

## Cardiac Electrolytes and Biomarkers

### Objectives

1. List and identify cardiac electrolyte abnormalities
2. Identify common causes of electrolyte disorders
3. List treatment options for electrolyte abnormalities
4. List the biomarkers associated with the cardiac system

Electrolyte abnormalities are commonly associated with cardiovascular emergencies. These abnormalities may cause or contribute to cardiac arrest and may hinder resuscitative efforts. In some cases therapy for life-threatening electrolyte disorders should be initiated before laboratory results become available.

### Potassium (K<sup>+</sup>)

The magnitude of the potassium gradient across cell membranes determines excitability of nerve and muscle cells, including the myocardium. Rapid or significant changes in the serum potassium concentration can have life-threatening consequences.

Evaluation of serum potassium must consider the effects of changes in serum pH. When serum pH falls, serum potassium rises because potassium shifts from the cellular to the vascular space. When serum pH rises, serum potassium falls because potassium shifts from the vascular space into the cells. Effects of pH changes on serum potassium should be anticipated during therapy for hyperkalemia or hypokalemia and during any therapy that may cause changes in serum pH (e.g., treatment of diabetic ketoacidosis).

### Hyperkalemia

Although hyperkalemia is defined as a serum potassium concentration  $>5$  mEq/L, it is moderate (6 to 7 mEq/L) and severe ( $>7$  mEq/L) hyperkalemia that are life-threatening and require immediate therapy. Hyperkalemia is most commonly seen in patients with end-stage renal disease. Many medications can contribute to the development of hyperkalemia. Identification of potential causes of hyperkalemia will contribute to rapid identification and treatment.

### Common Causes of Hyperkalemia

#### Endogenous Causes

- Chronic renal failure
- Metabolic acidosis (eg, diabetic ketoacidosis)
- Pseudohypoaldosteronism type II (also known as Gordon's syndrome; familial hyperkalemia and hypertension)
- Chemotherapy causing tumor lysis

Muscle breakdown (rhabdomyolysis)  
Renal tubular acidosis  
Hemolysis  
Hypoaldosteronism (Addison's disease, hyporeninemia)  
Hyperkalemic periodic paralysis

#### Exogenous Causes

Medications: K<sup>+</sup>-sparing diuretics, ACE inhibitors, nonsteroidal anti-inflammatory drugs, potassium supplements, penicillin derivatives, succinylcholine, heparin therapy (especially in patients with other risk factors), beta-blockers  
Blood administration (particularly with large transfusions of older "bank" blood)  
Diet (rarely the sole cause), salt substitutes  
Pseudohyperkalemia (due to blood sampling or hemolysis, high white blood cell count, high platelets, tumor lysis syndrome)

Signs and symptoms of hyperkalemia include weakness, ascending paralysis, and respiratory failure. A variety of electrocardiographic (ECG) changes suggest hyperkalemia. Early findings include peaked T waves (tenting). As the serum potassium rises further, flattened P waves, prolonged PR interval (first-degree heart block), widened QRS complex, deepened S waves, and merging of S and T waves can be seen. If hyperkalemia is left untreated, a sine-wave pattern, idioventricular rhythms, and asystolic cardiac arrest may develop.

#### Treatment of Hyperkalemia

The treatment of hyperkalemia is determined by its severity and the patient's clinical condition. Stop sources of exogenous potassium administration (eg, consider supplements and maintenance IV fluids) and evaluate drugs that can increase serum potassium (eg, potassium-sparing diuretics, angiotensin-converting enzyme [ACE] inhibitors, nonsteroidal anti-inflammatory agents). Additional treatment is based on the severity of the hyperkalemia and its clinical consequences. The following sequences list the treatments for hyperkalemia in order of priority.

For mild elevation (5 to 6 mEq/L), remove potassium from the body with

Diuretics: furosemide 40 to 80 mg IV  
Resins: Kayexalate 15 to 30 g in 50 to 100 mL of 20% sorbitol either orally or by retention enema

For moderate elevation (6 to 7 mEq/L), shift potassium intracellularly with

Glucose plus insulin: mix 25 g (50 mL of D50) glucose and 10 U regular insulin and give IV over 15 to 30 minutes  
Sodium bicarbonate: 50 mEq IV over 5 minutes (sodium bicarbonate alone is less effective than glucose plus insulin or nebulized albuterol, particularly for treatment of patients with renal failure; it is best used in conjunction with these medications)  
Nebulized albuterol: 10 to 20 mg nebulized over 15 minutes

For severe elevation ( $>7$  mEq/L with toxic ECG changes), you need to shift potassium into the cells and eliminate potassium from the body. Therapies that shift potassium will act rapidly but they are temporary; if the serum potassium rebounds you may need to repeat those therapies. In order of priority, treatment includes the following:

#### Shift potassium into cells:

Calcium chloride (10%): 500 to 1000 mg (5 to 10 mL) IV over 2 to 5 minutes to reduce the effects of potassium at the myocardial cell membrane (lowers risk of ventricular fibrillation)

