Preparation for Anaesthesia - Disorders of Calcium Metabolism

The three substances that regulate the serum concentrations of calcium, phosphorus, and magnesium—parathyroid hormone (parathyrin, PTH), calcitonin, and vitamin D—act on bone, kidney, and gut. PTH stimulates bone resorption and inhibits renal excretion of calcium, two conditions that lead to hypercalcemia. Calcitonin can be considered an antagonist to PTH. Through its metabolites, vitamin D aids in the absorption of calcium, phosphate, and magnesium from the gut and facilitates the bone resorptive effects of PTH. [200]

Hyperparathyroidism and Hypercalcemia

Primary hyperparathyroidism most commonly begins in the third to fifth decades of life and occurs two to three times more frequently in women than in men. Primary hyperparathyroidism usually results from enlargement of a single gland, commonly an adenoma and very rarely a carcinoma. Hypercalcemia almost always occurs.

Calcium is the chief mineral component of the body, providing structure to the skeleton and performing key roles in neural transmission, intracellular signaling, blood coagulation, and neuromuscular functioning. Ninety-nine percent of the 1,000 g of calcium present in the average human body is stored in bone. The normal total serum calcium level is 8.6 to 10.4 mg/dL, as measured in most laboratories. Fifty to sixty percent is bound to plasma proteins or is complexed with phosphate or citrate. The value is dependent on the albumin level, declining 0.8 mg/dL for each 1-g/dL drop in albumin. Calcium binding to albumin is pH dependent: binding decreases with acidic pH and increases with alkaline pH. It should be noted that serum calcium and not ionized calcium decreases with decreases in albumin levels. Although ionized calcium is the clinically significant fraction, the cost and technical difficulties of stabilizing the electrodes used for measurement have limited the available assays. Nevertheless, parathyroid hormone and vitamin D_3 work to keep the level stable within 0.1 mg/dL in any individual.

Many of the prominent symptoms of hyperparathyroidism are a result of the hypercalcemia that accompanies it. Regardless of the cause, hypercalcemia can produce any of a number of symptoms, the most prominent involving the renal, skeletal, neuromuscular, and GI systems—anorexia, vomiting, constipation, polyuria, polydipsia, lethargy, confusion, formation of renal calculi, pancreatitis, bone pain, and psychiatric abnormalities. Free intracellular calcium initiates and/or regulates muscle contraction, release of neurotransmitters, secretion of hormones, enzyme action, and energy metabolism.

Nephrolithiasis occurs in 60 to 70 percent of patients with hyperparathyroidism. Sustained hypercalcemia can result in tubular and glomerular disorders, including proximal (type II) renal tubular acidosis. Polyuria and polydipsia are common complaints.

Skeletal disorders related to hyperparathyroidism are osteitis fibrosa cystica and simple diffuse osteopenia. The rate of bone turnover is five times higher for patients with hyperparathyroidism than for normal controls. Patients may have a history of frequent fractures or complain of bone pain, the latter especially in the anterior margin of the tibia. Because free intracellular calcium initiates or regulates muscle contraction, neurotransmitter release, hormone secretion, enzyme action, and energy metabolism, abnormalities in these end organs are often symptoms of hyperparathyroidism. Patients may experience profound muscle weakness, especially in proximal muscle groups, as well as muscle atrophy. Depression, psychomotor retardation, and memory impairment may occur. Lethargy and confusion are frequent complaints.

Peptic ulcer disease is more common in these patients than in the rest of the population. Production of gastrin and gastric acid is increased. Anorexia, vomiting, and constipation may also be present.

Approximately one-third of all hypercalcemic patients are hypertensive; the hypertension usually resolves with successful treatment of the primary disease. Long-standing hypercalcemia can lead to calcifications in the myocardium, blood vessels, brain, and kidney. Cerebral calcifications may cause seizures, whereas renal calcifications lead to polyuria that is unresponsive to vasopressin.

The most useful confirmatory test for hyperparathyroidism is a radioimmunoassay for PTH. In fact, some surgeons follow PTH levels intraoperatively to determine if they have resected the causative adenoma. [201] In hyperparathyroid patients, the hormone levels are abnormal for a given level of calcium. The level of inorganic phosphorus in serum is usually low, but it may be within normal limits. Alkaline phosphatase is elevated if considerable skeletal involvement is present.

