ORTHOSTATIC intolerance syndrome is an unusual autonomic nervous system disorder characterized by episodic or postural tachycardia that occurs independent of alterations in arterial blood pressure and is associated with symptoms that include palpitations, tremulousness, light-headedness, fatigue, and syncope.1–3 Orthostatic intolerance syndrome is most often observed in young women and has also been described as postural orthostatic tachycardia syndrome,1 chronic orthostatic intolerance,4 or hyperadrenergic orthostatic tachycardia.4 This diverse terminology emphasizes the often confusing nature of this idiopathic disorder of primary autonomic failure.5 The medical treatment of orthostatic intolerance is controversial because the pathophysiology of the disease is complex. We describe the perioperative treatment of a patient with severe orthostatic intolerance syndrome who was scheduled for bilateral mastectomy.

Case Report

A 40-yr-old woman (height, 166 cm; weight, 55 kg) with recurrent breast cancer and familial breast-ovarian cancer syndrome presented for bilateral mastectomy and breast reconstruction with prostheses. Her medical history was remarkable for orthostatic intolerance syndrome, mitral valve prolapse, Reiter syndrome, and anorexia nervosa. The diagnosis of orthostatic intolerance syndrome was established based on postural sinus tachycardia that often approached 180 beats/min, palpitations, extreme lability of arterial blood pressure when standing, with periods of hyper- or hypotension, frequent syncopal episodes, periods of pronounced fatigue, and reduced cognitive function. The patient often experienced neck pain, migraine-like headaches, severe light-headedness, visual impairment, and an unstable gait within 2 min of standing. Many of her symptoms persisted when she resumed a recumbent posture. Autonomic diagnostic evaluation revealed several abnormal results of tilt-table examinations that closely reproduced her clinical symptoms, attenuated muscle sympathetic nerve activity in response to tilt testing, and elevated plasma catecholamine concentrations. Transthoracic echocardiography showed incidental mitral valve prolapse and normal left ventricular systolic function. Further extensive assessment excluded other possible causes of syncope. The patient remained symptomatic, despite medical treatment with oral atenolol (25 mg twice daily), midodrine (7.5 mg twice daily and 2.5 mg every night), fluoxetine (40 mg every day), and sodium and potassium supplements. The patient often required salt and fluid replacement at home, typically drank large quantities of fluids before rising in the morning, and wore compression stockings to prevent fainting.

The patient was admitted to the surgical intensive care unit the day before surgery. Catheters were inserted into a peripheral vein and into the radial and pulmonary arteries for fluid administration, measurement of continuous systemic and pulmonary arterial pressures, and management of vasoactive drugs. Crystalloid was administered to increase pulmonary capillary occlusion pressure from 5 to 12 mmHg before anesthetic induction. Premedication consisted of 20 mg intravenous famotidine and midazolam (4 mg in divided doses) the morning of surgery. At arrival in the operating room, standard monitors were placed, and an epidural catheter was inserted at the L1–L2 interspace for postoperative pain management. After preoxygenation, anesthesia was induced with 250 mg intravenous sodium thiopental, 50 mg lidocaine, and 120 mg succinylcholine maintained with isoflurane (0.2–2% end-tidal concentration) in an air–oxygen mixture (FiO2 = 0.5). Opioids were not administered because of the patient’s history of allergy. Ten to 30 mg rocuronium was administered as necessary to maintain neuromuscular blockade during surgery. Tidal volume and respiratory rate were adjusted to maintain normal acid–base status and PaCO2. The patient’s temperature was maintained between 35.7–37.5°C with use of a forced-air blanket. Subcutaneous infiltration of a mixture of 1% lidocaine and 0.5% bupivacaine was performed around each breast before incision by the attending surgeon. Using fluids, pulmonary capillary occlusion pressure was maintained between 12–15 mmHg during and after surgery.

The initial intraoperative course was remarkable for hemodynamic instability, with heart rate and mean arterial pressure ranging from 65 to 130 beats/min and from 55 to 120 mmHg, respectively. Low doses (0.2–0.5 μg·kg−1·min−1) of phenylephrine were infused, and the isoflurane concentration was titrated to attenuate this cardiovascular lability. Heart rate and mean arterial pressure were controlled between 86–98 beats/min and 75–90 mmHg, respectively, during the remainder of the case. A loading dose of 15 ml epidural ropivacaine, 0.5%, was administered, and 0.15% ropivacaine infusion (15 ml/h) was begun for perioperative Considerations in a Patient with Orthostatic Intolerance Syndrome

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Anesthesiology, V 93, No 2, Aug 2000
Discussion