Sodium bicarbonate: 50 mEq IV over 5 minutes (may be less effective for patients with end-stage renal disease)

Glucose plus insulin: mix 25 g (50 mL of D50) glucose and 10 units regular insulin and give IV over 15 to 30 minutes

Nebulized albuterol: 10 to 20 mg nebulized over 15 minutes

#### Promote potassium excretion:

Diuresis: furosemide 40 to 80 mg IV

Kayexalate enema: 15 to 50 g plus sorbitol PO or per rectum

Dialysis

#### Hypokalemia

Hypokalemia is defined as a serum potassium level  $<3.5$  mEq/L. The most common causes of low serum potassium are gastrointestinal loss (diarrhea, laxatives), renal loss (hyperaldosteronism, severe hyperglycemia, potassium-depleting diuretics, carbenicillin, sodium penicillin, amphotericin B), intracellular shift (alkalosis or a rise in pH), and malnutrition.

The major consequences of severe hypokalemia result from its effects on nerves and muscles (including the heart). The myocardium is extremely sensitive to the effects of hypokalemia, particularly if the patient has coronary artery disease or is taking a digitalis derivative. Symptoms of mild hypokalemia are weakness, fatigue, paralysis, respiratory difficulty, constipation, paralytic ileus, and leg cramps; more severe hypokalemia will alter cardiac tissue excitability and conduction. Hypokalemia can produce ECG changes such as U waves, T-wave flattening, and arrhythmias (especially if the patient is taking digoxin), particularly ventricular arrhythmias. Pulseless electrical activity or asystole may develop.

#### Treatment of Hypokalemia

The treatment of hypokalemia consists of minimizing further potassium loss and providing potassium replacement. IV administration of potassium is indicated when arrhythmias are present or hypokalemia is severe (potassium level of  $<2.5$  mEq/L). Gradual correction of hypokalemia is preferable to rapid correction unless the patient is clinically unstable.

Administration of potassium may be empirical in emergent conditions. When indicated, the maximum amount of IV potassium replacement should be 10 to 20 mEq/h with continuous ECG monitoring during infusion. A more concentrated solution of potassium may be infused if a central line is used, but the tip of the catheter used for the infusion should not extend into the right atrium.

If cardiac arrest from hypokalemia is imminent (i.e., malignant ventricular arrhythmias are present), rapid replacement of potassium is required. Give an initial infusion of 10 mEq IV over 5 minutes; repeat once if needed. Document in the patient's chart that rapid infusion is intentional, in response to life-threatening hypokalemia.

### Sodium (Na<sup>+</sup>)

Sodium is the major intravascular ion that influences serum osmolality. An acute increase in serum sodium will produce an acute increase in serum osmolality; an acute decrease in serum sodium will produce an acute fall in serum osmolality.

Sodium concentration and osmolality in the intravascular and interstitial spaces equilibrate across the vascular membrane. Acute changes in serum sodium will produce free water shifts into and out of the vascular space until osmolality equilibrates in these compartments. An acute fall in serum sodium will produce an acute shift of free water from the vascular into the interstitial space and may cause cerebral edema. An acute rise in serum sodium will produce an acute shift of free water from the interstitial to the vascular space. Rapid correction of hyponatremia has been associated with development of pontine myelinolysis and cerebral bleeding. For these reasons, monitor neurologic function closely in the patient with hypernatremia or hyponatremia, particularly during correction of these conditions. Whenever possible, correct serum sodium slowly, carefully controlling the total change in serum sodium over 48 hours and avoiding overcorrection.

### Hypernatremia

Hypernatremia is defined as a serum sodium concentration >145 to 150 mEq/L. It may be caused by a primary gain in Na<sup>+</sup> or excess loss of water. Gains in sodium can result from hyperaldosteronism (excess mineralocorticoid), Cushing's syndrome (excess glucocorticoid), or excessive hypertonic saline or sodium bicarbonate administration. Loss of free water can result from gastrointestinal losses or renal excretion (e.g., osmotic diuresis or diabetes insipidus).

Hypernatremia may cause neurologic symptoms such as altered mental status, weakness, irritability, focal neurologic deficits, and even coma or seizures. The severity of symptoms is determined by the speed and magnitude of the change in serum sodium concentration.

### Treatment of Hypernatremia

Treatment of hypernatremia includes reduction of ongoing water losses (by treating the underlying cause) and correction of the water deficit. For stable, asymptomatic patients, replacement of fluid by mouth or through a nasogastric tube is effective and safe.

In hypovolemic patients the extracellular fluid volume is typically restored with normal saline or a 5% dextrose in half-normal saline solution to prevent a rapid fall in the serum sodium concentration. Avoid D5W because it will reduce the serum sodium too rapidly. During rehydration, monitor serum sodium closely to ensure a gradual fall (and prevent rapid fall) in serum sodium.

