CHAPTER

# 34

# Anesthesia for Patients with Endocrine Disease

## KEY CONCEPTS

1. Diabetic autonomic neuropathy may limit the patient's ability to compensate (with tachycardia and increased peripheral resistance) for intravascular volume changes and may predispose the patient to cardiovascular instability (eg, postinduction hypotension) and even sudden cardiac death.
2. Temporomandibular joint and cervical spine mobility should be assessed preoperatively in diabetic patients to reduce the likelihood of unanticipated difficult intubation. Difficult intubation has been reported in as many as 30% of persons with type 1 diabetes.
3. Sulfonylureas and metformin have long half-lives and many clinicians will discontinue them 24–48 h before surgery. They can be started postoperatively when the patient resumes oral intake.
4. Incompletely treated hyperthyroid patients can be chronically hypovolemic and prone to an exaggerated hypotensive response during induction of anesthesia.
5. Clinically hypothyroid patients are more susceptible to the hypotensive effect of anesthetic agents because of their diminished cardiac output, blunted baroreceptor reflexes, and decreased intravascular volume.
6. Patients with glucocorticoid deficiency must receive adequate steroid replacement therapy during the perioperative period.
7. In patients with a pheochromocytoma, drugs or techniques that indirectly stimulate or promote the release of catecholamines (eg, ephedrine, hypoventilation, or bolus doses of ketamine), potentiate the arrhythmic effects of catecholamines (classically halothane), or consistently release histamine (eg, large doses of atracurium or morphine sulfate) may precipitate hypertension and are best avoided.
8. Obese patients may be difficult to intubate as a result of limited mobility of the temporomandibular and atlantooccipital joints, a narrowed upper airway, and a shortened distance between the mandible and sternal fat pads.
9. The key to anesthetic management of patients with carcinoid syndrome is to avoid anesthetic and surgical techniques or agents that could cause the tumor to release vasoactive substances.

The underproduction or overproduction of hormones can have dramatic physiological and pharmacological consequences. Therefore, it is not surprising that endocrinopathies affect anesthetic management. This chapter briefly reviews normal physiology and pathophysiology of four endocrine organs: the pancreas, the thyroid, the parathyroids, and the adrenal gland. It also considers obesity and carcinoid syndrome.

# The Pancreas

## Physiology

Adults normally secrete approximately 50 units of insulin each day from the β cells of the islets of Langerhans in the pancreas. The rate of insulin secretion is primarily determined by the plasma glucose concentration. Insulin, the most important anabolic hormone, has multiple metabolic effects, including facilitating glucose and potassium entry into adipose and muscle cells; increasing glycogen, protein, and fatty acid synthesis; and decreasing glycogenolysis, gluconeogenesis, ketogenesis, lipolysis, and protein catabolism.

In general, insulin stimulates anabolism, whereas lack of insulin is associated with catabolism and a negative nitrogen balance (Table 34–1).

**TABLE 34–1 Effects of insulin.[1]**

| |
|---|
| **Effects on liver** |
| Anabolic |
| Promotes glycogenesis |
| Increases synthesis of triglycerides, cholesterol, and VLDL[2] |
| Increases protein synthesis |
| Promotes glycolysis |
| Anticatabolic |
| Inhibits glycogenolysis |
| Inhibits ketogenesis |
| Inhibits gluconeogenesis |
| **Effects on muscle** |
| Anabolic |
| Increases amino acid transport |
| Increases protein synthesis |
| Anticatabolic |
| Increases glucose transport |
| Enhances activity of glycogen synthetase |
| Inhibits activity of glycogen phosphorylase |
| **Effects on fat** |
| Promotes triglyceride storage |
| Induces lipoprotein lipase, making fatty acids available for absorption into fat cells |
| Increases glucose transport into fat cells, thus increasing availability of α-glycerol phosphate for triglyceride synthesis |
| Inhibits intracellular lipolysis |

[1]Reproduced, with permission, from Gardner DG, Shoback D (editors): *Greenspan's Basic & Clinical Endocrinology*, 9th edition, McGraw-Hill, 2011.
[2]VLDL, very low-density lipoprotein.

# DIABETES MELLITUS

## Clinical Manifestations

Diabetes mellitus is characterized by impairment of carbohydrate metabolism caused by an absolute or relative deficiency of insulin or of insulin responsiveness, which leads to hyperglycemia and glycosuria. The diagnosis is based on an elevated fasting plasma glucose greater than 126 mg/dL or glycated hemoglobin ($HbA_{1c}$) of 6.5% or greater. Values are sometimes reported for blood glucose, which runs 12–15% lower than plasma glucose. Even when testing whole blood, newer glucose meters calculate and display plasma glucose.

Diabetes is classified in multiple ways (Table 34–2). Type 1 (insulin-requiring due to endogenous insulin deficiency) and type 2 (insulin-resistant) diabetes are the most common and well known. Diabetic ketoacidosis (DKA) is associated with type 1 diabetes mellitus, but rarely individuals with DKA appear phenotypically to have type 2 diabetes mellitus. Long-term complications of diabetes include retinopathy, kidney disease, hypertension, coronary artery disease, peripheral and cerebral vascular disease, and peripheral and autonomic neuropathies.

There are three life-threatening acute complications of diabetes and its treatment—DKA, hyperosmolar nonketotic coma, and hypoglycemia—in addition to other acute medical problems (such as sepsis) in which the presence of diabetes makes treatment more difficult. Decreased insulin activity allows the catabolism of free fatty acids into ketone bodies (acetoacetate and β-hydroxybutyrate), some of which are weak acids (see Chapter 50). Accumulation of these organic acids results in DKA,

**TABLE 34–2 Diagnosis and classification of diabetes mellitus.**

| | |
|---|---|
| **Diagnosis (based on blood glucose level)** | |
| Fasting | 126 mg/dL (7.0 mmol/L) |
| Glucose tolerance test | 200 mg/dL (11.1 mmol/L) |
| **Classification** | |
| Type 1 (juvenile) | Absolute insulin deficiency secondary to immune-mediated or idiopathic causes |
| Type 2 | Onset in childhood or adulthood secondary to insulin resistance (relative insulin insensitivity) |
| Gestational | Onset of disease during pregnancy; may or may not persist postpartum |

an anion-gap metabolic acidosis. DKA can easily be distinguished from lactic acidosis, with which it can coexist; lactic acidosis is identified by elevated plasma lactate (>6 mmol/L) and the absence of urine and plasma ketones (although they can occur concurrently and starvation ketosis may occur with lactic acidosis). Alcoholic ketoacidosis can follow heavy alcohol consumption (binge drinking) in a nondiabetic patient and may include a normal or slightly elevated blood glucose level. Such patients may also have a disproportionate increase in β-hydroxybutyrate compared with acetoacetate, in contrast to those with DKA.

Infection is a common precipitating cause of DKA in a known diabetic patient, and DKA may be the reason that a previously undiagnosed person with type 1 diabetes presents for medical treatment. Clinical manifestations of DKA include tachypnea (respiratory compensation for the metabolic acidosis), abdominal pain, nausea and vomiting, and changes in sensorium. The treatment of DKA should include correcting the often substantial hypovolemia, the hyperglycemia, and the total body potassium deficit. This is typically accomplished with a continuous infusion of isotonic fluids and potassium and an insulin infusion.

The goal for decreasing blood glucose in ketoacidosis should be 75–100 mg/dL/h or 10%/h. Therapy generally begins with an intravenous insulin infusion at 0.1 units/kg/h. DKA patients may be resistant to insulin, and the insulin infusion rate may need to be increased if glucose concentrations do not decrease. As glucose moves intracellularly, so does potassium. Although this can quickly lead to a critical level of hypokalemia if not corrected, overaggressive potassium replacement can lead to an equally life-threatening hyperkalemia. Potassium and blood glucose should be monitored frequently during treatment of DKA.

Several liters of 0.9% saline (1–2 L the first hour, followed by 200–500 mL/h) may be required to correct dehydration in adult patients. When plasma glucose decreases to 250 mg/dL, an infusion of $D_5W$ should be added to the insulin infusion to decrease the possibility of hypoglycemia and to provide a continuous source of glucose (with the infused insulin) for eventual normalization of intracellular metabolism. Patients may benefit from precise monitoring of urinary output during initial treatment of DKA.

