ment errors induced by methemoglobin. Although the error caused by a methemoglobin level of 5% would not be large, the SM-0100 would overestimate the Sv_{O_2} by an amount directly related to the methemoglobin level.[6]

Despite the return of the patient's methemoglobin to a normal level after discontinuation of flutamide, the possibility of an inherited basis for the patient's methemoglobinemia was considered. The absence of a history of congenital cyanosis or skin discoloration mitigated both a hemoglobin M disorder and a homozygous state of NADH-cytochrome $_b5$ reductase deficiency,[2] and this was confirmed by laboratory tests. The carrier or heterozygous state, characterized by an enhanced susceptibility to methemoglobin formation with exposure to oxidant drugs and chemicals also was ruled out by the normal level of NADH-cytochrome $_b5$ reductase activity. Both the normal blood glucose-6-dehydrogenase and the absence of a hemolytic anemia precluded any other inherited basis for a drug-induced methemoglobinemia. Therefore, the conclusion that this patient's methemoglobinemia was induced by flutamide is incontestable.

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Anesthesia for Aortic and Mitral Valve Replacement in a Patient with Carcinoid Heart Disease

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THE carcinoid syndrome is characterized by flushing, diarrhea, abdominal pain, bronchospasm, and right-sided valvular disease. Carcinoid tumors develop from enterochromaffin cells and may produce the carcinoid syndrome in the presence of hepatic metastases, *via* drainage directly into the systemic circulation, or with lung involvement.[1] Carcinoid tumors can secrete serotonin, histamine, kallikrein, bradykinins, prostaglandins, and neuropeptides. Severe hypotension and bronchospasm that is refractory to treatment may occur during a crisis.

There have been a limited number of reports of patients undergoing simultaneous tricuspid and pulmonic valve replacements.[2–4] Left-sided carcinoid valvular disease is rare and is thought to require pulmonary involvement by carcinoid disease or an intra-atrial com-

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munication.[5] There was one reported attempt to perform a left-sided double valve replacement, but the patient died intraoperatively from left ventricular failure.[6]

We present a case of left-sided valvular carcinoid heart disease in the absence of lung tumor and the first successful left-sided double valve replacement, in a patient who already had undergone a right-sided double valve replacement. Although epinephrine is thought to be contraindicated in the presence of carcinoid syndrome,[3] we report its successful use for treatment of hypotension in this patient after cardiopulmonary bypass (CPB).

Case Report

A 68-yr-old, 55-kg woman with carcinoid syndrome and liver metastases presented for aortic valve replacement. The mitral and tricuspid valves had been replaced with porcine valves 4 yr earlier because of involvement by carcinoid disease. She had done well since then until several months before the current admission, at which time she had multiple episodes of congestive heart failure. Cardiac catheterization 2 days before surgery was remarkable for severe aortic valve insufficiency and mild mitral regurgitation, right ventricular pressure 60/15 mmHg, RVEDP 20 mmHg, RA mean 26 mmHg, PA 52/20 mmHg, and PA mean 36 mmHg. The gradients across the tricuspid and pulmonic valves were 6 mmHg and 8 mmHg, respectively. The coronary arteries were normal.

The patient had a history of severe carcinoid syndrome for 7 yr, including flushing, abdominal pain, and diarrhea. The carcinoid crises were accompanied by hypertension. She had previous carcinoid treatment by hepatic artery chemoembolism, followed by chemotherapy treatment for many years. The patient also had a benign thyroid nodule but was now clinically euthyroid with medical treatment.

Her medications included 250 μg octreotide twice daily, 4 mg cyproheptadine three time daily, 1.5 million U interferon every sixth day, 10 U humulin insulin daily, 0.5 mg enalapril twice daily, 1.5 mg bumetanide twice daily, 0.275 mg quinidine three times daily, 20 mg nicardipine three times daily, 1 tablet Lomotil five times daily, 0.05 mg levothyroxine daily, and aspirin. The preoperative electrocardiogram showed atrial fibrillation.

The patient's medical regimen was continued preoperatively, but she received no preanesthetic medication. In the holding area, a 16-G catheter was placed intravenously, and a 20-G catheter was placed in the radial artery. Midazolam intravenously was administered for sedation before the placement of a 7.5-Fr pulmonary artery catheter *via* the right internal jugular vein. The initial mean pulmonary artery pressure was 27 mmHg, and the initial central venous pressure was 29 mmHg, which were similar to the data obtained during cardiac catheterization. Her systemic blood pressure was 140/50 with a mean of 80 mmHg and a pulse of 70 beat/min. The patient was treated with 1 g methylprednisolone and 500 μg octreotide intravenously.