The quantity of water needed to correct hypernatremia can be calculated by using the following equation:

$$\text{Water deficit (in liters)} = \frac{\text{plasma Na concentration} - 140}{140} \times \text{total body water}$$

Total body water is approximately 50% of lean body weight in men and 40% of lean body weight in women. For example, if a 70-kg man had a serum Na<sup>+</sup> level of 160 mEq/L, the estimated free water deficit would be:

$$\frac{160 - 140}{140} \times (0.5 \times 70) = 5 \text{ L}$$

Once the free water deficit is calculated, administer fluid to lower serum sodium at a rate of 0.5 to 1 mEq/h with a decrease of no more than approximately 12 mEq/L in the first 24 hours and the remainder over the next 48 to 72 hours.

### Hyponatremia

Hyponatremia is defined as a serum sodium concentration <130 to 135 mEq/L. It is caused by an excess of water relative to sodium. Most cases of hyponatremia are caused by reduced renal excretion of water with continued water intake or by loss of sodium in the urine.

Impairment of renal water excretion may be caused by:

- Use of thiazide diuretics
- Renal failure
- ECF depletion (eg, vomiting with continued water intake)
- Syndrome of inappropriate antidiuretic hormone (SIADH) secretion
- Edematous states (eg, congestive heart failure, cirrhosis with ascites)
- Hypothyroidism
- Adrenal insufficiency

Most cases of hyponatremia are associated with low serum osmolality (so-called hypo-osmolar hyponatremia). The one common exception to this is in uncontrolled diabetes, in which hyperglycemia leads to a hyperosmolar state despite a serum sodium that is below normal (hyperosmolar hyponatremia).

Hyponatremia is usually asymptomatic unless it is acute or severe (<120 mEq/L). An abrupt fall in serum sodium produces a free water shift from the vascular to the interstitial space that can cause cerebral edema. In this case the patient may present with nausea, vomiting, headache, irritability, lethargy, seizures, coma, or even death.

#### Treatment of Hyponatremia

Treatment of hyponatremia involves administration of sodium and elimination of intravascular free water. If SIADH is present, the treatment is restriction of fluid intake to 50% to 66% of estimated maintenance fluid requirement. Correction of asymptomatic hyponatremia should be gradual: typically increase the Na<sup>+</sup> by 0.5 mEq/L per hour to a maximum change of about 12 mEq/L in the first 24 hours. Rapid correction of hyponatremia can cause coma, which may be associated with osmotic demyelination syndrome or central pontine myelinolysis, lethal disorders thought to be caused by rapid fluid shifts into and out of brain tissue.

If the patient develops neurologic compromise, administer 3% saline IV immediately to correct (raise) the serum sodium at a rate of 1 mEq/L per hour until neurologic symptoms are controlled. Some experts recommend a faster rate of correction (i.e., increase concentration 2 to 4 mEq/L per hour) when seizures are present. After neurologic symptoms are controlled, provide 3% saline IV to correct (raise) the serum sodium at a rate of 0.5 mEq/L per hour.

To determine the amount of sodium (e.g., 3% saline) required to correct the deficit, calculate the total body sodium deficit. The following formula may be used:

$$\text{Na}^+ \text{ deficit} = (\text{desired [Na}^+]-\text{current [Na}^+]) \times 0.6 \times \text{body wt (kg)}$$

(\*use 0.6 for men and 0.5 for women)

Once the deficit is estimated, determine the volume of 3% saline (513 mEq/L Na<sup>+</sup>) necessary to correct the deficit (divide the deficit by 513 mEq/L). Plan to increase the sodium by 1 mEq/L per hour over 4 hours (or until neurologic symptoms improve); then increase the sodium by 0.5 mEq/L per hour. To calculate this amount, use the amount you wish to correct the sodium in an hour (eg, 0.5 mEq/L) and multiply by 0.6 (or 0.5 in women) and then multiply by the body weight; that will calculate the amount of sodium to administer that hour. Check serum sodium frequently and monitor neurologic status.

#### Magnesium (Mg<sup>++</sup>)

Magnesium is the fourth most common mineral and the second most abundant intracellular cation (after potassium) in the human body. Because extracellular magnesium is bound to serum albumin, magnesium levels do not reliably reflect total body magnesium stores. Magnesium is necessary for the movement of sodium, potassium, and calcium into and out of cells, and magnesium plays an important role in stabilizing excitable membranes. Low potassium in combination with low magnesium is a risk factor for severe arrhythmias. Thus, magnesium balance is closely tied to sodium, calcium, and potassium balance.

### Hypermagnesemia

Hypermagnesemia is defined as a serum magnesium concentration  $>2.2$  mEq/L (normal: 1.3 to 2.2 mEq/L). The most common cause of hypermagnesemia is renal failure. Note that pre-eclampsia in pregnant women is treated with magnesium administration, often titrated to maintain the serum magnesium near the maximum normal concentration, without complications of hypermagnesemia.

Neurologic symptoms of hypermagnesemia are muscular weakness, paralysis, ataxia, drowsiness, and confusion. Moderate hypermagnesemia can produce vasodilation; severe hypermagnesemia can produce hypotension. Extremely high serum magnesium levels may produce a depressed level of consciousness, bradycardia, cardiac arrhythmias, hypoventilation, and cardiorespiratory arrest.