Bicarbonate is rarely needed to correct severe acidosis (pH < 7.1) as the acidosis corrects with volume expansion and with normalization of the plasma glucose concentration.

Ketoacidosis is not a feature of **hyperosmolar nonketotic coma** possibly because enough insulin is available to prevent ketone body formation. Instead, a hyperglycemia-induced diuresis leads to dehydration and hyperosmolality. Severe dehydration may eventually lead to kidney failure, lactic acidosis, and a predisposition to form intravascular thromboses. Hyperosmolality (frequently exceeding 360 mOsm/L) induces dehydration of neurons, causing changes in mental status and seizures. Severe hyperglycemia causes a factitious hyponatremia: each 100 mg/dL increase in plasma glucose lowers plasma sodium concentration by 1.6 mEq/L. Treatment includes fluid resuscitation with normal saline, relatively small doses of insulin, and potassium supplementation.

Hypoglycemia in the diabetic patient is the result of an absolute or relative excess of insulin relative to carbohydrate intake and exercise. Furthermore, diabetic patients are incompletely able to counter hypoglycemia despite secreting glucagon or epinephrine (counterregulatory failure). The dependence of the brain on glucose as an energy source makes it the organ most susceptible to episodes of hypoglycemia. If hypoglycemia is not treated, mental status changes

can progress from anxiety, lightheadedness, or confusion to convulsions and coma. Systemic manifestations of hypoglycemia result from catecholamine discharge and include diaphoresis, tachycardia, and nervousness. Most of the signs and symptoms of hypoglycemia will be masked by general anesthesia. Although the lower boundary of normal plasma glucose levels is ill-defined, medically important hypoglycemia is present when plasma glucose is less than 50 mg/dL. The treatment of hypoglycemia in anesthetized or critically ill patients consists of intravenous administration of 50% glucose (each milliliter of 50% glucose will raise the blood glucose of a 70-kg patient by approximately 2 mg/dL). Awake patients can be treated orally with fluids containing glucose or sucrose.

## Anesthetic Considerations

### A. Preoperative

Abnormally elevated hemoglobin A1c concentrations identify patients who have maintained poor control of blood glucose over time. These patients may be at greater risk for perioperative hyperglycemia, perioperative complications, and adverse outcomes. The perioperative morbidity of diabetic patients is related to their preexisting end-organ damage. Unfortunately, one third to one half of patients with type 2 diabetes mellitus may be unaware of their condition.

A preoperative chest radiograph in a diabetic patient is more likely to uncover cardiac enlargement, pulmonary vascular congestion, or pleural effusion, but is not routinely indicated. Diabetic patients also have an increased incidence of ST-segment and T-wave-segment abnormalities on preoperative electrocardiograms (ECGs). Myocardial ischemia or old infarction may be evident on an ECG despite a negative history. Diabetic patients with hypertension have a 50% likelihood of coexisting **diabetic autonomic neuropathy** (Table 34–3). Reflex dysfunction of the autonomic nervous system may be increased by old age, diabetes of longer than 10 years' duration, coronary artery disease, or β-adrenergic blockade.

1 Diabetic autonomic neuropathy may limit the patient's ability to compensate (with tachycardia and increased peripheral resistance) for intravascular volume changes and may predispose the patient to cardiovascular instability (eg, postinduction hypotension) and even sudden cardiac death. The incidence of perioperative cardiovascular instability appears increased by the concomitant use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Autonomic dysfunction contributes to delayed gastric emptying (diabetic gastroparesis). Premedication with a nonparticulate antacid and metoclopramide is often used in an obese diabetic patient with signs of cardiac autonomic dysfunction. However, autonomic dysfunction can affect the gastrointestinal tract without any signs of cardiac involvement.

**TABLE 34–3 Clinical signs of diabetic autonomic neuropathy.**

| |
|---|
| Hypertension |
| Painless myocardial ischemia |
| Orthostatic hypotension |
| Lack of heart rate variability[1] |
| Reduced heart rate response to atropine and propranolol |
| Resting tachycardia |
| Early satiety |
| Neurogenic bladder |
| Lack of sweating |
| Impotence |

[1]Normal heart rate variability during voluntary deep breathing (6 breaths/min) should be >10 beats/min.

Diabetic renal dysfunction is manifested first by proteinuria and later by elevated serum creatinine. By these criteria, most patients with type 1 diabetes have evidence of kidney disease by 30 years of age. Because of an increased incidence of infections related to a compromised immune system, strict attention to aseptic technique, important for all patients, is especially important in those with diabetes.

Chronic hyperglycemia can lead to glycosylation of tissue proteins and limited mobility of joints.

2 Temporomandibular joint and cervical spine mobility should be assessed preoperatively in diabetic patients to reduce the likelihood of unanticipated difficult intubations. Difficult intubation has been reported in as many as 30% of persons with type 1 diabetes.

### B. Intraoperative

The goal of intraoperative blood glucose management is to avoid hypoglycemia while maintaining

blood glucose below 180 mg/dL. Attempting to maintain strict euglycemia is imprudent; "loose" blood glucose control (>180 mg/dL) also carries risk. The exact range over which blood glucose should be maintained in critical illness has been the subject of several much-discussed clinical trials. Hyperglycemia has been associated with hyperosmolarity, infection, poor wound healing, and increased mortality. Severe hyperglycemia may worsen neurological outcome following an episode of cerebral ischemia and may compromise outcome following cardiac surgery or after an acute myocardial infarction. Unless severe hyperglycemia is treated aggressively in type 1 diabetic patients, metabolic control may be lost, particularly in association with major surgery or critical illness. Maintaining blood glucose control (<180 mg/dL) in patients undergoing cardiopulmonary bypass decreases infectious complications. A benefit of true "tight" control (<150 mg/dL) during surgery or critical illness has not yet been demonstrated convincingly and in some studies has been associated with worse outcome than "looser" control (<180 mg/dL).

Lack of consensus regarding the appropriate target for blood glucose has not prevented perioperative glucose management from becoming yet another indicator of so-called "quality" anesthetic care. Consequently, anesthesia staff should carefully review their current practices to ensure that their glucose management protocols are in line with institutional expectations.

Control of blood glucose in pregnant diabetic patients improves fetal outcome. Nonetheless, as noted earlier, the brain's dependence on glucose as an energy supply makes it essential that hypoglycemia be avoided.

There are several common perioperative management regimens for insulin-dependent diabetic patients. In the most time-honored (but not terribly effective) approach, the patient receives a fraction—usually half—of the total morning insulin dose in the form of intermediate-acting insulin (**Table 34–4**). To decrease the risk of hypoglycemia, insulin is administered *after* intravenous access has been established and the morning blood glucose level is checked. For example, a patient who normally takes 30 units of NPH (neutral protamine Hagedorn; intermediate-acting) insulin and 10 units of regular or Lispro (short-acting) insulin or insulin analogue each morning and whose blood glucose is at least 150 mg/dL would receive 15 units (half the normal 30-unit morning dose) of NPH subcutaneously before surgery along with an infusion of 5% dextrose solution (1.5 mL/kg/h). Absorption of subcutaneous or intramuscular insulin depends on tissue blood flow, however, and can be unpredictable during surgery. Dedication of a small-gauge intravenous line for the dextrose infusion prevents interference with other intraoperative fluids and drugs. Supplemental dextrose can be administered if the patient becomes hypoglycemic (<100 mg/dL). However, intraoperative hyperglycemia (>150–180 mg/dL) is treated with intravenous regular insulin according to a sliding scale. One unit of regular insulin given to an adult usually lowers plasma glucose by 25–30 mg/dL. It must be stressed that these doses are approximations and do not apply to patients in catabolic states (eg, sepsis, hyperthermia).

**TABLE 34–4 Two common techniques for perioperative insulin management in diabetes mellitus.**

| | Bolus Administration | Continuous Infusion |
|---|---|---|
| Preoperative | $D_5W$ (1.5 mL/kg/h)<br>NPH[1] insulin (half usual AM dose) | $D_5W$ (1 mL/kg/h)<br>Regular insulin: $\text{Units/h} = \frac{\text{Plasma glucose}}{150}$ |
| Intraoperative | Regular insulin (as per sliding scale) | Same as preoperative |
| Postoperative | Same as intraoperative | Same as preoperative |

[1]NPH, neutral protamine Hagedorn.

