, intestinal absorption and bone resorption add calcium to the blood; on the other, calcium is lost from the blood by renal excretion, skeletal uptake, or abnormal deposition in soft tissues. A decrease in the serum ionized calcium activates the PTH-vitamin D system to increase the entry of calcium into the blood from the bone and gastrointestinal tract. A rise in the serum calcium suppresses the PTH-vitamin D system and increases the release of calcitonin, which decreases calcium entry into the blood.

Most hospital laboratories measure total serum calcium concentrations. Normal values range from 8.5 to 10.5 mg/dl. However, the total serum calcium is often a poor indicator of the ionized calcium status. Several factors may influence the measurement of the total serum calcium, irrespective of the ionized calcium.<sup>48</sup> Alterations in serum protein concentrations (primarily albumin) affect the total calcium. A decrease in albumin concentration will lower the measured serum calcium, and an increase will raise it. Physiologically this change is not of significance because the ionized calcium remains unchanged. A corrected serum calcium that accounts for changes in serum albumin concentrations can be calculated as follows:

$$\text{Corrected calcium} = \text{Serum calcium (mg/dl)} + 0.8[4 - \text{Serum albumin (gm/dl)}]$$

This formula is only an estimate, however, and the ionized calcium should be measured whenever hypocalcemia is suspected.<sup>49</sup> Currently available blood gas analyzers are capable of measuring ionized calcium from a sample of blood or serum. The normal range is 1.00 to 1.15 mmol/L.<sup>50</sup>

Changes in acid-base status influence the ratio of bound to ionized calcium without altering the total measured cal-

### BOX 145-7 Causes of Hypocalcemia

- I. Parathyroid hormone insufficiency
  - A. Primary hypoparathyroidism
    1. Congenital syndromes
    2. Maternal hyperparathyroidism
  - B. Secondary hypoparathyroidism
    1. Neck surgery
    2. Metastatic carcinoma
    3. Infiltrative disorders
    4. Hypomagnesemia, hypermagnesemia
    5. Sepsis
    6. Pancreatitis
    7. Burns
    8. Drugs (chemotherapeutics, ethanol, cimetidine)
- II. Vitamin D insufficiency
  - A. Congenital rickets
  - B. Malnutrition
  - C. Malabsorption
  - D. Liver disease
  - E. Renal disease
    1. Acute and chronic renal failure
    2. Nephrotic syndrome
  - F. Hypomagnesemia
  - G. Sepsis
  - H. Anticonvulsants (phenytoin, primidone)
- III. Parathyroid hormone resistance states (pseudohypoparathyroidism)
- IV. Calcium chelation
  - A. Hyperphosphatemia
  - B. Citrate
  - C. Free fatty acids
  - D. Alkalosis
  - E. Fluoride poisoning

cium. Acidosis decreases calcium binding to albumin; alkalosis increases binding. Thus acute changes in blood pH may have important physiologic effects by changing the ionized calcium even when the total serum calcium remains unchanged.<sup>44</sup>

### Hypocalcemia

**Etiology.** The causes of ionized hypocalcemia are numerous (Box 145-7) and can be divided into disorders of PTH insufficiency, vitamin D insufficiency, PTH resistance states, and calcium chelation.<sup>51-53</sup>

**Parathyroid Hormone Insufficiency.** PTH insufficiency may be due to either primary or secondary hypoparathyroidism. Primary hypoparathyroidism is rare and is usually congenital. Congenital syndromes that may cause hypoparathyroidism include DiGeorge syndrome (branchial cleft cystogenesis with parathyroid aplasia and thymic agenesis), idiopathic hypoparathyroidism (hypoparathyroidism), dysfunction of the adrenals, thyroid, and gonads; alopecia; vitiligo; pernicious anemia; mucocutaneous moles; and Kenny's syndrome (hypoparathyroidism, macrocephaly, ophthalmic abnormalities, growth retardation, and skin

abnormalities); and Kearns-Sayre syndrome (hypoparathyroidism, retinitis, ophthalmoplegia, and cardiac conduction abnormalities). Maternal hyperparathyroidism may result in fetal parathyroid hypoplasia and transient hypocalcemia.<sup>54,55</sup>

Secondary hypoparathyroidism is more common and is most often iatrogenic, resulting from inadvertent removal of the parathyroid glands or disruption of the vascular supply during parathyroid, thyroid, or carotid surgery. Permanent hypocalcemia is the usual consequence. Excision of a functional parathyroid adenoma, leaving only the chronically suppressed but otherwise unaffected parathyroid tissue, causes hypocalcemia that usually resolves over several days. Metastatic carcinoma or infiltrative disorders (including metastatic carcinoma, sarcoidosis, and Wilson's disease) may destroy parathyroid tissue and cause hypocalcemia.<sup>56-59</sup> Both severe hypomagnesemia and hypermagnesemia may impair the release of parathyroid hormone.<sup>60-62</sup> A number of drugs may suppress parathyroid function, including chemotherapeutic agents, cimetidine, and ethanol. Sepsis, rhabdomyolysis, and pancreatitis are other causes of secondary hypoparathyroidism.<sup>63-66</sup>

**Deficiency of Vitamin D.** Vitamin D deficiency may result in hypocalcemia because of decreased gastrointestinal calcium absorption. Nutritional vitamin D deficiency is rare in the United States owing to the fortification of milk. Nevertheless, it can occur when exposure to sunlight is limited, especially in the elderly, chronically ill, or debilitated patient. Children of mothers with vitamin D deficiency may be born with congenital rickets. Characteristic findings include hypocalcemia, hypophosphatemia, and specific radiographic findings (widening of the distal radius and ulna, craniotabes).<sup>67</sup> Vitamin D insufficiency resulting from intestinal malabsorption may occur in patients with small bowel or biliary disease or pancreatic endocrine failure. Cholestyramine may also prevent adequate vitamin D absorption.<sup>68</sup> Once absorbed, vitamin D is hydroxylated in the liver and kidney to its active form, 1,25-DHCC. Hepatic and renal disease may both lead to inadequate activation of the vitamin. Hypercatabolism of vitamin D may occur in association with agents that stimulate the hepatic microsomal oxidase system, such as the anticonvulsants phenytoin and primidone.<sup>68,69</sup>

**Parathyroid Hormone Resistance States.** PTH resistance states are termed pseudohypoparathyroidism. These syndromes are characterized by renal unresponsiveness to PTH and resultant parathyroid hyperplasia.<sup>70,71</sup> Associated phenotypic anomalies include short stature, mental retardation, dental abscesses, short fourth metacarpals and metatarsals, thickened calvaria, and ectopic calcification. These skeletal malformations are termed Albright's hereditary osteodystrophy.<sup>72</sup> Differentiation from hypoparathyroidism is based on elevated PTH levels and a lack of increase in urinary cyclic adenosine monophosphate (cAMP) after PTH administration.

The syndrome is common in patients with chronic renal disease. It results from vitamin D deficiency, impaired responsiveness to PTH, and phosphate retention. Generally, these patients are asymptomatic, possibly because of a protective effect of systemic acidosis. However, rapid correction of metabolic acidosis with exogenous sodium bicarbonate

may precipitate severe hypocalcemia, often causing tetany and seizures.