### Treatment of Hypermagnesemia

Hypermagnesemia is treated with administration of calcium, which removes magnesium from serum. It is important to eliminate sources of ongoing magnesium intake. Cardiorespiratory support may be needed until magnesium levels are reduced. Administration of 10% solution of calcium chloride (5 to 10 mL [500 to 1000 mg] IV) will often correct lethal arrhythmias. This dose may be repeated if needed.

Dialysis is the treatment of choice for severe hypermagnesemia. If renal function is normal and cardiovascular function adequate, IV saline diuresis (administration of IV normal saline and furosemide [1 mg/kg]) can be used to increase renal excretion of magnesium until dialysis can be performed. Diuresis can also increase calcium excretion; the development of hypocalcemia will make signs and symptoms of hypermagnesemia worse.

### Hypomagnesemia

Hypomagnesemia, defined as a serum magnesium concentration  $<1.3$  mEq/L, is far more common than hypermagnesemia. Hypomagnesemia usually results from decreased absorption or increased loss of magnesium from either the kidneys or intestines (diarrhea). Alterations in thyroid hormone function and certain medications (e.g., pentamidine, diuretics, alcohol) can also induce hypomagnesemia.

Hypomagnesemia interferes with the effects of parathyroid hormone, resulting in hypocalcemia. It may also cause hypokalemia. Symptoms of low serum magnesium are muscular tremors and fasciculations, ocular nystagmus, tetany, altered mental state, and cardiac arrhythmias such as torsades de pointes (multifocal ventricular tachycardia). Other possible symptoms are ataxia, vertigo, seizures, and dysphagia.

### Treatment of Hypomagnesemia

The treatment of hypomagnesemia is determined by its severity and the patient's clinical status. For severe or symptomatic hypomagnesemia, give 1 to 2 g of IV MgSO<sub>4</sub> over 5 to 60 minutes. For torsades de pointes with cardiac arrest, give 1 to 2 g of MgSO<sub>4</sub> IV push over 5 to 20 minutes. If torsades de pointes is intermittent and not associated with arrest, administer the magnesium over 5 to 60 minutes IV. If seizures are present, give 2

g IV MgSO<sub>4</sub> over 10 minutes. Administration of calcium is usually appropriate because most patients with hypomagnesemia are also hypocalcemic.

### Calcium (Ca<sup>++</sup>)

Calcium is the most abundant mineral in the body. Many processes depend on intracellular calcium, such as enzymatic reactions, receptor activation, muscle contraction, cardiac contractility, and platelet aggregation. Calcium is essential for bone strength and neuromuscular function. Half of all calcium in the ECF is bound to albumin; the other half is in the biologically active, ionized form. Calcium concentration is normally regulated by parathyroid hormone and vitamin D.

Total serum calcium is directly related to the serum albumin concentration. The total serum calcium will increase 0.8 mg/dL for every 1 g/dL rise in serum albumin and will fall 0.8 mg/dL for every 1 g/dL fall in serum albumin.

Although total serum albumin is directly related to total serum calcium, the ionized calcium is inversely related to serum albumin. The lower the serum albumin, the higher the portion of the total calcium that is present in ionized form. In the presence of hypoalbuminemia, although total calcium level may be low, the ionized calcium level may be normal.

Calcium antagonizes the effects of both potassium and magnesium at the cell membrane. For this reason it is extremely useful for treating the effects of hyperkalemia and hypermagnesemia.

### Hypercalcemia

Hypercalcemia is defined as a total serum calcium concentration >10.5 mEq/L (or an elevation in ionized calcium >4.8 mg/dL). Primary hyperparathyroidism and malignancy account for >90% of reported cases. In these and most forms of hypercalcemia, release of calcium from the bones and intestines is increased, and renal clearance may be compromised.

Symptoms of hypercalcemia usually develop when the total serum calcium concentration is 12 to 15 mg/dL. Neurologic symptoms are depression, weakness, fatigue, and confusion at lower levels. At higher levels patients may experience hallucinations, disorientation, hypotonicity, seizures, and coma. Hypercalcemia interferes with renal concentration of urine; the diuresis can cause dehydration.

Cardiovascular symptoms of hypercalcemia are variable. Myocardial contractility may initially increase until the calcium level reaches >15 mg/dL. Above this level myocardial depression occurs. Automaticity is decreased and ventricular systole is shortened. Arrhythmias occur because the refractory period is shortened. Hypercalcemia can worsen digitalis toxicity and may cause hypertension. In addition, many patients with hypercalcemia develop hypokalemia. Both of these conditions contribute to cardiac arrhythmias. The QT interval typically shortens when the serum calcium is >13 mg/dL, and the PR and QRS intervals are prolonged. Atrioventricular block may develop and

progress to complete heart block and even cardiac arrest when the total serum calcium is >15 to 20 mg/dL.

Gastrointestinal symptoms of hypercalcemia include dysphagia, constipation, peptic ulcers, and pancreatitis. Effects on the kidney include diminished ability to concentrate urine; diuresis, leading to loss of sodium, potassium, magnesium, and phosphate; and a vicious cycle of calcium absorption in the intestines and calcium release from the bones that worsens hypercalcemia.