An alternative method is to administer regular insulin as a continuous infusion. The advantage of this technique is more precise control of insulin delivery than can be achieved with a subcutaneous or intramuscular injection of NPH insulin, particularly in conditions associated with poor skin and muscle perfusion. Regular insulin can be added to normal saline in a concentration of 1 unit/mL and

the infusion begun at 0.1 unit/kg/h. As blood glucose fluctuates, the regular insulin infusion can be adjusted up or down as required. The dose required may be approximated by the following formula:

$$\text{Unit per hour} = \frac{\text{Plasma glucose (mg/dL)}}{150}$$

A general target for the intraoperative maintenance of blood glucose is less than 180 mg/dL. The tighter control afforded by a continuous intravenous technique may be preferable in patients with type 1 diabetes.

When administering an intravenous insulin infusion to surgical patients, adding some (eg, 20 mEq) KCl to each liter of fluid may be useful, as insulin causes an intracellular potassium shift. Because individual insulin needs can vary dramatically, any formula should be considered as only a crude guideline.

If the patient is taking an oral hypoglycemic agent preoperatively rather than insulin, the drug can be continued until the day of surgery. However, sulfonylureas and metformin have long half-lives and many clinicians will discontinue them 24–48 h before surgery. They can be started postoperatively when the patient resumes oral intake. Metformin is restarted if renal and hepatic function remain adequate. The effects of oral hypoglycemic drugs with a short duration of action can be prolonged in the presence of kidney failure. Many patients maintained on oral antidiabetic agents will require insulin treatment during the intraoperative and postoperative periods. The stress of surgery causes elevations in counterregulatory hormones (eg, catecholamines, glucocorticoids, growth hormone) and inflammatory mediators such as tumor necrosis factor and interleukins. Each of these contributes to stress hyperglycemia, which increases insulin requirements. In general, type 2 diabetic patients tolerate minor, brief surgical procedures without any exogenous insulin. However, many ostensibly "nondiabetic" patients show pronounced hyperglycemia during critical illness and require a period of insulin therapy.

The key to any management regimen is to monitor plasma glucose levels frequently. Patients receiving insulin infusions intraoperatively may need to have their glucose measured hourly. Those with type 2 diabetes vary in their ability to produce and respond to endogenous insulin, and measurement every 2 or 3 h may be sufficient. Likewise, insulin requirements vary with the extensiveness of the surgical procedure. Bedside glucose meters are capable of determining the glucose concentration in a drop of blood obtained from a finger stick (or withdrawn from a central or arterial line) within a minute. These devices measure the color conversion of a glucose oxidase–impregnated strip. Their accuracy depends, to a large extent, on adherence to the device's specific testing protocol. Monitoring urine glucose is of value only for detecting glycosuria.

Patients who take NPH or other protamine-containing insulin preparations have an increased risk of allergic reactions to protamine sulfate—including anaphylactoid reactions and death. Unfortunately, operations that require the use of heparin and subsequent reversal with protamine (eg, cardiopulmonary bypass) are more common in diabetic patients. The usefulness of a small protamine test dose of 1–5 mg over 5–10 min prior to the full reversal dose is unclear, although this is recommended by some clinicians.

Patients who use subcutaneous insulin infusion pumps for management of type 1 diabetes usually can leave the pump programmed to deliver "basal" amounts of regular insulin (or insulin glargine). This is the amount of insulin required during fasting. Such patients can safely undergo short outpatient surgery with the pump on the basal setting. If more extensive inpatient procedures are required, these patients will normally be managed with intravenous insulin infusions as described earlier.

### C. Postoperative

Close monitoring of blood glucose must continue postoperatively. There is considerable patient-to-patient variation in onset and duration of action of insulin preparations (Table 34–5). For example, the onset of action of subcutaneous regular insulin is less than 1 h, but in rare patients its duration of action may continue for 6 h. NPH insulin typically has an onset of action within 2 h, but the action can last longer than 24 h. Another reason for close

**TABLE 34–5 Summary of bioavailability characteristics of the insulins.[1]**

| | Insulin Type[2] | Onset | Peak Action | Duration |
|---|---|---|---|---|
| Short-acting | Lispro | 10–20 min | 30–90 min | 4–6 h |
| | Regular | 15–30 min | 1–3 h | 5–7 h |
| | Semilente, Semitard | 30–60 min | 4–6 h | 12–16 h |
| Intermediate-acting | Lente, Lentard, NPH | 2–4 h | 8–10 h | 18–24 h |
| Long-acting | Ultralente, Glargine, Insulatard | 4–5 h | 8–14 h | 25–36 h |

[1]There is considerable patient-to-patient variation. Not all formulations available in every country.
[2]NPH, neutral protamine Hagedorn; PZI, protamine zinc insulin.

monitoring is the progression of stress hyperglycemia in the recovery period.

# The Thyroid

## Physiology

Dietary iodine is absorbed by the gastrointestinal tract, converted to iodide ion, and actively transported into the thyroid gland. Once inside, iodide is oxidized back to iodine, which is bound to the amino acid tyrosine. The end result is two hormones—triiodothyronine ($T_3$) and thyroxine ($T_4$)—which are bound to proteins and stored within the thyroid. Although the gland releases more $T_4$ than $T_3$, the latter is more potent and less protein bound. Of all circulating $T_3$, most is formed peripherally from partial deiodination of $T_4$. An elaborate feedback mechanism controls thyroid hormone synthesis and involves the hypothalamus (thyrotropin-releasing factor [TRF] and thyrotropin-releasing hormone [TRH]), the anterior pituitary (thyroid-stimulating hormone [TSH]), autoregulation, and the adequacy of iodine intake.

Thyroid hormone ($T_3$) increases carbohydrate and fat metabolism and is an important factor in determining growth and metabolic rate. An increase in metabolic rate is accompanied by an increase in oxygen consumption and $CO_2$ production, indirectly increasing minute ventilation. Heart rate and contractility are also increased, presumably from an alteration in adrenergic-receptor physiology and other internal protein alterations, not from an increase in catecholamine concentrations.

# HYPERTHYROIDISM

## Clinical Manifestations

Excess thyroid hormone levels can be caused by Graves' disease, toxic multinodular goiter, TSH-secreting pituitary tumors, "toxic" or "hot" thyroid adenomas, or overdosage (accidental or intentional) of thyroid replacement hormone. Clinical manifestations of excess thyroid hormone concentrations include weight loss, heat intolerance, muscle weakness, diarrhea, hyperactive reflexes, and nervousness. A fine tremor, exophthalmos, or goiter may be noted, particularly when the cause is Graves' disease. New onset of atrial fibrillation is a classic presentation of hyperthyroidism, but cardiac signs also include sinus tachycardia and congestive heart failure. The diagnosis of hyperthyroidism is confirmed by abnormal thyroid function tests, which may include an elevation in serum $T_4$ and serum $T_3$ and a reduced TSH level.

Medical treatment of hyperthyroidism relies on drugs that inhibit thyroid hormone synthesis (eg, propylthiouracil, methimazole), prevent hormone release (eg, potassium, sodium iodide), or mask the signs of adrenergic overactivity (eg, propranolol). In addition, although β-adrenergic antagonists do not affect thyroid gland function, they do decrease the peripheral conversion of $T_4$ to $T_3$. Radioactive iodine destroys thyroid cell function and may result in hypothyroidism. Radioactive iodine is not recommended for pregnant patients. Subtotal thyroidectomy is rarely used as an alternative to medical therapy. Typically, it is reserved for patients with large toxic multinodular goiters or solitary toxic adenomas. Graves' disease is usually

treated with so-called antithyroid drugs or radioactive iodine.