Glucocorticoid administration reduces the level of calcium in the blood in many other conditions that cause hypercalcemia but usually not in primary hyperparathyroidism. In sarcoidosis, multiple myeloma, vitamin D intoxication, and some malignant diseases, all of which can cause hypercalcemia, administration of glucocorticoids may lower the serum calcium through an effect on gastrointestinal absorption. This effect occurs to a lesser degree in primary hyperparathyroidism.

Hypercalcemia may also occur as a consequence of secondary hyperparathyroidism in patients who have chronic renal disease. When phosphate excretion decreases as a result of a lower nephron mass, serum calcium levels fall because of deposition of calcium and phosphate in bone. Secretion of PTH subsequently increases, whereas the fraction of phosphate excreted by each nephron increases. Eventually, the chronic intermittent hypocalcemia of chronic renal failure leads to chronically high levels of serum PTH and hyperplasia of the parathyroid glands.

What should be done for asymptomatic patients with primary hyperparathyroidism? This question has become the subject of a major controversy, for which no definitive answer exists. *Symptomatic* primary hyperparathyroidism is usually treated surgically, as is hyperparathyroidism in young patients or in patients with azotemia, bone demineralization, or chronic total calcium elevations greater than 12 mg/dL. If the patient refuses surgery, or if other illnesses make surgery inadvisable, medical management can be difficult. This difficulty occurs when hyperfunctioning parathyroid glands secrete more hormone as the serum calcium is lowered, as if the calcium set point for feedback regulation of PTH secretion had been raised.

Patients with moderate hypercalcemia who have normal renal and cardiovascular function present no special preoperative problems. The electrocardiogram can be examined preoperatively and intraoperatively for shortened PR or QT intervals (Fig. 25–7). Because severe hypercalcemia can result in hypovolemia, normal intravascular volume and electrolyte status should be restored before anesthesia and surgery are begun.

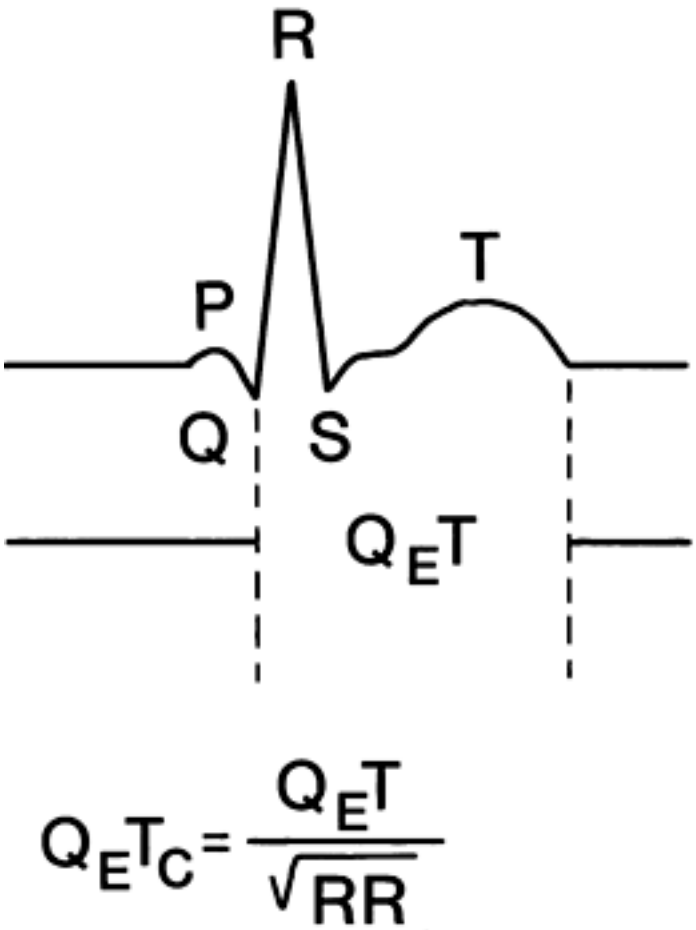

FIGURE 25–7 Measurement of the QT_c interval (properly termed Q_ET_c to indicate that it begins with the start of the Q wave, lasts throughout the QT interval, ends with the end of the T wave, and is corrected for heart rate). RR is the RR interval in seconds. (From Hensel and Roizen[200])

Management of hypercalcemia can include increasing the urinary calcium excretion by means of hydration and diuresis. Restoration of intravascular volume, augmentation of urinary sodium, excretion, and administration of diuretics (furosemide is commonly employed) usually increase urinary calcium excretion substantially. Complications of these interventions include hypomagnesemia and hypokalemia.