#### Treatment of Hypercalcemia

Treatment for hypercalcemia is required if the patient is symptomatic (typically a total serum concentration of approximately >12 mg/dL) or if the calcium level is >15 mg/dL. Immediate therapy is directed at restoring intravascular volume and promoting calcium excretion in the urine. In patients with adequate cardiovascular and renal function this is accomplished with infusion of 0.9% saline at 300 to 500 mL/h (saline diuresis) until any fluid deficit is replaced and diuresis occurs (urine output 200 to 300 mL/h). Once adequate rehydration has occurred, the saline infusion rate is reduced to 100 to 200 mL/h. During this therapy, monitor and maintain potassium and magnesium concentrations closely because the diuresis can reduce potassium and magnesium concentrations.

Hemodialysis is the treatment of choice to rapidly decrease serum calcium in patients with heart failure or renal insufficiency. Chelating agents (e.g., 50 mmol PO<sub>4</sub> over 8 to 12 hours or EDTA 10 to 50 mg/kg over 4 hours) may be used for extreme conditions.

Use of furosemide (1 mg/kg IV) for treatment of hypercalcemia is controversial. In the presence of heart failure, administration of furosemide is required, but it can actually foster release of calcium from bone, thus worsening hypercalcemia.

#### Hypocalcemia

Hypocalcemia is defined as a serum calcium concentration <8.5 mg/dL (or ionized calcium <4.2 mg/dL). Hypocalcemia may develop with toxic shock syndrome, with abnormalities in serum magnesium, after thyroid surgery, with fluoride poisoning, and with tumor lysis syndrome (rapid cell turnover with resultant hyperkalemia, hyperphosphatemia, and hypocalcemia).

Symptoms of hypocalcemia usually occur when ionized levels fall to <2.5 mg/dL. Symptoms include paresthesias of the extremities and face, followed by muscle cramps, carpopedal spasm, stridor, tetany, and seizures. Hypocalcemic patients show hyperreflexia and positive Chvostek and Trousseau signs. Cardiac effects include decreased myocardial contractility and heart failure. Hypocalcemia can exacerbate digitalis toxicity.

#### Treatment of Hypocalcemia

Treatment of hypocalcemia requires administration of calcium. Treat acute, symptomatic hypocalcemia with 10% calcium gluconate, 93 to 186 mg of elemental calcium (10 to 20 mL) IV over 10 minutes. Follow this with an IV infusion of 540 to 720 mg of elemental

calcium (58 to 77 mL of 10% calcium gluconate) in 500 to 1000 mL D5W at 0.5 to 2 mg/kg per hour (10 to 15 mg/kg). Alternatively, administer 10% calcium chloride, giving 5 mL (136.5 mg of elemental calcium) over 10 minutes, followed by 36.6 mL (1 g) over the next 6 to 12 hours IV. Measure serum calcium every 4 to 6 hours. Aim to maintain the total serum calcium concentration at 7 to 9 mg/dL. Correct abnormalities in magnesium, potassium, and pH simultaneously. Note that untreated hypomagnesemia will often make hypocalcemia refractory to therapy. Therefore, evaluate serum magnesium when hypocalcemia is present and particularly if hypocalcemia is refractory to initial calcium therapy.

Electrolyte abnormalities are among the most common causes of cardiac arrhythmias, and they can cause or complicate attempted resuscitation and postresuscitation care. A high degree of clinical suspicion and aggressive treatment of underlying electrolyte abnormalities can prevent these abnormalities from progressing to cardiac arrest.

### Cardiac Biomarkers

Cardiovascular disease is the leading cause of death in the United States; one death due to heart disease occurs every 34 seconds. Each year, 1.5 million persons experience acute myocardial infarction, and 500,000 of these die of the infarction. Of these deaths, 50% occur before medical treatment is provided. Prompt recognition of signs and symptoms, accurate diagnosis, and timely treatment are essential to limit the size of the infarct, preserve myocardial function, and reduce mortality.

Diagnosis of acute myocardial infarction is based on clinical features, presence of risk factors, electrocardiographic changes, and levels of cardiac biomarkers. Treatment includes administration of antiplatelet and anti-ischemic agents, thrombolytic therapy, and primary percutaneous transluminal coronary angioplasty (PTCA). Reperfusion therapy (thrombolysis or primary PTCA) works best when given within 4 to 6 hours of the onset of signs and symptoms.

Some patients with myocardial infarction have atypical signs and symptoms. Thirty percent have little or no chest discomfort, and the electrocardiographic changes may not indicate the diagnosis. Therefore, ancillary testing is necessary. Cardiac biomarkers are a useful diagnostic tool, especially 4 to 6 hours after the onset of signs and symptoms. Levels of biomarkers of cardiac injury are elevated only after irreversible cell injury.

Although measurement of levels of these proteins is a powerful way to detect even minor myocardial injury, assays of the proteins cannot be used to detect episodes of ischemia. In patients with possible acute myocardial infarction or myocardial ischemia who have atypical signs and symptoms and inconclusive electrocardiographic findings, measurements of levels of biomarkers are used to assist in the diagnosis and appropriate triage.