## Anesthetic Considerations

### A. Preoperative

All elective surgical procedures, including subtotal thyroidectomy, should be postponed until the patient is rendered clinically and chemically euthyroid with medical treatment. The patient should have normal $T_3$ and $T_4$ concentrations, and should not have resting tachycardia. Antithyroid medications and β-adrenergic antagonists are continued through the morning of surgery. Administration of propylthiouracil and methimazole is particularly important because of their relatively short half-lives. If emergency surgery must proceed despite clinical hyperthyroidism, the hyperdynamic circulation can be controlled by titration of an esmolol infusion.

### B. Intraoperative

Cardiovascular function and body temperature should be closely monitored in patients with a history of hyperthyroidism. The exophthalmos of Graves' disease increases the risk of corneal abrasion or ulceration.

Ketamine, indirect-acting adrenergic agonists, and other drugs that stimulate the sympathetic nervous system or are unpredictable muscarinic antagonists are best avoided in patients with current or recently corrected hyperthyroidism because of the possibility of exaggerated elevations in blood pressure and heart rate. Incompletely treated hyperthyroid patients can be chronically hypovolemic and prone to an exaggerated hypotensive response during induction of anesthesia. Adequate anesthetic depth must be obtained, however, before laryngoscopy or surgical stimulation to avoid tachycardia, hypertension, and ventricular arrhythmias.

Thyrotoxicosis is associated with an increased incidence of myopathies and myasthenia gravis; therefore, neuromuscular blocking agents (NMBs) should be administered cautiously. Hyperthyroidism does not increase anesthetic requirements; that is, there is no increase in minimum alveolar concentration.

### C. Postoperative

The most serious threat to a hyperthyroid patient undergoing surgery is **thyroid storm**, which is characterized by hyperpyrexia, tachycardia, altered consciousness (eg, agitation, delirium, coma), and hypotension. The onset is usually 6–24 h after surgery but can occur intraoperatively, mimicking malignant hyperthermia. Unlike malignant hyperthermia, however, thyroid storm is not associated with muscle rigidity, elevated creatine kinase, or a marked degree of metabolic (lactic) and respiratory acidosis. Treatment includes hydration and cooling, an esmolol infusion or another intravenous β blocker (with a target of maintaining heart rate <100/min), propylthiouracil (250–500 mg every 6 h orally or by nasogastric tube) followed by sodium iodide (1 g intravenously over 12 h), and correction of any precipitating cause (eg, infection). Cortisol (100–200 mg every 8 h) is recommended to prevent complications from coexisting adrenal gland suppression. Thyroid storm is a medical emergency that requires aggressive management and monitoring (see Case Discussion, Chapter 56).

Thyroidectomy is associated with several potential surgical complications. Recurrent laryngeal nerve palsy will result in hoarseness (unilateral) or aphonia and stridor (bilateral). Vocal cord function can be evaluated by laryngoscopy immediately following "deep extubation", however, this is rarely necessary. Failure of one or both cords to move may require reintubation and exploration of the wound. Hematoma formation may cause airway compromise from collapse of the trachea, particularly in patients with tracheomalacia. Dissection of the hematoma into the compressible soft tissues of the neck may distort the airway anatomy and may make intubation difficult. Immediate treatment includes opening the neck wound and evacuating the clot, then reassessing the need for reintubation. Anesthesia staff in the postoperative setting must be prepared to open the surgical wound and relieve airway compression if the surgeon is for any reason unavailable.

Hypoparathyroidism from unintentional removal of all four parathyroid glands will cause acute hypocalcemia within 12–72 h (see the section on Clinical Manifestations under Hypoparathyroidism).

Pneumothorax is an unusual complication of neck exploration.

# HYPOTHYROIDISM

## Clinical Manifestations

Hypothyroidism can be caused by autoimmune disease (eg, Hashimoto's thyroiditis), thyroidectomy, radioactive iodine, antithyroid medications, iodine deficiency, or failure of the hypothalamic–pituitary axis (secondary hypothyroidism). Hypothyroidism during neonatal development results in cretinism, a condition marked by physical and mental retardation. Clinical manifestations of hypothyroidism in the adult are usually subtle and include infertility, weight gain, cold intolerance, muscle fatigue, lethargy, constipation, hypoactive reflexes, dull facial expression, and depression. Heart rate, myocardial contractility, stroke volume, and cardiac output decrease, and extremities are cool and mottled because of peripheral vasoconstriction. Pleural, abdominal, and pericardial effusions are common. Hypothyroidism may be diagnosed by an elevated TSH concentration, or a reduced free (or total) $T_3$ level, or both. Primary hypothyroidism, the more common condition, is differentiated from secondary disease by an elevation in TSH in the former. Normal concentrations of TSH despite reduced $T_3$ concentrations (the so-called "euthyroid sick" syndrome) are often seen in critical illness. The treatment of hypothyroidism consists of oral replacement therapy with a thyroid hormone preparation, which takes several days to produce a physiological effect and several weeks to evoke clear-cut clinical improvement.

Myxedema coma results from extreme hypothyroidism and is characterized by impaired mentation, hypoventilation, hypothermia, hyponatremia (from inappropriate antidiuretic hormone secretion), and congestive heart failure. It is more common in elderly patients and may be precipitated by infection, surgery, or trauma. Myxedema coma is a life-threatening disease that can be treated with intravenous $T_3$. $T_4$ should not be used in this circumstance to avoid the need for peripheral conversion to $T_3$. The ECG should be monitored during therapy to detect myocardial ischemia or arrhythmias. Steroid replacement (eg, hydrocortisone, 100 mg intravenously every 8 h) is routinely given due to frequent coexisting adrenal gland suppression. Some patients may require ventilatory support and external warming.

## Anesthetic Considerations

### A. Preoperative

Patients with uncorrected severe hypothyroidism or myxedema coma should not undergo elective surgery. Such patients should be treated with $T_3$ intravenously prior to emergency surgery. Although a euthyroid state is ideal, mild to moderate hypothyroidism does not appear to be an absolute contraindication to surgery, for example, urgent coronary bypass surgery.

Hypothyroid patients usually require minimal preoperative sedation and are very prone to drug-induced respiratory depression. In addition, they may fail to respond to hypoxia with increased minute ventilation. Patients who have been rendered euthyroid may receive their usual dose of thyroid medication on the morning of surgery; it must be remembered, however, that most commonly used preparations have long half-lives (the half-life of $T_4$ is about 8 days); therefore, omission of a single dose should have no medical importance.

### B. Intraoperative

5 Clinically hypothyroid patients are more susceptible to the hypotensive effect of anesthetic agents because of their diminished cardiac output, blunted baroreceptor reflexes, and decreased intravascular volume. For these reasons, ketamine or etomidate can be recommended for induction of anesthesia. The possibility of coexistent primary adrenal insufficiency should be considered in cases of refractory hypotension. **Other potential coexisting conditions include hypoglycemia, anemia, hyponatremia, difficulty during intubation because of a large tongue, and hypothermia from a low basal metabolic rate.**

### C. Postoperative

Recovery from general anesthesia may be delayed in hypothyroid patients by hypothermia, respiratory depression, or slowed drug biotransformation; thus these patients may require mechanical ventilation. Because hypothyroidism increases vulnerability to

**TABLE 34–6 Actions of major calcium-regulating hormones.**

| | Bone | Kidney | Intestines |
|---|---|---|---|
| Parathyroid hormone (PTH) | Increases resorption of calcium and phosphate | Increases reabsorption of calcium; decreases reabsorption of phosphate; increases conversion of 25-$OHD_3$ to 1,25 $(OH)_2$ $D_3$;[1] decreases reabsorption of bicarbonate | No direct effects; increases renal production of vitamin D |
| Calcitonin | Inhibits osteoclastic resorption | Decreases reabsorption of calcium and phosphate | Inhibits reabsorption of phosphate; increases renal excretion of sodium and calcium |
| Vitamin D | Maintains $Ca^{2+}$ homeostasis | Decreases reabsorption of calcium (probably less important than PTH) | Increases absorption of calcium |

[1]25-$OHD_3$, 25-hydroxyvitamin $D_3$; 1,25 $(OH)_2D_3$, 1,25-dihydroxyvitamin $D_3$.

respiratory depression, a multimodal approach to postoperative pain management, rather than strict reliance on opioids would be appropriate.