**Calcium Chelation.** Calcium complexes with several different substances in serum, including proteins, fatty acids, and anions. Increases in the concentration of these substances may thus result in ionized hypocalcemia.<sup>45,46</sup> Citrate is used as a blood preservative and anticoagulant. The citrate load associated with massive blood transfusion (>6 U) causes hypocalcemia in up to 94% of patients.<sup>73-75</sup> Hypocalcemia is usually short-lived, and ionized calcium levels return to normal shortly after transfusion. Because citrate is metabolized by temperature-dependent enzymes in tissues and excreted by the liver, hypothermia and hepatic failure are important risk factors for protracted hypocalcemia after blood transfusion. Citrate is also a constituent of radiocontrast material, and hypocalcemia has been associated with the administration of these agents.<sup>76</sup> Exogenous administration of phosphate and endogenous hyperphosphatemia (e.g., with acute renal failure, rhabdomyolysis, or tumor lysis syndrome) are well-known causes of hypocalcemia.<sup>77-79</sup> Exogenously administered bicarbonate also complexes with calcium and may cause symptomatic hypocalcemia. Alkalosis, either metabolic or respiratory, enhances the binding of calcium to serum proteins, resulting in ionized hypocalcemia.<sup>45,48</sup> Free fatty acids liberated in various conditions (e.g., acute pancreatitis, hyperadrenergic states, acute ethanol ingestion) can chelate free calcium to form calcium soaps.<sup>80</sup> Fluoride poisoning may also cause hypocalcemia. This may occur after exposure to hydrofluoric acid or ammonium bifluoride, components of many household cleaners and rust removers. These compounds release free fluoride ion, a direct cellular toxin that binds calcium, forming calcium fluoride. Numerous cases of severe hypocalcemia, cardiac dysrhythmias, and death have been reported after ingestion, inhalation, or cutaneous exposure to these products.<sup>81-84</sup>

**Clinical Features.** The clinical manifestations of hypocalcemia depend not only on the serum level but also on the rapidity with which it declines. Although the signs and symptoms of hypocalcemia are numerous (Box 145-8), the effects on neuromuscular function predominate.

**Neuromuscular.** A declining serum calcium level is associated with progressive neuromuscular hyperexcitability. CNS manifestations may include depression, irritability, confusion, and focal or generalized seizures.<sup>54,85</sup> Peripheral nervous system manifestations include perioral paresthesias, muscle weakness and cramps, fasciculations, and tetany.<sup>44,54</sup> Latent tetany can often be demonstrated by eliciting Chvostek's or Trousseau's sign. Chvostek's sign is elicited by tapping over the facial nerve and causing twitching of the ipsilateral facial muscles. Trousseau's sign describes carpal spasm in response to inflation of an arm blood pressure cuff to 20 mm Hg above systolic blood pressure for 3 minutes.

**Cardiovascular.** Severe hypocalcemia causes a decrease in myocardial contractility and, rarely, bradycardia, hypotension, and symptomatic CHF.<sup>85,86</sup> Patients with preexisting cardiac dysfunction, and those taking digoxin or diuretics, are especially at risk. The EKG may demonstrate QT prolongation, and an inverse relationship exists between the serum calcium level and the QT interval. However, the EKG is a

### BOX 145-8 Clinical Manifestations of Hypocalcemia

<b>Neuromuscular</b>	Digitalis insensitivity
Paresthesias	Q-T prolongation
Muscle weakness	
Muscle spasm	<b>Pulmonary</b>
Tetany	Bronchospasm
Chvostek's and Trousseau's sign	Laryngeal spasm
Hyperreflexia	<b>Psychiatric</b>
Seizures	Anxiety
	Depression
<b>Cardiovascular</b>	Irritability
Bradycardia	Confusion
Hypotension	Psychosis
Cardiac arrest	Dementia

poor predictor of hypocalcemia and should not be used to rule in or rule out this disorder.<sup>87</sup>

**Pulmonary.** Bronchospasm and laryngeal spasm occur rarely.

**Psychiatric.** Symptoms and signs ranging from anxiety and depression to psychosis and dementia may be seen.

**Management.** In patients with suspected hypocalcemia or with a documented low total serum calcium level the first step in management should be the verification of true ionized hypocalcemia. When hypocalcemia is the presumed cause of tetany, seizures, hypotension, or dysrhythmias, it may be appropriate to initiate treatment before the ionized calcium level is available. All patients with symptomatic hypocalcemia should be treated with parenteral calcium. Two different formulations are readily available in most EDs: (1) 10 ml ampules of 10% calcium chloride, which contain 360 mg of elemental calcium; and (2) 10 ml ampules of 10% calcium gluconate, which contain 93 mg of elemental calcium. For the adult patient, the recommended initial dose is 100 to 300 mg of elemental calcium given as either calcium chloride or calcium gluconate. This dose of calcium will increase the serum ionized calcium for only a short period of time (1 to 2 hours) and should be followed by repeated doses or an infusion at a rate of 0.5 to 2 mg/kg/hr.<sup>44</sup> For neonates, infants, and children, the recommended initial dose is 0.5 to 1.0 ml/kg of 10% calcium gluconate administered over 5 minutes.<sup>88</sup>

The most common side effects of IV calcium administration are hypertension, nausea, vomiting, and flushing. Bradycardia and heart block occur in rare cases. Patients receiving IV calcium should be placed on a cardiac monitor, and administration should be discontinued if bradycardia ensues. Calcium should be administered with extra caution in patients taking digoxin because it may precipitate (or exacerbate) digoxin-induced cardiotoxicity. Because calcium may cause severe tissue irritation and necrosis if it extravasates, it should always be given through a well-functioning catheter. Whenever possible, calcium chloride should be diluted in D5W.<sup>44-46,88</sup>

Symptoms that are refractory to appropriate doses of cal-

cium may be due to coexisting hypomagnesemia. In patients with normal renal function, administration of 2 to 4 gm 10% magnesium sulfate should be considered.

Patients with asymptomatic hypocalcemia may be treated with oral calcium supplements. Several different preparations are available (calcium ascorbate, calcium gluconate, and calcium lactate). Most patients require 1 to 4 gm elemental calcium per day in divided doses.

### Hypercalcemia

**General.** Hypercalcemia is a relatively common medical disorder. Routine laboratory screening can be expected to detect hypercalcemia in 0.1% to 1.0% of patients, depending on the population being screened.<sup>89-91</sup> In most cases hypercalcemia is mild (<12 mg/dl) and asymptomatic, and the finding will rarely have implications for emergency treatment. Nevertheless hypercalcemia may be an important clue to a serious underlying medical disorder. Hypercalcemic crisis occurs in a subset of patients who have severe hypercalcemia (usually >14 mg/dl), and is generally associated with prominent signs and symptoms. In this situation immediate measures to lower the serum calcium are indicated.<sup>92</sup>

**Etiology.** Although there are many causes of hypercalcemia, more than 90% of cases result from either primary hyperparathyroidism or malignancy (Box 145-9).<sup>93-96</sup>

**Primary Hyperparathyroidism.** Primary hyperparathyroidism is the most common cause of hypercalcemia in outpatients, representing 25% to 50% of cases.<sup>96,97</sup> This is due to parathyroid adenoma (80%), parathyroid hyperplasia (15%), or parathyroid carcinoma (5%).<sup>98</sup> Hyperparathyroidism may also occur in association with other endocrine tumors as part of one of the familial syndromes—multiple endocrine adenomatosis. In primary hyperparathyroidism, PTH is elevated in more than 90% of cases; the remainder of patients have high-normal PTH levels that are inappropriate for the degree of hypercalcemia. An elevated PTH level leads to increased bone resorption, a relative decrease in renal calcium excretion, and increased intestinal calcium absorption. Patients typically develop hypercalcemia, phosphaturia, hypophosphatemia, and a hyperchloremic metabolic acidosis.

**Malignancy.** Malignancy is the most common cause of hypercalcemia in hospitalized patients, and hypercalcemia is the most common paraneoplastic complication of cancer. The reported prevalence of hypercalcemia in the setting of cancer ranges from 15% to 60%.<sup>99,100</sup> A multitude of solid tumors may cause hypercalcemia, including cancer of breast, lung, colon, stomach, cervix, uterus, ovary, kidney, bladder, and head and neck. Hypercalcemia is also seen with hematologic malignancies such as multiple myeloma and lymphoma.<sup>101</sup> Hypercalcemia in patients with cancer can result from several different mechanisms. The first is the production of parathyroid hormone-related protein (PTHrP) by the tumor.<sup>102-104</sup> This polypeptide is homologous to PTH in its first 13 N-terminal amino acids and binds to the PTH receptor, mimicking all the actions of the hormone. PTHrP is secreted by solid malignancies and their metastases and is not subject to normal feedback control mechanisms.<sup>105,106</sup> Assays for PTHrP are available to confirm this cause of cancer-related hypercalcemia.

