

itself with several systemic findings such as recurrent fever and chills related to pulmonary embolism.

References

1. Tanaka H, Ebato M, Narisawa T, et al. Atrial blood cysts with ischemic heart disease. *Circ J* 2003;67:1–2.
2. Sakakibara S, Katsuhara K, Iida Y, Iida Y, Nishida H. Pulmonary subvalvular tumor. *Dis Chest* 1967;51:637–42.
3. Eugene KWS, May LW, King TT, Sze KS. Blood cysts of the tricuspid valve. *Ann Thorac Surg* 1996;61:1012–3.
4. Boyd TAB. Blood cyst on the heart valves of infant. *Am J Pathol* 1949;25:757.
5. Ohmoto Y, Tsuchihashi K, Tanaka S, Shimamoto K, Iimura O. Giant endocardial blood cyst in left ventricle resected by transthoracic valve approach. *Chest* 1993;103:965–6.
6. Zhang C, Hu J, Ni Y-M, Jiang Z-N, Xu H-Y. Giant blood cyst tumor in the left ventricular outflow tract. *Chin Med J (Engl)* 2007;120:1109–10.
7. Jacob JJ, Jose J, John B, et al. Intracardiac blood-filled cysts of the heart: a rare cause of embolic stroke. *Singapore Med J* 2007;48:e125.
8. Stein PD, Willis PW III, DeMets DL. History and physical examination in acute pulmonary embolism in patients without preexisting cardiac or pulmonary disease. *Am J Cardiol* 1981;47:218–23.
9. Chirinos JA, Heresi GA, Velasquez H, et al. Elevation of endothelial microparticles, platelets, and leukocyte activation in patients with venous thromboembolism. *J Am Coll Cardiol* 2005;45:1467–71.
10. Pasaoglu I, Dogan R, Oram A, Ozyilmaz F, Bozer AY. Giant blood cyst of the left ventricle. *Jpn Heart J* 1991;32:147–51.
11. Eugene KWS, May LW, King TT, Sze KS. Blood cysts of the tricuspid valve. *Ann Thorac Surg* 1996;61:1012–3.

Use of Methylene Blue for Catecholamine-Refractory Vasoplegia from Protamine and Aprotinin

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We present two cases of catecholamine-refractory and vasopressin-refractory vasoplegic syndrome associated with intraoperative anaphylaxis during cardiac surgery. One case was related to the administration of protamine and the other case to the administration of aprotinin. Both cases were successfully managed using intravenous methylene blue. The use of methylene blue blocks accumulation of cyclic guanosine monophosphate by competitively inhibiting the enzyme guanylate cyclase. This results in reduced responsiveness of the vasculature to

cyclic guanosine monophosphate-mediated vasodilators, such as nitric oxide. This report provides a description of severe anaphylaxis induced by different agents, in which the use of methylene blue was associated with a significant clinical response.

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Severe anaphylactic reactions in patients treated with either protamine or aprotinin during cardiac surgery are among the most significant complications associated with the use of these agents. These reactions may be refractory to aggressive resuscitation using conventional therapy, including catecholamines, vasopressin, antihistamines, corticosteroids, and volume expansion. Methylene blue (methylthionine chloride) is an indicator dye that has been traditionally used in a number of clinical settings and more recently in the management of anaphylactic shock [1]. Although the use of methylene blue in anaphylaxis specifically associated with protamine has been described in one report [2], its use in the context of intraoperative aprotinin reactions has not been previously presented. We describe two cases in which methylene blue was successfully used in the treatment of severe anaphylactic reactions related to protamine (patient 1) and aprotinin (patient 2).

Case Reports

Patient 1

A 72-year-old man was referred for elective coronary artery bypass grafting. The patient's history included hypertension and diabetes mellitus type 2 for which he had been using neutral protamine Hagedorn insulin. During surgery, four coronary bypass grafts were performed using cardiopulmonary bypass. The patient was weaned from cardiopulmonary bypass and a protamine infusion was started. After the administration of approximately 100 mg of protamine, the blood pressure decreased from 90/50 to 50/25 mm Hg, and generalized urticaria appeared. The hypotension remained refractory to resuscitation using epinephrine, norepinephrine, vasopressin, diphenhydramine, hydrocortisone, calcium chloride, and crystalloid boluses. On examination, the heart continued to beat vigorously, with a rate between 100 and 110 beats per minute. The patient was placed back on cardiopulmonary bypass and an intra-aortic balloon pump was inserted, with minimal improvement in blood pressure. Methylene blue (100 mg) was administered intravenously. After 15 minutes, the blood pressure stabilized, allowing cardiopulmonary bypass to be discontinued. The cannulae were removed without the reversal of systemic anticoagulation. There were no postoperative neurologic deficits or any evidence of further anaphylaxis. Four weeks later, outpatient cutaneous allergy testing confirmed the presence of immunoglobulin E (IgE) specific to neutral protamine Hagedorn insulin and protamine sulfate.