Clinically, measurement of the level(s) of one or more specific cardiac biomarkers is used to determine the extent of myocardial damage and to assess a patient's prognosis. Creatine kinase (CK), CK-MB, CK mass, and lactate dehydrogenase have been used for

routine clinical management. However, these biomarkers are not without problems. New biomarkers are available that may be more specific and have a higher sensitivity in the diagnosis of acute coronary syndromes: cardiac troponins T and I and myoglobin.

### Creatine Kinase

Determinations of serum levels of CK and CK-MB have long been used for diagnosis of myocardial infarction. CK is an enzyme present in many parts of the body and can be fractionated into 3 isoenzymes: MM, MB, and BB. CK-MM occurs in high concentrations in skeletal muscle and heart. CK-MB is present in high concentrations in myocardium but is also present in the lungs, small intestine, uterus, prostate, and healthy skeletal muscle. Concentrations of CK-BB are highest in the brain; small amounts are present in the lungs, stomach, prostate, gastrointestinal tract, and bladder. Neither CK-MM nor CK-BB is clinically relevant for detecting myocardial necrosis.

Because of the poor specificity of total CK for myocardium, for many years, measurement of CK-MB has been the gold standard for diagnosis of myocardial infarction. However, healthy skeletal muscle can have up to 5% CK-MB, and higher levels occur in other conditions such as renal failure. This lack of absolute cardiac specificity in complex clinical situations has led to the development of assays of more specific proteins, particularly troponins.

A second weakness of CK-MB is that elevations are classically thought not to occur for up to 6 hours after myocardial injury. Because the first 4 to 6 hours are crucial for any reperfusion strategy, a biomarker that reaches elevated levels early is attractive. However, much of the data indicating a low sensitivity for CK-MB in the first 6 hours were obtained with an assay for enzyme activity. Currently, the most commonly used assay measures CK-MB mass, which increases earlier than activity does. Regardless, elevated levels of these biomarkers do not develop until after significant and irreversible myocardial damage has occurred.

With electrophoresis, additional types of CK-MB and CK-MM can be differentiated into tissue and circulating (partially degraded) isoforms. Isoforms of CK-MM have a relatively high sensitivity for detection of myocardial damage, but specificity is less than optimum because of the dominant presence of CK-MM in skeletal muscle. Because of this lack of specificity and other major concerns, measurements of levels of CK-MM isoforms have not been widely used in the clinical setting.

Four isoforms of CK-MB have been detected. Because the concentration of CK-MB isoforms increases in 94% of patients who have acute myocardial infarction, measurement of these isoforms can improve early diagnosis of myocardial infarction. The levels peak early after onset of signs and symptoms and are usually back to normal within 24 hours. However, reproducibility of the assay can be a major difficulty.

In conditions other than acute myocardial infarction, CK is present mostly as CK-MM, with little or no CK-MB or CK-BB. During an acute myocardial infarction, levels of CK-MB start to increase 4 to 8 hours after the occlusion, peak in 12 to 24 hours, and

usually return to normal within 3 days. Serial measurements of CK and CK-MB are more helpful and have greater sensitivity and specificity than nonserial measurements. Concentrations of total CK start to increase 3 to 8 hours after the onset of signs and symptoms, peak in 10 to 30 hours, and usually return to normal in 3 to 4 days. When a patient has had chest discomfort for 6 to 8 hours, measurements of levels of CK and CK-MB can be helpful in the differential diagnosis.

An earlier and higher increase in the levels of CK and CK-MB usually occurs after successful reperfusion with either thrombolytic therapy or primary PTCA. Because of CK washout, reperfusion causes the levels of CK and CK-MB to increase rapidly and peak faster. For this reason, for patients who do not receive thrombolytic therapy or primary PTCA, samples of blood for measurements of CK and CK-MB levels should be obtained at baseline and then every 8 hours for the next 24 hours. When thrombolytic therapy is administered or primary PTCA is performed, blood samples for CK and CK-MB can be obtained more often, although obtaining fewer samples is acceptable. Levels of CK and CK-MB are also increased in conditions other than myocardial infarction.

#### Lactate Dehydrogenase

Another enzyme released by ischemic heart muscle is lactate dehydrogenase. Like CK, lactate dehydrogenase also occurs in many other parts of the body, including the kidneys, red blood cells, brain, stomach, and skeletal muscle. Lactate dehydrogenase can be fractionated into 5 isoenzymes; however, only 2 of these, LD-1 and LD-2, are used to help diagnose myocardial ischemia. Levels of LD-1 are elevated in the presence of myocardial infarction and in other conditions such as leukemia. LD-2 occurs in all parts of the body except skeletal muscle but is present predominantly in the heart. The other 3 isoenzymes occur in small amounts throughout the body.