# The Parathyroid Glands

## Physiology

Parathyroid hormone (PTH) is the principal regulator of calcium homeostasis. It increases serum calcium concentrations by promoting resorption of bone and teeth, limiting renal excretion of calcium, and indirectly enhancing gastrointestinal absorption by its effect on vitamin D metabolism. PTH decreases serum phosphate by increasing renal excretion. The effects of PTH on calcium serum levels are countered in lower animals by calcitonin, a hormone excreted by parafollicular C-cells in the thyroid, but a physiological calcium-lowering effect for calcitonin has not been demonstrated in humans (Table 34–6). Of total body calcium, 99% is in the skeleton. Of the calcium in the blood, 40% is bound to proteins and 60% is ionized or complexed to organic ions. Unbound ionized calcium is physiologically the most important fraction.

# HYPERPARATHYROIDISM

## Clinical Manifestations

Causes of primary hyperparathyroidism include parathyroid adenomas, hyperplasia of the parathyroid gland, and certain carcinomas. Secondary hyperparathyroidism is an adaptive response to hypocalcemia produced by conditions such as kidney failure or intestinal malabsorption syndromes. Ectopic hyperparathyroidism is due to production of PTH by rare tumors outside the parathyroid gland. Parathyroid hormone–related peptide may cause significant hypercalcemia when secreted by a carcinoma (eg, bronchogenic [lung] carcinoma or hepatoma). Bone invasion with osteolytic hypercalcemia may complicate multiple myeloma, lymphoma, or leukemia. Overall, the most common cause of hypercalcemia in hospitalized patients is malignancy. Nearly all clinical manifestations of hyperparathyroidism are due to hypercalcemia (Table 34–7). Rarer causes of hypercalcemia include bone metastases of solid organ tumors, vitamin D intoxication, milk-alkali syndrome, lithium therapy, sarcoidosis, and prolonged immobilization. The treatment of hyperparathyroidism depends on the cause, but surgical removal of all four glands is often required in the setting of parathyroid hyperplasia. When there is a single adenoma, its removal cures many patients with sporadic primary hyperparathyroidism.

## Anesthetic Considerations

In patients with hypercalcemia due to hyperparathyroidism, hydration with normal saline and diuresis facilitated by furosemide will usually decrease serum calcium to acceptable values (<14 mg/dL, 7 mEq/L, or 3.5 mmol/L). More aggressive therapy with the intravenous bisphosphonates pamidronate (Aredia) or etidronate (Didronel) may be necessary for patients with hypercalcemia of malignancy.

**TABLE 34–7 Effects of hyperparathyroidism.**

| |
|---|
| **Cardiovascular** |
| Hypertension |
| Ventricular arrythmias |
| ECG[1] changes (shortened QT interval,[2] widened T wave) |
| **Renal** |
| Polyuria |
| Impaired renal concentrating ability |
| Kidney stones |
| Hyperchloremic metabolic acidosis |
| Dehydration |
| Polydipsia |
| Kidney failure |
| **Gastrointestinal** |
| Constipation |
| Nausea and vomiting |
| Anorexia |
| Pancreatitis |
| Peptic ulcer disease |
| **Musculoskeletal** |
| Muscle weakness |
| Osteoporosis |
| **Neurological** |
| Mental status change (eg, delirium, psychosis, coma) |

[1]ECG, electrocardiogram.

[2]The QT interval may be prolonged at serum calcium concentrations >16 mg/dL.

Plicamycin (Mithramycin), glucocorticoids, calcitonin, or dialysis may be necessary when intravenous bisphosphonates are not sufficient or are contraindicated. Hypoventilation should be avoided, as acidosis increases ionized calcium. Elevated calcium levels can cause cardiac arrhythmias. The response to NMBs may be altered in patients with preexisting muscle weakness caused by the effects of calcium at the neuromuscular junction. Osteoporosis worsened by hyperparathyroidism predisposes patients to vertebral compression and bone fractures during anesthetic procedures, positioning, and transport. The notable postoperative complications of parathyroidectomy are similar to those for subtotal thyroidectomy.

# HYPOPARATHYROIDISM

## Clinical Manifestations

Hypoparathyroidism is usually due to deficiency of PTH following parathyroidectomy. Clinical manifestations of hypoparathyroidism are a result of hypocalcemia (Table 34–8), which can also be caused by kidney failure, hypomagnesemia, vitamin D deficiency, and acute pancreatitis (see Chapter 49). Hypoalbuminemia decreases total serum calcium (a 1 g/dL drop in serum albumin causes a 0.8 mg/dL decrease in total serum calcium), but ionized calcium, the active entity, is unaltered. The archetypical presentation of hypocalcemia is tetany, classically diagnosed by Chvostek's sign (painful twitching of the facial musculature following tapping over the facial nerve) or Trousseau's sign (carpal spasm following inflation of an arm tourniquet above systolic blood pressure for 3 min). These signs are also occasionally present in nonhypocalcemic persons. Treatment of symptomatic hypocalcemia consists of intravenous administration of calcium salts.

**TABLE 34–8 Effects of hypoparathyroidism.**

| |
|---|
| **Cardiovascular** |
| ECG[1] changes (prolonged QT interval) |
| Hypotension |
| Congestive heart failure |
| **Neurological** |
| Neuromuscular irritability (eg, laryngospasm, inspiratory stridor, tetany, seizures) |
| Perioral paresthesia |
| Mental status changes (eg, dementia, depression, psychosis) |

[1]ECG, electrocardiogram.

Mild hypocalcemia is common following cardiopulmonary bypass or infusion of albumin solutions. In many adult patients this need not be treated as the response of the PTH–vitamin D axis will usually be sufficient to restore ionized calcium to normal values and mild hypocalcemia will usually have no hemodynamic consequences.

## Anesthetic Considerations

Serum calcium should be normalized in any patient who presents with cardiac manifestations of severe hypocalcemia. Alkalosis from hyperventilation or sodium bicarbonate therapy will further decrease ionized calcium. Although citrate-containing blood products usually do not lower serum calcium significantly, they should be administered cautiously in patients with preexisting hypocalcemia. Other

considerations include avoiding the use of albumin solutions (which bind and reduce ionized calcium concentrations) and being mindful of the possibility of coagulopathy.

# The Adrenal Gland

## Physiology

The adrenal gland is divided into the cortex and medulla. The adrenal cortex secretes androgens, mineralocorticoids (eg, aldosterone), and glucocorticoids (eg, cortisol). The adrenal medulla secretes catecholamines (primarily epinephrine, but also small amounts of norepinephrine and dopamine). The adrenal androgens have almost no relevance for anesthetic management and will not be considered further.

Aldosterone is primarily involved with fluid and electrolyte balance. Aldosterone secretion causes sodium to be reabsorbed in the distal renal tubule in exchange for potassium and hydrogen ions. The net effect is an expansion in extracellular fluid volume caused by fluid retention, a decrease in plasma potassium, and metabolic alkalosis. Aldosterone secretion is stimulated by the renin–angiotensin system (specifically, angiotensin II), pituitary adrenocorticotropic hormone (ACTH), and hyperkalemia. Hypovolemia, hypotension, congestive heart failure, and surgery result in an elevation of aldosterone concentrations. Blockade of the renin–angiotensin–aldosterone system with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, or both, is a cornerstone of therapy (and produces increased survival) in hypertension and chronic heart failure. Aldosterone receptor blockers (spironolactone or eplerenone) added to standard therapy prolong survival in patients with chronic heart failure.

Glucocorticoids are essential for life and have multiple physiological effects, including enhanced gluconeogenesis and inhibition of peripheral glucose utilization. These actions tend to raise blood glucose and worsen diabetic control. Glucocorticoids are required for vascular and bronchial smooth muscle to respond to catecholamines. Because glucocorticoids are structurally related to aldosterone, most tend to promote sodium retention and potassium excretion (a mineralocorticoid effect). ACTH released by the anterior pituitary is the principal regulator of glucocorticoid secretion. Basal secretion of ACTH and glucocorticoids exhibits a diurnal rhythm. Stressful conditions promote secretion of ACTH and cortisol, while circulating glucocorticoids inhibit ACTH and cortisol secretion. Endogenous production of cortisol, the most important endogenous glucocorticoid, averages 20 mg/d.