Hypomagnesemia has been associated with a wide range of EKG findings including prolongation of the PR, QRS, and QT intervals, ST-T segment abnormalities, flattening and widening of the T wave, and the presence of U waves.<sup>230,231</sup> These findings, however, are nonspecific and may be at least in part due to associated hypokalemia. The EKG should thus not be used to rule out magnesium disturbances.

The relationship between hypomagnesemia and ischemic heart disease is hotly debated. Hypomagnesemia is common in ED patients with chest pain and in those admitted to the coronary care unit.<sup>232</sup> Patients who "rule in" for myocardial infarction are more likely to be hypomagnesemic than those who do not. This finding has been shown to be independent of concurrent diuretic usage.<sup>233,234</sup> Serum magnesium levels decline transiently after acute myocardial infarction, increasing the risk of dysrhythmia.<sup>235-240</sup> Proposed mechanisms include transcellular shifts of the cation and chelation with free fatty acids released after acute infarction. Although several studies demonstrate a benefit of empiric magnesium administration after acute myocardial infarction, the largest trial to date (ISIS IV) fails to confirm a significant benefit.<sup>241-248</sup>

**Management.** Because the serum magnesium level is often an inaccurate reflection of total-body magnesium stores, this should not be used alone to guide therapy. However, magnesium administration is appropriate in patients with a low serum level (<1.2 mg/dl), as well as in those with a normal serum magnesium level and symptoms suggestive of hypomagnesemia. For life-threatening conditions (dysrhythmias, seizures) in which hypomagnesemia is the suspected cause, parenteral magnesium should be given. In patients with normal renal function, 2 to 4 gm of 50% magnesium sulfate (16.6 to 33.3 mEq) is a reasonable initial dose. This should be diluted in saline or dextrose and given over 30 to 60 minutes. More rapid administration may result in venous irritation and phlebitis. Bolus administration should be avoided because this may cause bradycardia and varying degrees of heart block, as well as hypotension. Magnesium should be administered with caution, if at all, in patients with AV block or renal insufficiency. Most of an administered dose of magnesium is promptly excreted in the urine. Total-body magnesium repletion therefore requires administration of more than a single dose, generally over days.

Several different oral magnesium formulations are available. Preparations of magnesium gluconate, magnesium carbonate, magnesium oxide, and magnesium chloride each provide different doses of elemental magnesium. Large doses of magnesium salts may cause diarrhea. Magnesium as the chloride salt or as enteric-coated tablets (e.g., Slow-Mag) is usually better tolerated.

## Hypermagnesemia

### Etiology

**Renal insufficiency.** Hypermagnesemia is a fairly rare disorder. Under normal circumstances the kidneys increase magnesium excretion as the magnesium load increases. A healthy adult can excrete more than 6 gm of magnesium per day.<sup>249</sup> For this reason, clinically significant hypermagnesemia is encountered almost exclusively in the setting of renal insufficiency (Box 145-13).<sup>250-252</sup> Serum magnesium levels rise as the creatinine clearance falls below 30 ml/min and

### BOX 145-13 Causes of Hypermagnesemia

<b>Impaired renal magnesium excretion</b>	Chronic constipation Bowel obstruction Gastric dilatation Colitis
<b>Exogenous magnesium administration</b>	<b>Miscellaneous</b> Rhabdomyolysis Tumor lysis syndrome Adrenal insufficiency Hyperparathyroidism Hypothyroidism Lithium therapy
Antacids	
Laxatives	
Cathartics	
Dialysate	
Parenteral	
<b>Impaired GI magnesium elimination</b>	
Anticholinergics	
Narcotics	

typically reach approximately 2.5 mEq/L as renal function nears zero.<sup>253</sup> Although severe renal failure alone may cause symptomatic hypermagnesemia, this is more likely when a patient with preexisting renal failure is challenged with an exogenous magnesium load.<sup>254</sup> Clinically significant hypermagnesemia can be produced even by usual therapeutic doses of magnesium-containing preparations in patients with renal insufficiency. Elderly patients misusing over-the-counter medications are particularly at risk.<sup>255</sup>

**Exogenous Administration.** Iatrogenic hypermagnesemia may result from parenteral magnesium administration, excessive magnesium in dialysate solutions, or ingestion of magnesium-containing antacids or laxatives.<sup>256-258</sup> Severe hypermagnesemia may rarely occur in the patient with normal renal function, but only when such massive magnesium loads are administered that magnesium absorption exceeds the normal renal excretory capacity. IV magnesium infusion for the treatment of preeclampsia and eclampsia is a common cause of hypermagnesemia but leads to problems only when excessive doses are given or when renal function is compromised. Another situation particularly relevant to the EP is multiple-dose administration of magnesium-containing cathartics during overdose management. Although several case reports document severe hypermagnesemia in this setting, clinically significant hypermagnesemia is rare in the absence of preexisting renal insufficiency.<sup>259-263</sup> A recent review of 102 patients receiving multiple doses of magnesium citrate during overdose management (mean dose 9.22 gm) reports only modest rises in serum magnesium, with no clinically significant side effects.<sup>264</sup>

**Impaired Gastrointestinal Elimination.** Decreased GI motility may cause an increase in the absorption of magnesium-containing substances and result in toxicity. This may occur after the ingestion of certain drugs (e.g., anticholinergics, narcotics) or in patients with hypomotility disorders (chronic constipation, colitis, bowel obstruction, gastric dilatation). Although symptomatic hypermagnesemia is more likely in patients with preexisting renal insufficiency, it has been reported in patients with normal renal function.<sup>265-267</sup>

## Medical Emergency Management

# Hyperkalemia and Hypokalemia

Stephen R. Newmark, MD, Robert G. Dluhy, MD

ONE of the most common disorders encountered in clinical medicine is abnormal potassium metabolism resulting in either hyperkalemia or hypokalemia. In a healthy person, potassium balance is a function of oral intake and renal excretion. On a normal daily oral intake of 40 to 100 mEq, the urinary potassium excretion varies between 40 and 90 mEq/24 hr. Only small amounts of potassium are normally excreted through sweating and fecal excretion; however, substantial potassium wasting can occur in cases of severe sweating or gastrointestinal disease (usually diarrhea, vomiting, or fistulae).

The regulation of potassium excretion is dependent on renal function, total body potassium content, acid-base balance, delivery of sodium to the distal nephron, and mineralocorticoid secretion. Acidosis, decreased total body potassium content, decreased sodium delivery to the distal tubule, and mineralocorticoid insufficiency are associated with decreased potassium excretion. In contrast, alkalosis, increased total body potassium content, increased urinary sodium excretion, and mineralocorticoid excess favor increased potassium excretion.

As the relative concentrations of intracellular to extracellular potassium in part determine the excitability of biological membranes, changes in potassium metabolism may be reflected in increased or decreased excitability of neuromuscular tissue. The rate of change of potassium stores is of primary importance in the expression of clinical toxicity, for rapid increases or decreases in the serum potassium level may seriously alter membrane potential, resulting in either decreased or enhanced polarization. Slowly developing changes in the serum potassium level may be compensated by potassium fluxes across the cellular membranes, thus maintaining a normal extracellular to intracellular ratio. Hyperkalemia subsequent to acute renal insufficiency produces neuromuscular dysfunction

and cardiac arrhythmias more frequently than a comparable degree of hyperkalemia with chronic renal failure.

Although small elevations or decreases in the serum potassium level ordinarily do not produce symptoms and do not require treatment, extreme hyperkalemia or hypokalemia may constitute a medical emergency. We present the management of acute potassium intoxication and severe potassium depletion.

### Hyperkalemia

**Diagnosis and Clinical Presentation.**—Common clinical situations where hyperkalemia is encountered include acute renal failure (occasionally chronic renal failure); potassium-sparing diuretics (such as triameterene and spiroñolactone); excessive parenteral administration of potassium, including blood transfusions; hyperkalemic periodic paralysis; excessive amounts of orally administered potassium, usually in the setting of renal insufficiency; severe acidosis; trauma with muscle necrosis; and adrenal insufficiency.<sup>1,2</sup> (Hyperkalemia secondary to adrenal insufficiency should be treated by rapid volume expansion with saline and appropriate steroid therapy. The treatment program was outlined in an earlier article in this series.) Most cases of severe potassium intoxication occur in the setting of compromised renal function.