In emergency situations, vigorous expansion of intravascular volume usually reduces serum calcium to a safe level (<14 mg/dL); administration of furosemide is also often helpful in these situations. Phosphate should be given to correct hypophosphatemia, which decreases calcium uptake into bone, increases calcium, and stimulates breakdown of bone. Hydration and diuresis, accompanied by phosphate repletion, suffice in the management of most hypercalcemic patients. If additional intervention is needed, glucocorticoids, mithramycin, or calcitonin may be given. Corticosteroids inhibit further gastrointestinal absorption of calcium. Mithramycin lowers calcium levels by approximately 2 mg/dL in 36 to 48 hours through its effect on osteoclasts. Its toxic effects include thrombocytopenia, decreased levels of clotting factors, hepatotoxicity, azotemia, proteinuria, hypocalcemia, hypophosphatemia, and hypokalemia. Most of these side effects can be reversed simply by

discontinuation of the drug. Consultation with an endocrinologist or oncologist is advisable before mithramycin is given, because it has a narrow therapeutic-to-toxic ratio.
Calcitonin lowers serum calcium levels through direct inhibition of bone resorption. It can decrease serum calcium levels within minutes after its intravenous administration. Calcitonin is less effective than phosphate or mithramycin, however, for patients with hypercalcemia caused by hyperparathyroidism. Side effects include urticaria and nausea.
It is especially important to know whether hypercalcemia has been chronic, because serious cardiac, renal, or CNS abnormalities may have resulted.

Hypocalcemia

Hypocalcemia (caused by hypoalbuminemia, hypoparathyroidism, hypomagnesemia, or chronic renal disease) is not usually accompanied by a clinically evident cardiovascular disorder. However, myocardial contractility does vary directly with levels of blood ionized calcium, although contractility decreased only 20 percent when ionized calcium levels changed from 1.68 to 1.34 mmol/L. [202] The clinical signs of hypocalcemia are clumsiness; convulsions; laryngeal stridor; depression; muscle stiffness; paresthesia (oral and perioral); parkinsonism; tetany; Chvostek sign; dry, scaly skin, brittle nails, and coarse hair; low serum concentrations of calcium; prolonged QT intervals; soft tissue calcifications; and Trousseau sign.
Hypocalcemia delays ventricular repolarization, hence increasing the QT_c interval (normal, 0.35–0.44 second). With electrical systole prolonged, the ventricles may fail to respond to the next electrical impulse from the sinoatrial node, causing 2:1 heart block. Prolongation of the QT interval is a moderately reliable ECG sign of hypocalcemia, not for the population as a whole, but for the individual patient. [203] Thus, following the QT interval as corrected for heart rate (see Fig. 25–7) is a useful but not always accurate means of monitoring hypocalcemia in any one patient. CHF may also occur with hypocalcemia, but this is rare. Because CHF in patients with coexisting heart disease is reduced in severity when calcium and magnesium ion levels are restored to normal, these levels might be normal before surgery in the patient with impaired exercise tolerance or signs of cardiovascular dysfunction. [200, 202] Sudden decreases in blood levels of ionized calcium (as with chelation therapy) can result in severe hypotension.
Patients with hypocalcemia may have seizures. These may be focal, jacksonian, petit mal, or grand mal in appearance, indistinguishable from such seizures in the absence of hypocalcemia. Patients may also have a type of seizure called cerebral tetany, which consists of generalized tetany followed by tonic spasms. Therapy with standard anticonvulsants is ineffective and may even exacerbate these seizures (by an anti-vitamin D effect). In long-standing hypoparathyroidism, calcifications may appear above the sella, representing deposits of calcium in and around small blood vessels of the basal ganglia. These may be associated with a variety of extrapyramidal syndromes.
The most common cause of *acquired hypoparathyroidism* is surgery of the thyroid or parathyroid glands. Other causes include therapy with iodine-131, hemosiderosis, neoplasia, and granulomatous disease. *Idiopathic hypoparathyroidism* has been divided into three categories: an isolated persistent neonatal form, branchial dysembryogenesis, and multiple endocrine deficiency autoimmune candidiasis.
Pseudohypoparathyroidism and pseudopseudohypoparathyroidism are rare hereditary disorders characterized by short stature, obesity, rounded face, and shortened metacarpals. Patients with pseudohypoparathyroidism have hypocalcemia and hyperphosphatemia despite high serum levels of PTH. These patients have a deficient end-organ response to PTH because of abnormalities in G-protein function.
Because treatment of hypoparathyroidism is not surgical, hypoparathyroid patients who come to the operating room are those who require surgery for an unrelated condition. Their