The structure, biosynthesis, physiological effects, and metabolism of catecholamines are discussed in Chapter 14. Epinephrine constitutes 80% of adrenal catecholamine output in humans. Catecholamine release is regulated mainly by sympathetic cholinergic preganglionic fibers that innervate the adrenal medulla. Stimuli include exercise, hemorrhage, surgery, hypotension, hypothermia, hypoglycemia, hypercapnia, hypoxemia, pain, and fear.

# MINERALOCORTICOID EXCESS

## Clinical Manifestations

Hypersecretion of aldosterone by the adrenal cortex (primary aldosteronism) can be due to a unilateral adenoma (aldosteronoma or Conn syndrome), bilateral hyperplasia, or in very rare cases carcinoma of the adrenal gland. Some disease states stimulate aldosterone secretion by affecting the renin–angiotensin system. For example, congestive heart failure, hepatic cirrhosis with ascites, nephrotic syndrome, and some forms of hypertension (eg, renal artery stenosis) can cause secondary aldosteronism. Although both primary and secondary aldosteronism are characterized by increased levels of aldosterone, only the latter is associated with increased renin activity. The usual clinical manifestations of mineralocorticoid excess include hypokalemia and hypertension, and an increased ratio of aldosterone–plasma renin activity has been noted in laboratory studies.

## Anesthetic Considerations

Fluid and electrolyte disturbances can be corrected preoperatively using spironolactone. This aldosterone antagonist is a potassium-sparing diuretic with

antihypertensive properties. Intravascular volume can be assessed preoperatively by testing for orthostatic hypotension.

# MINERALOCORTICOID DEFICIENCY

## Clinical Manifestations & Anesthetic Considerations

Atrophy or destruction of both adrenal glands results in a combined deficiency of mineralocorticoids and glucocorticoids (see the section on Glucocorticoid Deficiency). Isolated deficiency of mineralocorticoid activity almost never occurs.

# GLUCOCORTICOID EXCESS

## Clinical Manifestations

Glucocorticoid excess may be due to exogenous administration of steroid hormones, intrinsic hyperfunction of the adrenal cortex (eg, adrenocortical adenoma), ACTH production by a nonpituitary tumor (ectopic ACTH syndrome), or hypersecretion by a pituitary adenoma (Cushing's disease). Regardless of the cause, an excess of corticosteroids produces Cushing's syndrome, characterized by muscle wasting and weakness, osteoporosis, central obesity, abdominal striae, glucose intolerance, menstrual irregularity, hypertension, and mental status changes.

## Anesthetic Considerations

Patients with Cushing's syndrome may be volume overloaded and have hypokalemic metabolic alkalosis resulting from the mineralocorticoid activity of glucocorticoids. These abnormalities should be corrected preoperatively in the manner previously described. Patients with osteoporosis are at risk for fracture during positioning. If the cause of Cushing's syndrome is exogenous glucocorticoids, the patient's adrenal glands may not be able to respond to perioperative stresses, and supplemental steroids are indicated (see the section on Glucocorticoid Deficiency). Likewise, patients undergoing adrenalectomy require intraoperative glucocorticoid replacement (in adults, intravenous hydrocortisone succinate, 100 mg every 8 h). Other complications of adrenalectomy may include significant blood loss during resection of a highly vascularized tumor and unintentional pneumothorax. On the other hand, many adrenal tumors are removed uneventfully during laparoscopic surgery.

# GLUCOCORTICOID DEFICIENCY

## Clinical Manifestations

Primary adrenal insufficiency (Addison's disease) is caused by destruction of the adrenal gland, which results in a combined mineralocorticoid and glucocorticoid deficiency. Clinical manifestations are due to aldosterone deficiency (hyponatremia, hypovolemia, hypotension, hyperkalemia, and metabolic acidosis) and cortisol deficiency (weakness, fatigue, hypoglycemia, hypotension, and weight loss).

Secondary adrenal insufficiency is a result of inadequate ACTH secretion by the pituitary. The most common cause of secondary adrenal insufficiency is iatrogenic, the result of prior administration of exogenous glucocorticoids. Because mineralocorticoid secretion is usually adequate in secondary adrenal insufficiency, fluid and electrolyte disturbances are not present. Acute adrenal insufficiency (addisonian crisis), however, can be triggered in steroid-dependent patients who do not receive appropriate glucocorticoid doses during periods of stress (eg, infection, trauma, surgery), and in patients who receive infusions of etomidate. The clinical features of this medical emergency include fever, abdominal pain, orthostatic hypotension, and hypovolemia that may progress to circulatory shock unresponsive to resuscitation.

## Anesthetic Considerations

6 Patients with glucocorticoid deficiency must receive adequate steroid replacement therapy during the perioperative period. All patients who have received potentially suppressive doses of steroids (eg, the daily equivalent of 5 mg of prednisone) by any route of administration (topical, inhalational, or oral) for a period of more than 2 weeks any time in the previous 12 months may be unable to respond

appropriately to surgical stress and should receive perioperative glucocorticoid supplementation.

What represents adequate steroid coverage is controversial, and there are those who advocate variable dosing based on the extent of the surgery. Although adults normally secrete 20 mg of cortisol daily, this may increase to over 300 mg under conditions of maximal stress. Thus, a traditional recommendation was to administer 100 mg of hydrocortisone phosphate every 8 h beginning on the morning of surgery. An alternative low-dose regimen (25 mg of hydrocortisone at the time of induction followed by an infusion of 100 mg during the subsequent 24 h) maintains plasma cortisol levels equal to or higher than those reported in healthy patients undergoing similar elective surgery. This second regimen might be particularly appropriate for diabetic patients, in whom glucocorticoid administration often interferes with control of blood glucose.

# CATECHOLAMINE EXCESS

## Clinical Manifestations

Pheochromocytoma is a catecholamine-secreting tumor that consists of cells originating from the embryonic neural crest. This tumor accounts for 0.1% of all cases of hypertension. Although the tumor is usually localized in a single adrenal gland, 10–15% are bilateral or extraadrenal. Approximately 10% of tumors are malignant. The cardinal manifestations of pheochromocytoma are paroxysmal hypertension, headache, sweating, and palpitations. Unexpected intraoperative hypertension and tachycardia during manipulation of abdominal structures may occasionally be the first indications of an undiagnosed pheochromocytoma. The pathophysiology, diagnosis, and treatment of these tumors require an understanding of catecholamine metabolism and of the pharmacology of adrenergic agonists and antagonists. The Case Discussion in Chapter 14 examines these aspects of pheochromocytoma management.

## Anesthetic Considerations

**Preoperative assessment should focus on the adequacy of α-adrenergic blockade and volume replacement.** Specifically, resting arterial blood pressure, orthostatic blood pressure and heart rate, ventricular ectopy, and electrocardiographic evidence of ischemia should be evaluated.

A decrease in plasma volume and red cell mass contributes to the severe chronic hypovolemia seen in these patients. The hematocrit may be normal or elevated, depending on the relative contribution of hypovolemia and anemia; thus neither hematocrit nor hemoglobin concentration reliably defines the adequacy of intravenous volume. Preoperative α-adrenergic blockade with phenoxybenzamine (a noncompetitive inhibitor) helps correct the volume deficit, in addition to correcting hypertension. β Blockade should not be initiated prior to initiation of α blockade but may be added if there is a need to control heart rate and to reduce arrhythmias provoked by excess catecholamine concentrations. A drop in hematocrit should accompany the expansion of circulatory volume, sometimes unmasking an underlying anemia.

Potentially life-threatening variations in blood pressure—particularly during induction and manipulation of the tumor—indicate the usefulness of invasive arterial pressure monitoring and of adequate intravenous access. Young patients with minimal or no heart disease may not need a central venous line. Patients with evidence of cardiac disease (or in whom cardiac disease is suspected) may benefit from having a central line (a convenient route of access for administering catecholamines, should they be required) and from intraoperative transesophageal echocardiography.

Intubation should not be attempted until a deep level of general anesthesia (possibly also including local anesthesia of the trachea) has been established. Intraoperative hypertension can be treated with phentolamine, nitroprusside, nicardipine, or clevidipine. Phentolamine specifically blocks α-adrenergic receptors and blocks the effects of excessive circulating catecholamines. Nitroprusside has a rapid onset of action, a short duration of action, and as a nitric oxide donor can be effective in cases where calcium channel blockers are ineffective. Nicardipine and clevidipine are being used more frequently preoperatively and intraoperatively.