Artifactual elevation of the serum potassium level may be seen in conditions associated with thrombocytosis as the platelets release potassium within the collection tube, or with hemolysis within the collection tube. If plasma potassium samples are obtained in these conditions, the potassium level will not be elevated because the anti-coagulant in the tubes will retard hemolysis.

Levinsky<sup>3</sup> considers hyperkalemia minimal when the potassium level does not exceed 6.5 mEq/liter, moderate hyperkalemia when the potassium level is between 6.5 and 8.0 mEq/liter, and severe hyperkalemia when the potassium level exceeds 8.0 mEq/liter. Clinically, symptomatic hyperkalemia (lassitude, fatigue, and weakness) occurs when the serum potassium level exceeds 6.5 mEq/liter. Neurological examination usually discloses weakness or

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incipient paralysis, decreased reflex response, and paresthesias. When potassium exceeds 8.0 mEq/liter, complete neuromuscular paralysis may dominate the clinical picture.

The major life-threatening aspect of untreated hyperkalemia, however, is its effect on the cardiovascular system, where bradycardia, vascular collapse, and cardiac arrest may rapidly develop. Although the correlation between electrocardiographic changes and the serum potassium level is not precise, a progression of electrocardiographic changes generally precedes cardiac arrhythmias and, thus, serves to warn of an impending cardiac arrest. As serum potassium exceeds 5.5 mEq/liter, there is a peaking of the T waves, although this is not specific for hyperkalemia. When the potassium exceeds 6.5 mEq/liter, the QRS complexes widen. With further increases in serum potassium, the P wave amplitude diminishes and the P-R interval is prolonged. As the serum potassium exceeds 7.5 to 8.0 mEq/liter, the P wave may disappear, and the widened QRS complex resembles a sine wave. Ventricular fibrillation or standstill will rapidly follow the late changes unless treatment is initiated. Generally, hyperkalemia should be treated immediately if the serum potassium level exceeds 6.5 mEq/liter or if cardiac arrhythmias are present.

**Treatment of Hyperkalemia.**—Treatment of hyperkalemia can be considered in two parts. The first urgent consideration is the rapid reversal of the cardiac abnormalities; the second is the lowering of the serum potassium level.

1. *Treatment of Hyperkalemic Cardiac Toxicity.*—One ampule of 10% calcium gluconate or 10% calcium chloride administered intravenously for five to ten minutes will immediately revert to normal the electrocardiographic sine wave or widened QRS complex of hyperkalemia. However, this effect will last only as long as the calcium is infused; therefore, calcium should be repeatedly administered at a rate that will keep the ECG normal until other treatment measures have been successful in decreasing the serum potassium level. Constant electrocardiographic monitoring is required. As this method is transitory and will not lower the serum potassium level by itself, other methods must be instituted to reverse the hyperkalemia.

2. *Treatment of Hyperkalemia.*—**INFUSION OF SODIUM BICARBONATE.**—The rapid intravenous infusion of 1 ampule of sodium bicarbonate ( $\text{NaHCO}_3$ ), 44 mEq, for five to ten minutes will lower the serum potassium level by increasing the blood pH and causing potassium to move intracellularly. For each 0.1 unit rise in the blood pH, the serum potassium level will decrease by 0.5 to 1.0 mEq/liter. After the initial rapid infusion of  $\text{NaHCO}_3$ , the patient should receive 2 to 3 ampules of  $\text{NaHCO}_3$ , in a continuous intravenous infusion each hour. Rapidly effective bicarbonate therapy, however, only transfers potassium from extracellular to intracellular sites. Once the bicarbonate infusion is terminated, the potassium level will slowly rise as the pH declines.

**GLUCOSE AND INSULIN.**—Intravenously administered glucose will decrease the serum potassium level by increasing glycogen and potassium storage and by facilitating intracellular transport of potassium. Insulin is

generally given with the parenterally administered glucose to facilitate the glucose action. Usually, 500 to 1,000 ml of 10% dextrose is given intravenously over one hour along with 10 to 15 units of regular insulin given either subcutaneously or placed in the intravenously administered solution. Like the infusion of bicarbonate, the method serves only to temporarily transfer potassium from extracellular to intracellular sites and once terminated will result in the potassium level slowly rising again to hyperkalemic levels.

**SODIUM BICARBONATE AND GLUCOSE THERAPY.**—Sodium bicarbonate and glucose therapies can be combined in the treatment of hyperkalemia. After the patient has been given 1 ampule of  $\text{NaHCO}_3$  intravenously for five to ten minutes, 1,000 ml of 10% dextrose with 2 to 3 ampules of  $\text{NaHCO}_3$ , can be given for one to two hours. Ten units of regular insulin may be given subcutaneously at the beginning of the infusion.

**ION EXCHANGE RESINS.**—Cation-exchange resins (polystyrene sodium sulfonate [Kayexalate]) given as a retention enema will slowly lower the serum potassium level by exchanging sodium for potassium ions, thus facilitating an actual removal of excess potassium from the body. Generally, 30 gm of polystyrene are suspended in 100 to 200 ml of solution and administered as a high-retention enema for four hours; usually 1 mEq of potassium is exchanged for each gram of polystyrene. This can be repeated two or three times a day, but care must be taken not to overload the patient with sodium. Polystyrene, administered in a sorbitol solution, can also be administered orally two to four times daily. These methods are useful to remove an excess of total body potassium but do not act rapidly enough to treat acute hyperkalemia. Therefore, the other methods described should be applied first to treat severe crisis.

**PERITONEAL DIALYSIS AND HEMODIALYSIS.**—Hemodialysis and peritoneal dialysis are effective methods for the removal of potassium from the body, but generally are too slow to be useful in the treatment of acute hyperkalemia. In the management of acute and chronic renal failure, dialysis will effectively control uremia and other electrolyte disorders and can also be used to control the serum potassium concentration.

#### Summary of Treatment of Hyperkalemia

1. Obtain serum electrolyte, blood urea nitrogen, and blood pH levels, and take an electrocardiogram.
2. If the ECG shows QRS widening, sinus arrest, or represents a sine-wave appearance, administer 10 to 20 ml of 10% calcium gluconate intravenously for 10 minutes. Repeat if necessary to maintain normal ECG.
3. For less severe electrocardiographic abnormalities, administer 1 ampule of sodium bicarbonate intravenously for five to ten minutes, then infuse 2 to 3 ampules of sodium bicarbonate intravenously for one to two hours.
4. Alternatively, infuse 500 to 1,000 ml of 10% dextrose in water for one hour along with 10 units of regular insulin subcutaneously.
5. Steps 3 and 4 can be combined by infusion of 1,000 ml of 10% dextrose and water with 2 to 3 ampules of sodium

bicarbonate for one to two hours intravenously. Give 10 units of regular insulin subcutaneously at the beginning of the infusion.

6. Begin administration of polystyrene either as a retention enema or orally (with sorbitol) to remove excess potassium stores.

### Hypokalemia

**Diagnosis and Clinical Presentation.**—Hypokalemia is usually secondary to inadequate intake of potassium or to excessive gastrointestinal loss of potassium (eg, vomiting, diarrhea, fistulae), or renal loss (especially secondary to diuretics). Less often glucocorticoid or mineralocorticoid therapy, Cushing syndrome, primary or secondary aldosteronism, or rarely hypokalemic periodic paralysis will be responsible for a hypokalemic state. As the serum potassium level decreases below 3.5 mEq/liter, the patient may experience weakness and lethargy. If the potassium level declines below 2.5 mEq/liter, anorexia, nausea, vomiting, abdominal distention, and ileus may result. Severe potassium deficiency has caused paralysis, coma, and severe cardiac disturbances, such as arrhythmias, left ventricular dilatation, and asystole.

Electrocardiographic changes of hypokalemia consist of T wave flattening, ST segment depression, and the appearance of a prominent U wave that gives the impression of a prolonged QT interval.

**Treatment of Hypokalemia.**—Treatment should consist of correcting both the underlying cause of the hypokalemia and replacing the decreased potassium stores. As most causes of hypokalemia are associated with a loss of chlo-

ride, it is usually necessary to also replace chloride, because renal potassium wasting is perpetuated by the presence of alkalosis and intracellular hydrogen ion depletion. This can be accomplished by the administration of potassium chloride.