calcium, phosphate, and magnesium levels should be measured both preoperatively and postoperatively. Patients with symptomatic hypocalcemia might be treated with intravenous calcium gluconate before surgery. Initially, 10 to 20 mL of 10 percent calcium gluconate may be given at a rate of 10 mL/min. The effect on serum calcium levels is of short duration, but a continuous infusion with 10 mL/min of 10 percent calcium gluconate in 500 mL of solution over 6 hours helps keep serum calcium at adequate levels.

The objective of therapy is to bring the symptoms under control before surgery and anesthesia. For patients with chronic hypoparathyroidism, the objective is to keep the serum calcium level in the lower half of the normal range. A preoperative ECG is useful for maintaining the QT_c interval. The preoperative QT_c value may be used as a guide to the serum calcium level if rapid laboratory assessment is not possible.

The intimate involvement of the parathyroid gland with the thyroid gland can result in unintentional hypocalcemia during surgery for diseases of either organ. Because of the affinity of their bones for calcium, this relationship is crucial for patients having advanced osteitis. Internal redistribution of magnesium and/or calcium ions may occur (into "hungry bones") after parathyroidectomy, causing either hypomagnesemia or hypocalcemia, or both. Because the tendency to tetany increases with alkalosis, hyperventilation is usually assiduously avoided. The most prominent manifestations of acute hypocalcemia are distal paresthesias and muscle spasm (tetany). Potentially fatal complications of severe hypocalcemia include laryngeal spasm and hypocalcemic seizures. The clinical sequelae of magnesium deficiency include cardiac arrhythmias (principally ventricular tachyarrhythmias), hypocalcemic tetany, and neuromuscular irritability independent of hypocalcemia (tremors, twitching, asterixis, and seizures).

In addition to monitoring total serum calcium or ionized calcium postoperatively, one can test for Chvostek sign and Trousseau sign. (Note that serum calcium, and not ionized calcium, is dependent on albumin level, declining about 0.8 mg/dL for each 1-g/dL drop in serum albumin level.) Because Chvostek sign can be elicited in 10 to 15 percent of patients who are not hypocalcemic, an attempt should be made to elicit it preoperatively to ensure its appearance is meaningful. Chvostek sign is a contracture of the facial muscles produced by tapping the ipsilateral facial nerves at the angle of the jaw. Trousseau sign is elicited by applying a blood pressure cuff at a level slightly above the systolic level for a few minutes. The resulting carpopedal spasm, with contractions of the fingers and inability to open the hand, stems from the increased muscle irritability in hypocalcemic states, aggravated by ischemia produced by the blood pressure cuff.

Osteoporosis

Fifty percent of women older than 65 years suffer an osteoporotic fracture. (Because men are living longer, osteoporosis will probably become an increasing problem for them, too.) Osteoporosis is the thinning of bone that causes low bone mass and thus weakening of this living tissue to the point of breakage. Known risk factors include age, relative lifetime estrogen deficiency (late menarche, amenorrhea, early menopause, nulliparity), deficiency of dietary calcium, tobacco usage, increased aerobic exercise in combination with decreased weight-bearing exercise, decreased weight-bearing exercise by itself, soft drink usage, and Asian or caucasian ancestry. Although therapy for osteoporosis (use of biphosphates, bone mineral depositors, weight-bearing exercises, calcium, vitamin D, estrogen—and now designer estrogens that may be useful for men, such as Evista) does not have major known implications for anesthesia care, bone fractures in such patients have occurred on movement to and from an operating table. Thus, the precautions mentioned earlier for hyperparathyroid patients relative to self-positioning and careful positioning may be useful.