The pathophysiology of orthostatic intolerance syndrome is unclear, despite extensive study. Various potential mechanisms for this disorder have been proposed, including enhanced sensitivity of $\beta_1$ adrenoceptors, baseline absolute hypovolemia, excessive venous pooling during standing, primary dysautonomia, and lower extremity sympathetic nervous system denervation. Volume loading and $\alpha_1$, but not $\alpha_2$, adrenoceptor agonists improve clinical symptoms in patients with orthostatic intolerance syndrome. Increases in plasma catecholamine concentrations observed in these patients appear to result from chronic hypovolemia and reduced lower extremity vascular tone and not from primary adrenal disease or excessive central sympathetic outflow. Hypovolemia may also be related to primary reductions in plasma renin activity and plasma aldosterone concentration. Recent evidence indicates that orthostatic intolerance syndrome is characterized by augmented resting sympathetic nerve activity and attenuated peripheral postganglionic sympathetic responses to standing, concomitant with enhanced cardiac sympathetic activity. Despite these abnormalities in sympathetic nervous system responses to postural change, baroreceptor reflex–mediated control of the circulation appears to be relatively preserved in this disorder. Orthostatic intolerance may also result from failure of effector pathways of the baroreceptor reflex circuit, $\alpha$-adrenoceptor dysfunction, or failure of vascular smooth muscle intracellular signaling or contractile function, and is further complicated because abnormalities may be observed only in regional arterial or venous vascular beds. A less severe presentation of orthostatic intolerance may also occur during conditions of profound cardiovascular deconditioning, such as prolonged bed rest.

Medical treatment of patients with orthostatic intolerance syndrome is directed at correcting the volume deficit, improving lower extremity sympathetic tone, and, if possible, attenuating tachycardia in response to standing. Lower extremity compression and increased sodium and water intake, concomitant with administration of mineralocorticoids have been shown to reduce symptoms in patients with this disease, presumably by increasing venous return and expanding plasma volume. Long-term administration of low doses of $\alpha_1$-adrenoceptor agonists may compensate for lower extremity sympathetic denervation and may reduce heart rate responses to standing by activating baroreceptor reflexes without producing baseline hypertension. However, $\alpha_1$-adrenoceptor agonists must be used judiciously because enhanced sensitivity of $\alpha_1$ adrenoceptors has been described. Other drugs that cause arterial vasoconstriction, including the ergot alkaloid dihydroergotamine and the somatostatin analog octreotide, have been shown to attenuate abnormal hemodynamic responses to upright posture in these patients. However, expansion of erythrocyte volume with long-term erythropoietin therapy did not improve symptoms. $\beta_1$-Adrenoceptor antagonists may partially inhibit abnormal postural tachycardia but may also contribute to syncopal symptoms by further decreasing plasma renin activity and worsening the intravascular volume deficit in severely affected patients.

The clinical presentation and long-term medical treatment described in the present case is very typical of patients with severe orthostatic intolerance syndrome. A thorough preoperative evaluation was necessary to identify the major pathophysiologic components and to optimize medical treatment of the disease, and to detect the presence and determine the severity of associated disorders, including mitral valve prolapse, irritable bowel syndrome, chronic fatigue syndrome, and inflammatory bowel disease. Intravascular volume expansion by administration of crystalloid was guided by invasive cardiac monitoring and used to preoperatively correct the underlying relative hypovolemia. $\alpha_1$-Adrenoceptor agonists, including phenylephrine, norepinephrine, and midodrine, enhance vascular tone in patients with orthostatic intolerance syndrome but must be carefully titrated because lower extremity sympathetic denervation may cause up-regulation of peripheral $\alpha_1$ adrenoceptors and contribute to receptor hypersensitivity. Therefore, a low-dose phenylephrine infusion was used in conjunction with volume expansion to augment peripheral vascular tone, maintain mean arterial pressure at or near baseline values, and reduce autonomic lability during and after surgery in the presence of inhaled isoflurane or epidural ropivacaine, drugs that are known to cause arterial and venous vasodilation.

The perioperative treatment of the current patient was further complicated by a history that strongly suggested
opioid allergy. Severe allergic reactions to opioids are rare, but this patient previously had experienced a severe anaphylactoid-type reaction to meperidine. Immunoglobulin E antibodies specific to meperidine were not obtained after this episode, but results of subsequent intradermal skin tests for morphine and oxycodone were positive. As a result of this medical history, options for postoperative analgesia were substantially limited. Epidural local anesthetics were used successfully for postoperative analgesia in conjunction with intravascular volume expansion and continued monitoring of cardiac filling pressures. In other patients with orthostatic intolerance syndrome, however, neuraxial opioids may be especially effective in reducing autonomic nervous system responses to intra- and postoperative pain.

References