If the patient is clinically well and can take medications orally, potassium chloride replacement can be accomplished by oral administration of 40 mEq three to four times daily with daily monitoring of serum electrolytes. If parenterally administered medication is necessary, 40 mEq of potassium chloride in 1,000 ml of physiological saline can be administered over a two- to four-hour period. If possible, it is best to avoid glucose solutions, as glucose tends to lower the serum potassium level. Potassium can safely be given at a rate of 20 to 40 mEq/hr in normal subjects without inducing hyperkalemia or electrocardiographic changes. However, potassium should not be given intravenously at a rate greater than 40 mEq/hr. The rate of administration should be reduced in the presence of azotemia. Usually, rapid rates of potassium infusion are not necessary unless the patient has severe cardiac or central nervous system symptoms or both. However, even in severe hypokalemic states, usually no more than 160 mEq of potassium chloride should be administered during the first 24 hours.

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Barlene DeWenise 8



# Textbook of Advanced Cardiac Life Support

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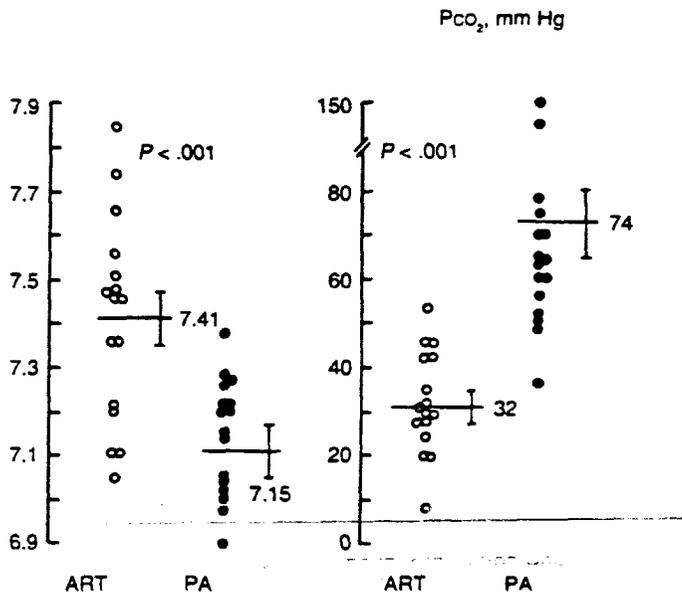


Fig 13. Differences in systemic arterial (ART) and pulmonary artery (PA) pH and Pco<sub>2</sub> in 16 patients during CPR. Measurements were made at a median of 23 minutes after onset of arrest. Average dose of NaHCO<sub>3</sub> (+SEM) was 130 + 30 mEq over a median interval of 23 minutes. Numerical mean values for each measurement are indicated on the graph. Mixed venous acidemia from CO<sub>2</sub> retention is evident. NaHCO<sub>3</sub> would be expected to worsen this acidosis from CO<sub>2</sub> formation. From Weil et al.<sup>175</sup>

experimental acute myocardial ischemia has been shown to rise to more than 300 mm Hg, and corresponding intracellular pH falls to as low as 6.1. Liberation of CO<sub>2</sub> and its rapid intracellular diffusion after sodium bicarbonate administration may produce cerebrospinal fluid acidosis and central venous acidosis during CPR (Fig 13).<sup>175, 181</sup>

Other adverse effects from sodium bicarbonate include hypernatremia and hyperosmolality (Fig 14).<sup>185, 186</sup> Severe hyperosmolal states during resuscitation may compromise survival.<sup>186</sup> Shift in the oxyhemoglobin saturation curve caused by sodium bicarbonate can inhibit oxygen release to the tissues.

## Morphine

### Mechanism of Action

Morphine is effective treatment for ischemic chest pain and for acute pulmonary edema.<sup>198</sup> It manifests both analgesic and hemodynamic effects.<sup>199</sup> It increases venous capacitance and reduces systemic vascular resistance, relieving pulmonary congestion.<sup>200</sup> In doing so, it reduces intramyocardial wall tension, which decreases myocardial oxygen requirements.<sup>201</sup> Morphine's hemodynamic effects may be mediated by sympatholytic effects on the central nervous system since they are most pronounced in patients with heightened sympathetic activity.<sup>202</sup>

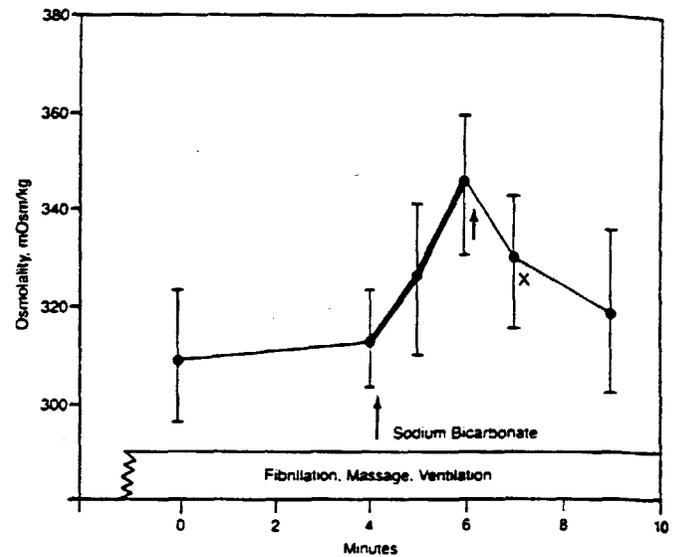


Fig 14. Arterial osmolality in six patients during cardiac resuscitation. Note significant and persistent rise in osmolality after sodium bicarbonate administration (x indicates P < .05). From Bishop and Weisfeldt.<sup>186</sup>

## Indications

Morphine is the traditional drug of choice for the treatment of pain and anxiety associated with acute myocardial infarction. It is also useful for treating patients with acute cardiogenic pulmonary edema.

## Dosage

Morphine should be administered IV in small incremental doses of 1 to 3 mg slow IV (over 1 to 5 minutes) until the desired effect is achieved.

## Precautions

Like other narcotic analgesics, morphine is a respiratory depressant. Small incremental doses at frequent intervals make serious depression less likely than a single large bolus. Excessive narcosis can be reversed with IV naloxone (0.4 to 0.8 mg). Hypotension is most common and most severe in volume-depleted patients and in patients who are dependent on elevated systemic resistance for maintenance of blood pressure.<sup>203</sup> Hypotension and an inappropriate heart rate response that appears to be vagally mediated also have been described.<sup>203</sup>

## Calcium Chloride

### Mechanism of Action

Calcium ions increase the force of myocardial contraction.<sup>204</sup> In response to electrical stimulation of muscle, calcium ions enter the sarcoplasm from the extracellular space.<sup>205, 206</sup> Calcium ions contained in the sarcoplasmic

reticulum are rapidly transferred to the sites of interaction between the actin and myosin filaments of the sarcomere to initiate myofibril shortening.<sup>207</sup> Thus, calcium increases myocardial contractile function. The positive inotropic effects of calcium are modulated by its action on systemic vascular resistance. Calcium may either increase or decrease systemic vascular resistance.<sup>208-210</sup> In normal hearts calcium's positive inotropic and vasoconstricting effects produce a predictable rise in systemic arterial pressure.<sup>208,211</sup>

## Indications

Although calcium ions play a critical role in myocardial contractile performance and impulse formation, retrospective and prospective studies in the cardiac arrest setting have not demonstrated benefit from the use of calcium.<sup>212,213</sup> In addition, there is considerable theoretical reason to believe that the high levels induced by calcium administration may be detrimental.<sup>214,215</sup> When hyperkalemia, hypocalcemia (eg, after multiple blood transfusions), or calcium channel blocker toxicity is present, calcium is probably helpful. Otherwise, calcium should not be used. Some clinical experience has observed calcium to be useful to prevent the hypotensive effects of calcium channel blocking agents (IV verapamil and diltiazem).