7 Drugs or techniques that indirectly stimulate or promote the release of catecholamines

(eg, ephedrine, hypoventilation, or large bolus doses of ketamine), potentiate the arrhythmic effects of catecholamines (classically halothane), or consistently release histamine (eg, large doses of atracurium or morphine sulfate) are best avoided.

After ligation of the tumor's venous supply, the primary problem frequently becomes *hypotension* from hypovolemia, persistent adrenergic blockade, and tolerance to the high levels of endogenous catecholamines that have been abruptly withdrawn. Appropriate fluid resuscitation should reflect surgical bleeding and other sources of fluid loss. Assessment of intravascular volume can be guided by echocardiographic assessment of left ventricular filling using transesophageal echocardiography or other noninvasive measures of cardiac output and stroke volume. Infusions of adrenergic agonists, such as phenylephrine or norepinephrine, often prove necessary. Postoperative *hypertension* is rare and may indicate the presence of unresected occult tumors.

## Obesity

Overweight and obesity are classified using the body mass index (BMI). Overweight is defined as a BMI of 24 kg/m$^2$ or higher, obesity as a BMI of 30 or higher, and extreme obesity (formerly termed "morbid obesity") as a BMI of more than 40. BMI is calculated by dividing the weight (in kilograms) by the height (in meters) squared. Health risks increase with the degree of obesity and with increased abdominal distribution of weight. Men with a waist measurement of 40 in. or more and women with a waist measurement of 35 in. or more are at increased health risk. For a patient 1.8 m tall and weighing 70 kg, the BMI would be as shown in the following formula:

$$\text{BMI} = \frac{\text{Weight (kg)}}{(\text{Height [meters]})^2} = \frac{70\text{ kg}}{1.8^2} = \frac{70}{3.24}$$
$$= 21.6\text{ kg/m}^2$$

### Clinical Manifestations

Obesity is associated with many diseases, including type 2 diabetes mellitus, hypertension, coronary artery disease, obstructive sleep apnea, degenerative joint disease (osteoarthritis), and cholelithiasis. Even in the absence of obvious coexisting disease, however, extreme obesity has profound physiological consequences. Oxygen demand, $CO_2$ production, and alveolar ventilation are elevated because metabolic rate is proportional to body weight. Excessive adipose tissue over the thorax decreases chest wall compliance even though lung compliance may remain normal. Increased abdominal mass forces the diaphragm cephalad, yielding lung volumes suggestive of restrictive lung disease. Reductions in lung volumes are accentuated by the supine and Trendelenburg positions. In particular, functional residual capacity may fall below closing capacity. If this occurs, some alveoli will close during normal tidal volume ventilation, causing a ventilation/perfusion mismatch.

Whereas obese patients are often hypoxemic, only a few are hypercapnic, which should be a warning of impending complications. Obesity-hypoventilation syndrome, or obstructive sleep apnea (OSA), is a complication of extreme obesity characterized by hypercapnia, cyanosis-induced polycythemia, right-sided heart failure, and somnolence. These patients appear to have blunted respiratory drive and often suffer from loud snoring and upper-airway obstruction during sleep. OSA patients often report dry mouths and daytime somnolence; bed partners frequently describe apneic pauses. OSA has also been associated with increased perioperative complications including hypertension, hypoxia, arrhythmias, myocardial infarction, pulmonary edema, stroke, and death. The potential for difficult mask ventilation and difficult intubation, followed by upper airway obstruction during recovery, should be anticipated.

OSA patients are vulnerable during the postoperative period, particularly when sedatives or opioids have been given. When OSA patients are placed supine, the upper airway is even more prone to obstruction. For patients with known or suspected OSA, postoperative continuous positive airway pressure (CPAP) should be considered until the anesthesiologist can be sure that the patient can protect his or her airway and maintain spontaneous ventilation without evidence of obstruction. Both the American

Society of Anesthesiologists and the Society of Ambulatory Anesthesia offer guidelines on perioperative management of the patient with OSA.

An OSA patient's heart has an increased workload, as cardiac output and blood volume rise to perfuse additional fat stores. The elevation in cardiac output (0.1 L/min/kg of adipose tissue) is achieved through an increase in stroke volume—as opposed to heart rate. Arterial hypertension leads to left ventricular hypertrophy. Elevations in pulmonary blood flow and pulmonary artery vasoconstriction from persistent hypoxia can lead to pulmonary hypertension and cor pulmonale.

Obesity is also associated with gastrointestinal pathophysiology, including hiatal hernia, gastroesophageal reflux disease, delayed gastric emptying, and hyperacidic gastric fluid, as well as with an increased risk of gastric cancer. Fatty infiltration of the liver also occurs and may be associated with abnormal liver tests, but the extent of infiltration does not correlate well with the degree of liver test abnormality.

## Anesthetic Considerations

### A. Preoperative

For the reasons outlined above, obese patients are at an increased risk for developing aspiration pneumonia. Pretreatment with $H_2$ antagonists and metoclopramide should be considered. Premedication with respiratory depressant drugs must be avoided in patients with OSA.

Preoperative evaluation of extremely obese patients undergoing major surgery should attempt to assess cardiopulmonary reserve. Preoperative testing may include such items as chest radiograph, ECG, and arterial blood gas analysis. Physical signs of cardiac failure (eg, sacral edema) may be difficult to identify. Blood pressures must be taken with a cuff of the appropriate size. Potential sites for intravenous and intraarterial access should be checked in anticipation of technical difficulties. Obscured landmarks, difficult positioning, and extensive layers of adipose tissue may make regional anesthesia difficult with standard equipment and techniques. Obese patients may be difficult to intubate as a result of limited mobility of the temporomandibular and atlantooccipital joints, a narrowed upper airway, and a shortened distance between the mandible and sternal fat pads.

### B. Intraoperative

Because of the risks of aspiration and hypoventilation, morbidly obese patients are usually intubated for all but short general anesthetics. If intubation appears likely to be difficult, the use of a fiberoptic bronchoscope or video laryngoscopy is recommended. Positioning the patient on an intubating ramp is helpful. Auscultation of breath sounds may prove difficult. Even controlled ventilation may require relatively increased inspired oxygen concentrations to prevent hypoxia, particularly in the lithotomy, Trendelenburg, or prone positions. Subdiaphragmatic abdominal laparotomy packs can cause further deterioration of pulmonary function and a reduction of arterial blood pressure by increasing the resistance to venous return. Volatile anesthetics may be metabolized more extensively in obese patients. Increased metabolism may explain the increased incidence of halothane hepatitis observed in obese patients. Obesity has little clinical effect on the rate of decline of alveolar anesthetic concentrations and wake-up time, even following long surgical procedures.

Theoretically, greater fat stores would increase the volume of distribution for lipid-soluble drugs (eg, benzodiazepines, opioids) relative to a lean person of the same body weight. However, the volume of distribution of, for example, fentanyl or sufentanil is so large that obesity has minimal influence. Water-soluble drugs (eg, NMBs) have a much smaller volume of distribution, which is minimally increased by body fat. Nonetheless, the dosing of water-soluble drugs should be based on ideal body weight to avoid overdosing. In reality, of course, clinical practice does not always validate these expectations.

Although dosage requirements for epidural and spinal anesthesia are difficult to predict, obese patients typically require 20–25% less local anesthetic per blocked segment because of epidural fat and distended epidural veins. Continuous epidural anesthesia has the advantage of providing pain relief and the potential for decreasing respiratory complications in the postoperative period. Regional nerve blocks, when appropriate for the

surgery, have the additional advantages of not interfering with the postoperative deep vein thrombosis prophylaxis, rarely producing hypotension, and of reducing the need for opioids.