Levels of lactate dehydrogenase start to increase 24 to 48 hours after occlusion of the coronary artery, peak in 3 to 6 days, and return to normal in 8 to 14 days. Levels of LD-1 are elevated 10 to 12 hours after the acute myocardial infarction, peak in 2 to 3 days, and return to normal in approximately 7 to 10 days. Thus, measurement of the level of lactate dehydrogenase allows a prolonged retrospective diagnosis of myocardial infarction.

Usually the amount of LD-2 in the blood is higher than the amount of LD-1. Patients with acute myocardial infarction have more LD-1 than LD-2. This flipped ratio usually returns to normal in 7 to 10 days. If this pattern continues, further necrosis may be occurring, and shorter-lived markers or those markers that are at elevated levels for shorter periods (CK-MB or myoglobin) can be used for confirmation.

An elevated level of LD-1 with a flipped ratio has a sensitivity and specificity of approximately 75% to 90% for detection of acute myocardial infarction. Because of technical concerns, measurement of lactate dehydrogenase has largely been replaced by measurement of troponins because of the improved specificity and duration of elevated levels of the latter enzymes.

## Myoglobin

Myoglobin is a protein found in both cardiac and skeletal muscle but not in smooth muscle. It is released from the myocardium within 2 hours of coronary occlusion and peaks in 6 to 7 hours. Levels of myoglobin are elevated in 65% of patients who have acute myocardial infarction. Because of the short half-life of myoglobin, levels must be measured at frequent intervals. Any injury to skeletal muscle, including intramuscular injections, can also cause elevated levels of myoglobin.

In patients with acute myocardial infarction or unstable angina, measurements of myoglobin may show a series of short-term peaks of the protein. This series of peaks most likely reflects a pattern of reperfusion and reocclusion. With reocclusion, further release of bursts of myoglobin occurs, which results in multiple short-term peaks. When thrombolytic therapy results in successful reperfusion, this pattern disappears.

In one study to determine the usefulness of serial measurements of myoglobin levels in the differential diagnosis of chest discomfort, blood samples were obtained from 133 subjects at baseline and 2, 3, 4, and 6 hours later. The results indicated that myoglobin had 95% specificity for detection of acute myocardial infarction within 1 to 2 hours after presentation. The serum level of myoglobin doubled in that interval. Sensitivity was 37% at 2 hours and 86% at 6 hours. The study concluded that measurement of myoglobin levels could be used to detect acute myocardial infarction before measurements of CK and CK-MB indicated injury and that this earlier detection facilitated diagnosis and treatment.

Because myoglobin is released rapidly after occlusion of coronary arteries, measurement of myoglobin levels has been used for the early diagnosis of acute myocardial infarction. Although measurement of myoglobin is superior to measurement of CK-MB activity in the first few hours, it has less additional benefit when compared with measurement of CK-MB mass. Myoglobin is not released for approximately 1 to 2 hours after the onset of the myocardial infarction, so a normal myoglobin level does not exclude marked cardiac disease or myocardial infarction in patients who seek treatment immediately after the onset of signs and symptoms of cardiac abnormalities. How often measurement of myoglobin levels results in alterations in treatment and its impact on prognosis must be determined.

## Cardiac Troponins

Troponin is a regulatory protein found in striated muscle that is responsible for calcium interaction. Cardiac troponin occurs in 3 forms: I, T, and C. Both troponin I and troponin C have isoforms, which have been used to develop monoclonal antibodies used in various assays. Measurement of troponins is beneficial in the management of patients with a broad spectrum of coronary syndromes. Serum levels of cardiac troponins are usually low (below the level of detection) but increase quickly when acute myocardial infarction occurs.

Injured or ischemic myocardium releases cardiac troponins within 6 hours after the injury or onset of ischemia, a situation similar to the onset of elevated serum levels of CK-MB.

However, levels remain elevated longer than do levels of CK-MB or lactate dehydrogenase. Cardiac troponin I becomes elevated within 6 hours after myocardial infarction and remains in the bloodstream for up to 5 to 10 days; troponin T may be present for up to 7 to 10 days in patients with acute myocardial infarction.

The duration of the elevation is shorter in patients with unstable angina or non-Q wave myocardial infarction. In patients who do not have acute myocardial infarction but have had cardiac trauma, such as that associated with open heart surgery, measurement of levels of troponins can replace measurement of the level of lactate dehydrogenase in establishing the late retrospective diagnosis of acute myocardial infarction.

Assays of cardiac troponins are used to determine whether myocardial necrosis has occurred. Both troponin I and troponin T are highly sensitive markers for cardiac injury and appear to be even more sensitive than CK-MB for the detection of small amounts of myocardial injury. Troponin I is a uniquely specific marker of cardiac injury; detectable amounts of this troponin appear in blood only after myocardial necrosis.

In subjects with musculoskeletal disorders but normal myocardium, levels of cardiac troponin I are normal, whereas levels of CK-MB are elevated. Therefore, in patients with musculoskeletal disorders, measurement of troponin I is a more specific assay than measurement of CK-MB and can be used to determine if elevations in CK-MB reflect a cardiac or noncardiac cause.