## Dosage

### Hyperkalemia and Calcium Channel Overdose

Give 8 to 16 mg/kg of 10% solution. Repeat if necessary.

### Prophylaxis of Calcium Channel Blockers

A 10-mL prefilled syringe or ampule of 10% solution of calcium chloride (1 mL = 100 mg) contains 13.6 mEq of calcium. Calcium chloride can be given IV in a dose of 2 to 4 mg/kg of 10% solution (1.36 mEq of calcium per 100 mg of salt per milliliter) and repeated if necessary at 10-minute intervals. Two other calcium salts are available, calcium gluceptate and calcium gluconate. Calcium gluceptate can be given in a dose of 5 to 7 mL; the dose of calcium gluconate is 5 to 8 mL. Calcium chloride is preferable because it produces consistently higher and more predictable levels of ionized calcium in plasma.<sup>216</sup>

## Precautions

If the heart is beating, rapid administration of calcium can produce slowing of the cardiac rate. Calcium must be used cautiously in the patient receiving digitalis, because calcium increases ventricular irritability and may precipitate digitalis toxicity. In the presence of sodium bicarbonate, calcium salts will precipitate as carbonates. Thus these drugs cannot be administered together. Calcium may produce vasospasm in coronary and cerebral arteries.

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# Cardiology

THIRD EDITION

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Accurate indications, adverse reactions, and dosage schedules for drugs are provided in this book, but it is possible that they may change. The reader is urged to review the package information data of the manufacturers of the medications mentioned.

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## Preface

Many recent changes in the practice of Cardiology necessitated extensive revisions in this third edition. The application of new diagnostic tests, therapeutic procedures, and drugs are introduced throughout the text.

The authors wish to acknowledge the housestaff and students of Harbor/UCLA Medical Center and Huntington Memorial Hospital for their suggestions and criticisms. We are grateful to previous contributors from Richard Haskell, M.D., Milton Smith, M.D., and Keith Bowman, M.D., as well as the recent assistance from Gary Conrad, M.D. We especially thank Diana Barnes of Cyber Scribe for the preparation of the manuscript.

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v

### Sodium Bicarbonate

Limited systemic perfusion and oxygen delivery during cardiopulmonary arrest and CPR result in the production of lactic acid, the end product of anaerobic metabolism. Sodium bicarbonate may be administered during CPR to treat the resultant metabolic acidosis. **Sodium bicarbonate should not be administered indiscriminately**; when used in excess, metabolic alkalosis, hypernatremia, and hyperosmolality may result.<sup>27</sup> In addition, hypertonic buffer solutions may affect peripheral arterial tone and decrease the likelihood of successful cardiac resuscitation.<sup>28</sup>

#### Dose

The use of sodium bicarbonate during cardiac arrest and resuscitation should be guided by arterial blood gas and pH determinations and assessment of base deficit using standard formula as guidelines:

pH decrease of 0.15 units = base deficit of 10 mEq/L.

Dose of bicarbonate (mEq) = base deficit (mEq/L)  
 × body weight (kg) × 0.25  
 (the bicarbonate "space")

It is recommended that 50% of the calculated dose be given initially with subsequent doses determined by reassessment of acid-base status. Sodium bicarbonate should not be used to treat respiratory acidosis.

### Calcium Chloride

The calcium ion is known to have a positive effect upon the contractile state of the myocardium mediated through excitation-contraction coupling. Additional electrophysiologic effects mediated via "slow channels" have also been described.<sup>29</sup> The role of slow channel or calcium-mediated responses in the genesis of arrhythmias in the hypoxic myocardium and following reperfusion is presently under active investigation.<sup>30</sup>

Several studies indicate that "routine" calcium administration during cardiac arrest is of limited value.<sup>31</sup> It is of no value in asystole and of questionable benefit in electromechanical dissociation (EMD). Calcium administration may in fact be detrimental, as intracellular calcium accumulation may play a role in cell death.<sup>31</sup> At present, cal-

cium use during CPR is recommended only in selected situations, i.e., cardiac arrest due to hyperkalemia, hypocalcemia, or following use of calcium blocking agents.

Recent clinical studies have demonstrated that ionized calcium levels decrease during prolonged cardiac arrest and CPR.<sup>32,33</sup> The mechanism of ionized hypocalcemia during prolonged CPR is uncertain. It is also uncertain if the observed decrease in free calcium alters the outcome of resuscitation efforts.

#### Dose

Calcium chloride is usually given in a dose of 5 ml of a 10% solution and repeated if necessary in 10 min. The 10% solution contains 1.36 mEq Ca<sup>2+</sup>/100 mg of salt (100 mg of salt = 1.36 mEq of Ca<sup>2+</sup> = 1 ml). Calcium should never be given in the same intravenous line with bicarbonate, since it will precipitate.

### Lidocaine

Lidocaine is currently the drug of choice for the management of ventricular ectopy in the setting of cardiopulmonary arrest. Its effect on spontaneous phase 4 depolarization, conduction velocity in the Purkinje network, and dispersion of recovery of excitability (refractory period) combine to make it an effective agent in the management of ventricular arrhythmias due to reentry or ectopic, automatic foci. It is recommended for use in the treatment of ventricular extra systoles, ventricular tachycardia, and ventricular fibrillation when countershock has failed. It should also be administered following successful defibrillation.

#### Dose

Lidocaine is administered as a slow intravenous bolus (1 mg/kg of body weight) to achieve a therapeutic blood level followed by a constant infusion at a rate of 1-4 mg/min using a controlled infusion device. If ventricular ectopy persists after the initial bolus, additional slow 50-mg boluses may be given every 5 min until the arrhythmia is suppressed or until 225 mg has been given.<sup>34</sup> After each additional bolus, the constant infusion rate should be increased by 1 mg/min to a maximum of 4 mg/min. The bolus dose should be decreased by 50% in the presence of reduced cardiac output, liver dysfunction, or in patients over 65 years of age.

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5<sup>TH</sup> EDITION

# HEART DISEASE

*A Textbook of Cardiovascular Medicine*

Edited by

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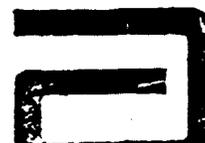
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TABLE 24-6 ADVANCED LIFE SUPPORT FOR CARDIAC ARREST VICTIMS—Continued

C. ASYSTOLE/SEVERE BRADYCARDIA	
<ul style="list-style-type: none"> <li>Continue CPR</li> <li>Intubate at once</li> <li>Obtain IV access</li> <li>Confirm asystole in more than one lead</li> </ul>	
<p>Consider possible causes</p> <ul style="list-style-type: none"> <li>Hypoxia</li> <li>Hyperkalemia</li> <li>Hypokalemia</li> <li>Preexisting acidosis</li> <li>Drug overdose</li> <li>Hypothermia</li> </ul>	
<p>Consider immediate transcutaneous pacing (TCP)*</p>	
<ul style="list-style-type: none"> <li>Epinephrine 1 mg IV push,† repeat every 3-5 min</li> </ul>	
<ul style="list-style-type: none"> <li>Atropine 1 mg IV, repeat every 3-5 min up to a total of 0.04 mg/kg‡</li> </ul>	
<p>Consider</p> <ul style="list-style-type: none"> <li>Termination of efforts¶</li> </ul>	
<p>* TCP is a Class IIb intervention. Lack of success may be due to delays in pacing. To be effective, TCP must be performed simultaneously with drugs. Evidence does not support routine use of TCP for asystole.</p> <p>† The recommended dose of epinephrine is 1 mg IV push every 3-5 min. If this approach fails, several Class IIb dosing regimens can be considered:</p> <ul style="list-style-type: none"> <li>Intermediate: epinephrine 2-5 mg IV push, every 3-5 min</li> <li>Escalating: epinephrine 1 mg-3 mg-5 mg IV push (3 min apart)</li> <li>High: epinephrine 0.1 mg/kg IV push, every 3-5 min</li> </ul> <p>‡ Sodium bicarbonate 1 mEq/kg is Class I if patient has known preexisting hyperkalemia.</p>	<p>§ Shorter atropine dosing intervals are Class IIb in asystolic arrest.</p> <p>¶ Sodium bicarbonate 1 mEq/kg</p> <p>Class IIa</p> <ul style="list-style-type: none"> <li>if known preexisting bicarbonate-responsive acidosis</li> <li>if overdose with tricyclic antidepressants</li> <li>to alkalinize the urine in drug overdoses</li> </ul> <p>Class IIb</p> <ul style="list-style-type: none"> <li>if intubated and continued long arrest interval</li> <li>upon return of spontaneous circulation after long arrest interval</li> </ul> <p>Class III</p> <ul style="list-style-type: none"> <li>hypoxic lactic acidosis</li> </ul> <p>¶ If patient remains in asystole or other agonal rhythms after successful intubation and initial medications and no reversible causes are identified, consider termination of resuscitative efforts by a physician. Consider interval since arrest.</p>