### C. Postoperative

Respiratory failure is a major postoperative problem of morbidly obese patients. The risk of postoperative hypoxia is increased in patients with preoperative hypoxia, following surgery involving the thorax or upper abdomen (particularly vertical incisions). Extubation should be delayed until the effects of NMBs are completely reversed and the patient is awake. An obese patient should remain intubated until there is no doubt that an adequate airway and tidal volume will be maintained. This does *not* mean that all obese patients need be ventilated overnight in an intensive care unit. If the patient is extubated in the operating room, supplemental oxygen should be provided during transportation to the postanesthesia care unit. A 45° modified sitting position will improve ventilation and oxygenation. The risk of hypoxia extends for several days into the postoperative period, and providing supplemental oxygen or CPAP, or both, should be routinely considered. Other common postoperative complications in obese patients include wound infection, deep venous thrombosis, and pulmonary embolism. Morbidly obese and OSA patients may be candidates for outpatient surgery provided they are adequately monitored and assessed postoperatively before discharge to home, and provided the surgical procedure will not require large doses of opioids for postoperative pain control.

## Carcinoid Syndrome

Carcinoid syndrome is the complex of symptoms and signs caused by the secretion of vasoactive substances (eg, serotonin, kallikrein, histamine) from enteroepinephrine tumors (carcinoid tumors). Because most of these tumors are located in the gastrointestinal tract, their metabolic products are released into the portal circulation and destroyed by the liver before they can cause systemic effects. However, the products of nonintestinal tumors (eg, pulmonary, ovarian) or hepatic metastases bypass the portal circulation and, therefore, can cause a variety of clinical manifestations. Many patients undergo surgery for resection of carcinoid tumors; most such patients have not experienced carcinoid syndrome.

**TABLE 34–9 Principal mediators of carcinoid syndrome and their clinical manifestations.**

| Mediator | Clinical Manifestations |
|---|---|
| Serotonin | Vasoconstriction (coronary artery spasm, hypertension), increased intestinal tone, water and electrolyte imbalance (diarrhea), tryptophan deficiency (hypoproteinemia, pellagra) |
| Kallikrein | Vasodilation (hypotension, flushing), bronchoconstriction |
| Histamine | Vasodilation (hypotension, flushing), arrhythmias, bronchoconstriction |

### Clinical Manifestations

The most common manifestations of carcinoid syndrome are cutaneous flushing, bronchospasm, profuse diarrhea, dramatic swings in arterial blood pressure (usually hypotension), and supraventricular arrhythmias (Table 34–9). **Carcinoid syndrome is associated with right-sided heart disease caused by valvular and myocardial plaque formation, and, in some cases, implantation of tumors on the tricuspid and pulmonary valves.** The diagnosis of carcinoid syndrome is confirmed by detection of serotonin metabolites in the urine (5-hydroxyindoleacetic acid) or suggested by elevated plasma levels of chromogranin A. Treatment varies depending on tumor location but may include surgical resection, symptomatic relief, or specific serotonin and histamine antagonists. Somatostatin, an inhibitory peptide, reduces the release of vasoactive tumor products.

### Anesthetic Considerations

9 The key to perioperative management of patients with carcinoid syndrome is to avoid anesthetic and surgical techniques or agents that could cause the tumor to release vasoactive

substances. Regional anesthesia may limit release of stress hormones perioperatively. Large bolus doses of histamine-releasing drugs (eg, morphine and atracurium) should be avoided. Surgical manipulation of the tumor can cause a massive release of hormones. Monitoring likely will include an arterial line. If there are concerns about hemodynamic instability or intrinsic heart disease caused by carcinoid syndrome, transesophageal echocardiography may be helpful. Alterations in carbohydrate metabolism may lead to unsuspected hypoglycemia or hyperglycemia. Consultation with an endocrinologist may help clarify the role of antihistamine, antiserotonin drugs (eg, methysergide), octreotide (a long-acting somatostatin analogue), or antikallikrein drugs (eg, corticosteroids) in specific patients.

## CASE DISCUSSION

### Multiple Endocrine Neoplasia

**An isolated thyroid nodule is discovered during physical examination of a 36-year-old woman complaining of diarrhea and headaches. Workup of the tumor reveals hypercalcemia and an elevated calcitonin level, which leads to the diagnosis of medullary cancer of the thyroid and primary hyperparathyroidism. During induction of general anesthesia for total thyroidectomy, the patient's blood pressure rises to 240/140 mm Hg and her heart rate approaches 140 beats/min, with frequent premature ventricular contractions. The operation is canceled, an arterial line is inserted, and the patient is treated with intravenous esmolol and nicardipine.**

#### *What could be the cause of this patient's hypertensive crisis during induction of general anesthesia?*

Multiple endocrine neoplasia (MEN) is characterized by tumor formation in several endocrine organs. MEN type 1 consists of pancreatic (gastrinomas, insulinomas), pituitary (chromophobes), and parathyroid tumors. MEN type 2 consists of medullary thyroid carcinoma, pheochromocytoma, and hyperparathyroidism (type 2a) or multiple mucosal neuromas (type 2b or type 3). The hypertensive episode in this case may be due to a previously undiagnosed pheochromocytoma. The pheochromocytoma in MEN may consist of small multiple tumors. These patients are typically young adults with strong family histories of MEN. If multiple surgeries are planned, pheochromocytoma resection will usually be scheduled first.

#### *What is calcitonin, and why is it associated with medullary cancer?*

Calcitonin is a polypeptide manufactured by the parafollicular cells (C cells) in the thyroid gland. It is secreted in response to increases in plasma ionic calcium and tends to lower calcium levels by affecting kidney and bone function. Therefore, it acts as an antagonist of parathyroid hormone (see Table 34–6).

#### *Why is this patient hypercalcemic if calcitonin lowers serum calcium?*

An excess or deficiency of calcitonin has minor effects in humans compared with the effects of parathyroid disorders. This patient's hypercalcemia is most likely due to coexisting primary hyperparathyroidism (MEN type 2a).

#### *Are headache and diarrhea consistent with the diagnosis of MEN?*

The history of headaches suggests the possibility of pheochromocytoma, whereas diarrhea may be due to calcitonin or one of the other peptides often produced by medullary thyroid carcinoma (eg, ACTH, somatostatin, β-endorphin).

#### *What follow-up is required for this patient?*

Because of the life-threatening hemodynamic changes associated with pheochromocytoma, this entity must be medically controlled before surgery can be considered (see Case Discussion, Chapter 14). Because MEN syndromes are hereditary, family members should be screened for early signs of pheochromocytoma, thyroid cancer, and hyperparathyroidism.

## GUIDELINES

Gross JB, Bachenberg KL, Benumof JL, et al: Practice guidelines for the perioperative management of patients with obstructive sleep apnea: A report by the American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea. Anesthesiology 2006;104:1081.

Society for Ambulatory Anesthesia Consensus Statement on Selection of Patients With Obstructive Sleep Apnea Undergoing Ambulatory Surgery. Available at: http://www.sambahq.org/main/clinical-practice-guidelines/(accessed July 18, 2012).

## SUGGESTED READING

Adesanya AO, Lee W, Greilich NB, Joshi GP: Perioperative management of obstructive sleep apnea. Chest 2010;138:1489.

Arlt W, Allolio B: Adrenal insufficiency. Lancet 2003;361:1881.

Jones GC, Macklin JP, Alexander WD: Contraindications to the use of metformin. Evidence suggests that it is time to amend the list. BMJ 2003;326:4.

King DR, Velmahos GC: Difficulties in managing the surgical patient who is morbidly obese. Crit Care Med 2010;38:S478.

Kohl BA, Schwartz S: How to manage perioperative endocrine insufficiency. Anesthesiol Clin 2010;28:139.

NICE-SUGAR Study Investigators, Finfer S, Chittock DR, et al: Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283.

Petri BJ, van Eijck CH, de Herder WW, et al: Phaeochromocytomas and sympathetic paragangliomas. Br J Surg 2009;96:1381.

Van den Berghe G, Schetz M, Vlasselaers D, et al: Clinical review: Intensive insulin therapy in critically ill patients: NICE-SUGAR or Leuven blood glucose target? J Clin Endocrinol Metab 2009;94:3163.

Zaghiyan KN, Murrell Z, Melmed GY, Fleshner PR: High-dose perioperative corticosteroids in steroid-treated patients undergoing major colorectal surgery: Necessary or overkill? Am J Surg 2012 Jun 28. [Epub ahead of print].