Anesthesia was induced with sufentanil and midazolam, and vecuronium was used to facilitate tracheal intubation. After induction of anesthesia, the blood pressure was 120/45 mmHg, with a mean of 70, and the pulse was 45 beats/min. The vital signs remained stable during the prebypass period. Anesthesia was maintained with sufentanil, midazolam, and pancuronium. A transesophageal echocardiography probe was inserted atraumatically, which revealed thickened aortic valve leaflets and 4+ aortic insufficiency. The leaflets of the mitral valve were slightly thickened, and there was slight limitation of movement. There was 1+ mitral regurgitation. The left ventricle had good contractility with an ejection fraction greater than 50%.

An additional dose of 500 μg octreotide was administered intravenously before the onset of CPB. The lungs remained clear to auscultation, with no wheezing. The vital signs remained stable before the onset of CPB.

Direct inspection during CPB revealed that the aortic valve was fibrotic and retracted, with slight constriction of the aortic annulus. Although the mitral valve was functioning well, there was already carcinoid involvement of the valve; inspection through the aortic annulus revealed thickening of the leaflets and the chordae of the mitral valve. It was decided to replace the mitral valve as well, due to likely worsening of native valve function and to avoid a third operation in the near future. Porcine valves were placed in both the aortic and the mitral valve positions. The aorta was cross-clamped for 138 min, and the duration of CPB was 189 min. Three units of packed erythrocytes were administered during CPB.

Before discontinuation of CPB, 50 mg amrinone was administered intravenously, followed by an infusion of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Because of hypotension following separation from CPB (mean arterial pressure of 40 mmHg), an intravenous bolus of 8 μg epinephrine was administered, followed by an intravenous infusion of 75 $\mu g \cdot kg^{-1} \cdot min^{-1}$ epinephrine. The contractility of the left ventricle improved, the mean pulmonary artery pressure decreased from 38 to 20 mmHg, and the systemic blood pressure increased to 100/50 mmHg, with a mean of 70 mmHg. The patient required ventricular pacing at 80 beats/min because of bradycardia. The mean arterial blood pressure was maintained at 65–75 mmHg.

Because of persistent bleeding and an apparent coagulopathy, the patient received 2 units of packed erythrocytes, 4 units of fresh frozen plasma, and 12 units of platelets. After these transfusions, the prothrombin time was 17.9/11.6, and the partial thromboplastin time 47/28. The platelet count was 110,000/mm^3. The patient received an additional 2 units of fresh frozen plasma and 6 units of platelets. Five grams epsilon aminocaproic acid was administered intravenously, followed by an infusion of 1 g/h.

Shortly after arrival in the cardiac intensive care unit, pacing was terminated because the patient's heart was in sinus rhythm at 70 beats/min. The mean arterial pressure was 63–68 mmHg, left atrial pressure 20–30 mmHg, and central venous pressure 12–23 mmHg. The infusions of epinephrine, amrinone, and epsilon aminocaproic acid were continued postoperatively. The patient was treated with several doses of calcium gluconate for hypocalcemia. Reexploration of the mediastinum was required on postoperative day 1 due to persistent bleeding, and surgical hemostasis was obtained. The amrinone was discontinued subsequently on postoperative day 1, and a sodium nitroprusside infusion was begun to control pressure. The patient received a fentanyl infusion for analgesia and sedation. A maintenance regimen of 250 μg octreotide subcutaneously twice daily was begun. The trachea was extubated on postoperative day 2. The epinephrine and sodium nitroprusside infusions were discontinued gradually on postoperative days 3 and 4, respectively. The patient had a complete recovery and was discharged home 4 weeks after the operation.

Discussion

Carcinoid heart disease results from the accumulation of fibrous material on the valve cusps and the endocardium of the heart. This generally occurs on the right side of the heart, but rarely may involve the left side if there is lung involvement. The tricuspid valve tends to become regurgitant and the pulmonic valve stenotic. This combination of effects may result in right-sided heart failure. Our patient had a rare variant of carcinoid heart disease, having severe left-sided involvement without the presence of lung tumor. The aortic valve was fibrotic and retracted and had severe insufficiency. Although the mitral valve functioned well, direct inspection during CPB revealed thickened chordae and leaflets.