## Advanced Life Support and Definitive Resuscitation

This next step in the sequence of resuscitative efforts is designed to achieve definitive support and stabilization of the patient.<sup>289</sup> The implementation of advanced life support does not indicate abrupt cessation of basic life support activities, but rather a transition from one level of activity to the next. In the past, advanced life support required judgments and technical skills which removed it from the realm of activity of lay bystanders and even emergency medical technicians, limiting these activities to specifically trained paramedical personnel, nurses, and physicians. With further education of emergency technicians, most community-based CPR programs now permit them to carry out advanced life support activities.<sup>289,298,320</sup> In addition, the development and testing of equipment—the automatic external defibrillator—which has the ability to sense and analyze air flow, sense cardiac electrical activity, and provide definitive electrical intervention<sup>323,347</sup> may provide a role for less highly trained rescue personnel (i.e., police, ambulance drivers) and perhaps even trained lay bystanders in advanced life support.

The general goals of advanced life support are to optimize ventilation, revert the cardiac rhythm to one which is hemodynamically effective, and maintain and support the restored circulation. Thus, during advanced life support, the patient (1) is intubated and well oxygenated, (2) is defibrillated, cardioverted, or paced, and (3) has an intravenous line established to deliver necessary medications. After intubation, the goal of ventilation is to reverse hypoxemia and not merely achieve a high alveolar pO<sub>2</sub>. Thus oxygen rather than room air should be used to ventilate the patient; if possible, the arterial pO<sub>2</sub> should be monitored. Respirator support in hospital and AMBU bag by means of an endotracheal tube or face mask in the out-of-hospital setting usually are used.

**DEFIBRILLATION-CARDIOVERSION** (Table 24-6A). Rapid conversion to an effective cardiac electrical mechanism is a key step for successful resuscitation.<sup>292,308</sup> Delay should be minimal, even when conditions for CPR are optimal. When VF or a rapid VT is recognized on a monitor or by telemetry, defibrillation should be carried out immediately with a shock of 200 joules. Up to 90 per cent of VF victims weighing up to 90 kg can be successfully resuscitated with a 200-joule shock,<sup>248</sup> and a 300- or 360-joule shock may be used if this is not successful.<sup>289</sup> Failure of the initial shocks to successfully cardiovert to an effective rhythm is a poor prognostic sign.<sup>289</sup> After failure of three shocks up to a maximum of 360 joules of energy, CPR should be continued while the patient is intubated and intravenous access achieved. Epinephrine, 1 mg IV, is administered and followed by repeated defibrillation attempts at 360 joules. Epinephrine may be repeated at 3- to 5-minute intervals with defibrillator shocks in between. Simultaneously, the rescuer should focus on ventilation to correct the biochemistry of the blood, efforts which render the heart more likely to reestablish a stable rhythm (i.e., improved oxygenation, reversal of acidosis, and improvement of the underlying electrophysiological condition). Although adequate oxygenation of the blood is crucial in the immediate management of the metabolic acidosis of cardiac arrest, additional correction may be achieved if necessary by intravenous administration of sodium bicarbonate. This is recommended for circumstances of known or suspected preexisting bicarbonate-responsive causes of acidosis, certain drug overdoses, and prolonged resuscitation runs.<sup>289</sup> The more general role for bicarbonate during cardiac arrest has been questioned<sup>349-351</sup>; but in any circumstance, much less sodium bicarbonate than was previously recommended is adequate for treatment of acidosis in this setting.<sup>352</sup> Excessive quantities can be deleterious.<sup>351,352</sup> Although some investigators have questioned the use of sodium bicarbonate at all because

...with improved cerebral perfusion,<sup>335,339,340</sup> and the reduction in coronary blood flow caused by elevated intracranial pressures by certain techniques<sup>335,341</sup> may be too high a price for the improved peripheral flow. In addition, a splanchnic-to-abdominal gradient has been demonstrated in experimental SCV,<sup>342</sup> which could divert flow from the abdomen in the absence of concomitant abdominal binding. Comparative hemodynamics of models of conventional chest compression and techniques based on chest (thoracic) compression suggest that blood movement is based on both mechanisms in experimental<sup>343</sup> and clinical<sup>344</sup> studies. Based upon these observations, new mechanically assisted techniques for improving circulation during CPR are being evaluated.<sup>344-346</sup> More clinical studies are needed

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When the ECG shows "fine" fibrillation waves, defibrillation efforts are often unsuccessful. The administration of epinephrine (5 to 10 mL of 1:10,000) intravenously (IV) results in a more vigorous and coarse fibrillation that is more responsive to defibrillation. This effect is likely due to improved coronary flow following epinephrine administration (see below) and perhaps direct myocardial effects on the electrical properties for defibrillation. If defibrillation fails, it is likely that marked acidosis or hypoxemia is present. Emphasis should be on hyperventilation with supplemental oxygen to correct both hypoxemia and metabolic acidosis.<sup>45</sup> Sodium bicarbonate might then be administered (1 meq/kg) to aid in the management of acidosis, and defibrillation should be repeated with 320 to 400 J. By using instantaneous Fourier transformation analysis, Brown et al. have demonstrated that the coarseness of the waveform of ventricular fibrillation may be highly predictive of subsequent survival and appears to correlate with coronary flow.<sup>46</sup> Animal data suggest that techniques or drugs that increase the "coarseness" of the ventricular fibrillation waveform may increase the likelihood of successful defibrillation. Preliminary human data to confirm these observations is encouraging, though the technique of instantaneous waveform analysis is still undergoing clinical testing.<sup>46</sup>

For recurrent ventricular fibrillation, the administration of 75 to 100 mg IV of lidocaine followed by repeat defibrillation may increase the likelihood of returning to a stable rhythm. Lidocaine is an effective antiarrhythmic agent for recurrent ventricular fibrillation. Amiodarone (a bolus of 150 to 300 mg over 10 min, 1.0 to 2.0 mg/min for 6 h, then 0.5 to 1.0 mg/min for 6 to 24 h) intravenously has recently been shown to be of modest benefit for recurrent ventricular fibrillation in patients failing treatment with lidocaine alone. Procainamide or bretylium can additionally be used in patients failing lidocaine, but both can cause considerable hypotension.<sup>29,47,48</sup> For recurrent ventricular fibrillation in the setting of ischemia, intravenous propranolol or other intravenous beta blockers are remarkably effective drugs. Beta blockers seem particularly helpful in the setting of primary ventricular fibrillation complicating acute myocardial infarction.

Hyperkalemia is a readily treated condition that can cause atrioventricular (AV) block, impaired intraatrial and intraventricular conduction, and occasionally ventricular fibrillation or, less commonly, asystole. It can be recognized by the development of tall, peaked T waves with a normal QT interval and sine wave-like ventricular tachycardia. Life-threatening hyperkalemia responds most readily to calcium infusion; 10 to 30 mL of 10% calcium gluconate is infused intravenously over 1 to 5 min, under constant ECG monitoring. Calcium counteracts the adverse effects of potassium on the neuromuscular membranes but does not alter plasma potassium. Its effect, though immediate, is transient. Hyperkalemia should subsequently be treated by glucose-insulin or ion-exchange resins (see also Chap. 27). Sodium bicarbonate is used as an agent to lower potassium.