Questions about the cardiac specificity of cardiac troponin T remain. Some subjects with musculoskeletal or renal disease have elevated levels of cardiac troponin T without any other evidence of myocardial injury; this marker may not be as sensitive as cardiac troponin I for detection of myocardial injury. Also levels of troponin T are elevated in other conditions.

With recent improved assays for cardiac troponin T, the number of false-positive elevations (indication of myocardial injury when no injury is present) is less than before. Further studies are needed to address this important issue. Troponin T is a sensitive marker for acute myocardial infarction, and measurement of this troponin is useful in diagnosis for a longer time than is measurement of CK-MB. Measurement of troponin provides powerful prognostic information on patients with acute coronary syndromes such as unstable angina, non-Q wave myocardial infarction, and Q wave myocardial infarction.

Measurement of troponins has been used in diverse clinical settings in which detection or exclusion of cardiac injury is important. Measurement of troponin levels is largely replacing measurement of levels of lactate dehydrogenase for the late, retrospective diagnosis of myocardial infarction and is being used more often to replace measurement of CK-MB levels.

Measurements of troponins, especially of cardiac troponin I, have been used in complex clinical scenarios, particularly in patients with skeletal muscle injury, to detect or exclude

cardiac injury. Measurement of troponin I is accurate for detecting cardiac injury after trauma, orthopedic surgery, marathons, and noncardiac surgery. Preliminary studies in small numbers of subjects suggest that measurement of levels of both troponin I and troponin T can provide useful information about perioperative myocardial infarction after coronary artery bypass grafting.

Measurements of both cardiac troponins have greater sensitivity and specificity than measurements of CK and CK-MB in the diagnosis of acute myocardial infarction, especially in patients with other medical conditions such as renal disease or severe musculoskeletal disorders. Also, measurements of both troponins have successfully replaced measurements of lactate dehydrogenase.

Cardiac troponins, particularly troponin I, may be more useful than other cardiac biomarkers in diagnosing myocardial ischemia or injury in patients undergoing coronary artery bypass grafting. Further research is necessary in certain subsets of patients, such as those who are undergoing cardiac surgery or have unstable angina or chest discomfort of unknown etiology, to determine if measurement of serum levels of cardiac troponins can aid in the diagnosis of myocardial injury, ischemia, or necrosis.

A significant revolution in the evaluation and treatment of patients with acute coronary syndromes is under way. A reevaluation of the application of biomarkers and the availability of new assays have redefined how measurements of marker proteins are used. Currently, there is no single right way to approach a patient with chest discomfort. However, the following points should be considered:

1. With any marker, serial measurements are paramount. By definition, myocardial necrosis results in a pattern of increasing and decreasing levels of cardiac biomarkers. Any persistent elevation of protein must be viewed with suspicion. Also, because of the delay in the appearance of any biomarker in the circulation and the uncertainty in the exact onset of ischemia or necrosis as indicated by the medical history, a single sample obtained at the time of presentation will never be adequate for the exclusion of myocardial necrosis.
2. All current assays of biomarkers detect myocardial necrosis only, not myocardial ischemia. Normal levels of any of these biomarkers can indicate that a patient does not have myocardial infarction but do not guarantee the absence of coronary artery disease or myocardial ischemia.
3. The selection of which biomarker to use should, in part, be determined by the strengths of the healthcare facility. Some facilities have invested the necessary time and effort to train personnel in the use of markers such as CK-MB isoforms or myoglobin, which are somewhat more difficult to measure. Staff at other facilities who have neither a true understanding of the limitations of these markers nor adequate analytical sophistication will have more difficulty in making successful primary use of such assays.
4. The time required for triage in the emergency department also plays a role in selecting

which markers should be measured. In situations in which a chest pain emergency center is available or in which all patients with chest pain are admitted to the hospital for 23 hours to rule out myocardial infarction, a less comprehensive biomarker profile could be used. The less time available for triage, the more markers in general should be used.

On the basis of these points, it is recommended that for routine assessment of patients with acute coronary syndromes, serial measurements of cardiac troponins should be used. Until the question of the specificity of troponin T levels is resolved, measurement of troponin I levels is favored. Serial testing is necessary; the most widely used protocol requires obtaining blood samples at baseline and at 3, 6, and 9 hours, although modifications may be appropriate.

Measurements of levels of lactate dehydrogenase and CK-MB add little to the information provided by measurements of levels of troponins and can safely be discontinued. If myocardial necrosis must be detected more rapidly after onset (a situation that usually means a shorter time available for triage) than is possible with measurements of troponin levels, then adding measurements of myoglobin levels (obtained at 0 and 2 hours) to the panel of markers is indicated, but in most institutions, this step is unnecessary.

Interest in cardiac biomarkers is increasing. New indications for their use, such as the diagnosis of perioperative myocardial infarction in patients undergoing coronary artery bypass grafting, are being investigated. The need to find or develop an assay to help diagnose acute coronary syndromes within the first few hours of their occurrence is essential. Prompt diagnosis is critical to reducing mortality and morbidity. The appropriate use of biomarkers can help practitioners make the correct diagnosis and start treatment promptly.

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