Medical treatment may include chemotherapy and prevention of hormonal release. Traditional chemotherapy has had a limited success rate, with only 10–30% of patients responding.[7] Octreotide, an analog of somatostatin, prevents release of these chemical mediators and provides symptomatic relief but does not prevent tumor growth. Interferon may provide a biochemical response and tumor shrinkage.[7] Clinically, most patients show improvement of diarrhea, flushing, and bronchoconstriction. Methysergide and cyproheptadine have been used as inhibitors of serotonin release.[8] Steroids have been used to inhibit bradykinin secretion, and diphenhydramine and histamine blockers, such as ranitidine, can inhibit histamine production.

Anesthesia management focuses on the prevention of a carcinoid crisis, which can accompany stress, physical stimulation, or manipulation of tumor, chemical stimulation, or tumor necrosis from chemotherapy or hepatic artery ligation or embolization. The medical regimen should be continued preoperatively. Anesthetic premedication may be useful to alleviate anxiety. Benzodiazepines are preferable to morphine or meperidine, which may cause histamine release. Other histamine-releasing drugs, such as d-tubocurarine and atracurium, theoretically also should be avoided. There is concern that fasciculations from succinylcholine may increase intraabdominal pressure and release chemical mediators from tumors.[3] Drugs that have been reported to produce a carcinoid crisis include epinephrine, norepinephrine, histamine, dopamine, and isoproterenol.[3]

The use of the intraoperative somatostatin analog octreotide has been recommended for prevention of a carcinoid crisis and treatment if one occurs. The intraoperative treatment regimen of somatostatin used in our patient has been described as an effective technique.[3] Other methods include an infusion at 100 μg/h for valve surgery[9] and an intravenous bolus of 100 μg for treatment of a crisis.[10] The use of high-dose methylprednisolone has been used and recommended.[3]

Aprotinin, a kallikrein inhibitor, has been used in the treatment of carcinoid syndrome intraoperatively.[4] Treatment regimens have included intravenous doses ranging from 20,000 to 400,000 KIU.[11,12] Infusions of 50,000 and 100,000 KIU/h also have been reported.[1,13] Recent data suggest larger doses of aprotinin are required, and a level of 200 KIU/ml of aprotinin is necessary to inhibit kallikrein.[14] Because aprotinin inhibits kallikrein and reduces blood loss during cardiac surgery, it would have been an excellent addition to the intraoperative management for our patient; however, it was unavailable for clinical use at the time.

Amrinone has been recommended for separation from CPB if inotropic stimulation is needed, as catecholamines have been thought to be contraindicated.[1,3] Administration of catecholamines may lead to release of kallikrein, which activates bradykinins and may produce hypotension. They also can cause release of serotonin, leading to further vasoconstriction. In one case report of a carcinoid crisis during laparotomy, epinephrine was unsuccessful in treatment of the crisis, but a somatostatin analog was successful.[10] Hypotension following separation from CPB in a patient with carcinoid syndrome may be due to hypovolemia, vasodilation, myocardial dysfunction, or carcinoid crisis. Initially, the intravascular volume status should be optimized. Excessive vasodilation should be treated with direct-acting vasoconstrictors. After restoration of adequate preload and systemic vascular resistance, if hypotension is still present and is thought to be secondary to myocardial failure rather than carcinoid crisis, epinephrine may be administered.

If epinephrine is to be used after CPB, a small bolus should be administered initially for evaluation of the response. If there is a beneficial result, epinephrine administration can be continued as an infusion. The response should be monitored with continuous blood pressure measurement and, preferably, pulmonary artery catheter measurement and transesophageal echocardiography. If hypotension after separation from CPB is accompanied by flushing and is thought to be due to carcinoid crisis, administration of epinephrine would not be indicated. Rather, octreotide could be used.

In one previous case report, epinephrine was used successfully to treat hypotension after CPB, although transesophageal echocardiography was not used in that case to evaluate cardiac function.[1] In our patient, the filling pressures were increased, there was no sign of flushing, and the hypotension was not thought to be due to carcinoid syndrome. The episodes of carcinoid crisis that our patient experienced preoperatively were accompanied by hypertension and not hypotension. Thus, as in our case, we suggest that epinephrine be used to facilitate separation from CPB when hypotension is present and is due to myocardial dysfunction rather than carcinoid crisis.

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