With ventricular tachycardia, cough may reverse the arrhythmia without defibrillation, and repeated cough may maintain the conscious state as a result of the rise in intrathoracic

pressure.<sup>10,49</sup> The efficacy of the precordial thump (precordial chest blows) has been variably reported in patients with ventricular tachycardia. A thump is generally ineffective for terminating prehospital ventricular fibrillation or asystole. Hence, it should never be used in the patient with ventricular tachycardia and a pulse unless a defibrillator is immediately available.

### Asystole or Heart Block

For patients with prehospital cardiac arrest, asystole has been shown to be an ominous rhythm with a very low likelihood of successful resuscitation.<sup>30</sup> On the other hand, asystole due to vagal stimulation is the commonest cause of cardiac arrest associated with anesthesia induction and surgical procedures. Asystole also occurs as a result of heart block or sinus node disease (see Chap. 27). Atropine (0.5 mg) given intravenously and repeated in 5 min can be used acutely to prevent or reverse severe bradycardia in many of these settings.

If asystole is witnessed or of short duration, vigorous blows to the precordium may sometimes restart the heart. Rhythmic chest blows may maintain limited perfusion and can be continued if needed while palpating the femoral or carotid pulse until other treatment is available. If the chest blow fails, cardiopulmonary resuscitation should be initiated and intravenous epinephrine (5 to 10 mL of 1:10,000) administered. Possible treatable causes of asystole—such as acidosis, hypoxemia, hyper- or hypokalemia, and hypothermia—should be considered and treated appropriately if suspected. If an overdose of calcium channel blocker is suspected, calcium chloride, 1 g given as an intravenous bolus may be very effective (class IIA recommendation). Resuscitation measures may result in the return of a slow ventricular rhythm, which can subsequently be supported with atropine (1 to 2 mg IV) until a temporary pacemaker is placed. Temporary pacing is the optimal treatment for true asystole or profound bradycardia. Obviously, considerable skill and training are required for temporary transvenous pacemaker placement (see Chap. 34). Transcutaneous pacing has been developed as a noninvasive and simple technique that can be implemented rapidly. It uses external surface electrodes with a high-voltage pacing source. Higher voltages are required to overcome transthoracic resistance, but they are painful and are therefore used mainly on unconscious patients. The energy delivered to the heart by this technique is variable, as is its efficacy. Recently, pacing sources with longer pacing stimulus duration have been developed and may offer less painful and more effective pacing. Prehospital studies of transcutaneous pacing for asystole have not confirmed an improvement in survival.<sup>50</sup> It may, however, be of some benefit for patients early in asystole (class IIB intervention). Clinical evidence does not support its routine use in all patients with asystole.

In rare instances, very fine ventricular fibrillation may result in an almost straight line on a single-lead ECG and thus be mistaken for "asystole." In such cases, where the diagnosis of asystole is in question, it is suggested that a perpendicular ECG lead be viewed. Rotation of "quick look" ECG paddles

by 90° easily achieves this. If ventricular fibrillation is present, the perpendicular ECG lead will demonstrate a typical fibrillation pattern, whereas in true asystole, a straight line will be seen in all ECG leads. If ventricular fibrillation is diagnosed, the initial treatment should be according to the outline above—i.e., three successive countershocks. There is little value in defibrillating true asystole.

### Electromechanical Dissociation

In electromechanical dissociation (EMD), there is evidence of organized electrical activity on the ECG at a reasonable rate but failure of effective perfusion (no pulse or blood pressure). The most treatable causes of this condition are hypovolemia due to severe hemorrhage, pericardial tamponade, tension pneumothorax, hypoxia, hypothermia, acidosis, hyperkalemia, and massive pulmonary embolism. Signs of these problems should be sought and definitive therapy undertaken with fluids and/or blood replacement, pericardiocentesis, placement of a pleural needle or tube, endotracheal intubation, and other maneuvers as deemed necessary. These conditions should also be strongly considered if CPR results in no palpable pulse or evidence of perfusion. Unfortunately, many patients with electromechanical dissociation have primary myocardial failure. Following diagnosis, ventilation should be optimized and epinephrine administered. Calcium chloride was used for EMD, but prospective studies have not shown it to improve survival.<sup>51</sup> In acute myocardial infarction, sudden electromechanical dissociation is a sign of myocardial rupture. In such cases, pericardiocentesis and surgical repair can rarely result in survival.

### ESTABLISHMENT OF AN INTRAVENOUS ROUTE

While external chest compression and artificial ventilation are continued, a plastic catheter should be inserted into a large peripheral vein. Drug administration during CPR should be accomplished only from a source above the diaphragm, since there is little cephalad flow from veins below the diaphragm. If a peripheral vein cannot be cannulated, a cutdown should be attempted or a central venous line placed by a percutaneous route. If CPR is properly performed, drugs administered through a peripheral line will often reach the arterial circulation within 15 to 30 s.<sup>45</sup> Recent data suggest that a 20-mL fluid bolus significantly improves peripheral drug delivery to the central compartment. Intracardiac injections are unnecessary except when there is no intravenous access. If an intravenous route is unavailable, epinephrine (1 to 2 mg in 10 mL of sterile distilled water) and lidocaine (50 to 100 mg in 10 mL of sterile distilled water) can be administered by way of the endotracheal tube into the bronchial tree. The drug should be injected through a long catheter passed beyond the tip of the endotracheal tube. Cardiac compression should be withheld, and several insufflations with an Ambu bag should immediately follow drug administration to aid drug absorption through aerosolization.

### MAJOR DRUGS USED DURING CARDIOPULMONARY RESUSCITATION

Drugs that are used for the treatment of various arrhythmias are mentioned above. Catecholamines are used in cardiac arrest to (1) increase arterial and coronary perfusion during CPR, (2) stimulate spontaneous contractions during asystole, (3) make fine ventricular fibrillation responsive to defibrillation, and (4) act as an inotropic agent.

Epinephrine is effective in achieving all these goals. Numerous studies have extensively evaluated the hemodynamic effects of epinephrine during resuscitation and have clearly shown it to be the singularly most important drug for common use during CPR. Animal studies show that during conventional CPR, cerebral and myocardial perfusion pressures are low. Epinephrine increases brain and heart flow by two mechanisms: (1) It prevents carotid artery collapse and raises arterial pressure during both chest compression and the release of chest compression (i.e., "systole" and "diastole," respectively). This results in higher carotid arterial "systolic" and "diastolic" pressures, which, in turn, are reflected as higher cerebral perfusion and myocardial perfusion pressures and flow. (2) It preferentially reduces blood flow to the renal, carotid, renal, and splanchnic beds, thereby redirecting flow toward the brain and heart.<sup>52,53</sup>

Arterial collapse at the thoracic inlet has been shown to be the critical limiting factor for cerebral perfusion pressure and flow during prolonged CPR. Arterial collapse results in high extravascular intrathoracic pressures, low intravascular volumes, and loss of arterial tone. Collapse results in a precipitous fall in carotid arterial and hence cerebral perfusion pressure. Epinephrine during CPR can not only reverse arterial collapse but also prevent it from developing. With the administration of epinephrine during conventional manual CPR in the dog, cerebral blood flow can be maintained at approximately 15 percent and myocardial flow at approximately 5 percent of prearrest values for 20 min.

These data strongly support the early and frequent use of epinephrine during CPR in an effort to optimize the perfusion of vital organs. Hence, once the diagnosis of cardiac arrest is established and CPR initiated, epinephrine should be administered as soon as possible. The recommended dose is 0.5 to 1 mg IV, and this dose should be repeated at approximately 3- to 5-min intervals unless effective cardiac activity is restored. Although promising in the animal model, large clinical trials failed to demonstrate improved survival with high-dose epinephrine.<sup>54,55</sup> Hence, most experts would use 1 mg IV uniformly. Higher doses may be used for the second and third dose (3 and 5 mg) if the initial dose, CPR, and defibrillation fail.<sup>29</sup> If an intravenous route is not available, epinephrine can be administered down the endotracheal tube; 10 mL of a 1:10,000 solution should be used, and this can also be repeated every 3 to 5 min.

The benefits of epinephrine are principally due to the alpha vasoconstriction induced by this agent. The inotropic effects of the drug may not be helpful, since these effects increase myocardial oxygen demand, even during ventricular fibrillation.

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