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Patient 2

A 72-year-old woman was referred for elective replacement of a stenotic aortic valve bioprosthesis. Her past medical history included hypertension, recurrent urticaria, and aortic valve replacement for aortic stenosis 5 years earlier. The patient had received aprotinin at the primary operation without any adverse reaction. Aprotinin was used for the reoperation due to the increased risk of bleeding. While preparing for cardiopulmonary bypass, a 20,000 KIU test dose of aprotinin was administered. This was followed by a sudden drop in blood pressure from 115/60 to 39/20 mm Hg. The hypotension remained refractory to treatment with epinephrine, norepinephrine, vasopressin, diphenhydramine, and dexamethasone. The heart rate varied between 100 and 120 beats per minute and on examination, the cardiac contractility appeared depressed, but the heart was not distended. Cardiopulmonary bypass was instituted 9 minutes later. The aortic valve was replaced uneventfully, and this was followed by reperfusion on cardiopulmonary bypass for 35 minutes. Weaning from bypass remained difficult, despite the use of epinephrine and norepinephrine infusions. An intra-aortic balloon pump was inserted, and 100 mg of methylene blue was administered intravenously. After 10 minutes, cardiopulmonary bypass was discontinued, and the patient's blood pressure remained stable. The patient recovered without neurologic deficit and was discharged from the hospital 8 days later. Outpatient skin testing confirmed the presence of aprotinin-specific IgE.

Comment

Protamine, which is a fish-derived arginine-rich peptide, was discovered in 1868 and is used for the reversal of heparin-induced anticoagulation in more than 2 million patients annually. The adverse reactions associated with protamine were classified by Horrow [3] as systemic hypotension related to rapid protamine administration, antibody-mediated anaphylactic and complement-mediated anaphylactoid responses, and catastrophic pulmonary vasoconstriction. In our patient, the presence of protamine-specific IgE suggests that the adverse reaction was anaphylactic. The general incidence of significant adverse reactions to protamine has been reported as 0.9%. Among patients having previous exposure to neutral protamine Hagedorn-based insulin regimens, the incidence may be as high as 2.8% [4]. The mechanism by which protamine causes a systemic vasodilatory response, as seen in our patient, likely involves the cross-linking of protamine-specific IgE on mast cell surfaces resulting in the release of several mediators, some of which lead to increased nitric oxide (NO) production by upregulating nitric oxide synthase. Another possible mechanism is that protamine may directly stimulate endothelial cell-mediated conversion of the amino acid L-arginine to NO [5]. The release of NO leads to activation of the enzyme guanylate cyclase, thereby resulting in

increased synthesis of cGMP, a mediator of vascular smooth muscle relaxation.

Aprotinin, a serine protease inhibitor derived from bovine lung, is a member of the class of anti-fibrinolytic agents that include the lysine analogues aminocaproic acid and tranexamic acid. The incidence of adverse clinical reactions on primary exposure to aprotinin is 0.09%. Among patients having re-exposure to aprotinin, the incidence increases to 1.5%. However, the frequency and severity of these reactions may be reduced as the time interval since primary exposure is increased [6]. The presence of aprotinin-specific IgE in our patient suggests that the adverse reaction was anaphylactic. The use of aprotinin during cardiac surgery has recently been associated with an increased risk of perioperative renal failure, myocardial infarction, heart failure, stroke, and encephalopathy, which was not observed in patients receiving aminocaproic acid or tranexamic acid [7]. For these reasons, tranexamic acid has replaced aprotinin as the first-line anti-fibrinolytic agent used in high-risk cardiac surgical cases at our institution.

The indicator dye, methylene blue, is currently used in a number of clinical settings. It has a role in the management of methemoglobinemia, and may be used in the treatment of chronic urolithiasis. More recently, methylene blue has been used in the context of refractory vasoplegia and anaphylaxis [1], and it has been associated with improved hemodynamics in septic shock [8]. Dose-related toxicities include hemolytic anemia, cardiac arrhythmias, skin desquamation, abdominal pain, bluish skin and urine discoloration, and hyperbilirubinemia in neonates. Methylene blue is a competitive inhibitor of the enzyme guanylate cyclase, and thereby interferes with nitric oxide-mediated vascular smooth muscle relaxation by indirectly decreasing cGMP production. The dose used in our experience has been 1.5 mg/kg, which is administered intravenously.

The use of protamine and aprotinin during cardiac surgery may cause anaphylaxis with significant vasoplegia in which the endothelial synthesis and release of nitric oxide play a central role. The two cases presented here suggest that methylene blue, through its effect on the nitric oxide pathway, may have an important role in the treatment of refractory anaphylactic reactions associated with either of these two agents. Due to its inhibitory role in a pathway common to allergic reactions, methylene blue may be effective in the management of refractory anaphylaxis induced by different triggering agents.

References

1. Evora PRB, Roselino CHCD, Schiaveto PM. Methylene blue in anaphylactic shock. *Ann Emerg Med* 1997;30:240.
2. Viaro F, Dalio MB, Evora PRB. Catastrophic cardiovascular adverse reactions to protamine are nitric oxide/cyclic guanosine monophosphate dependent and endothelium mediated: should methylene blue be the treatment of choice? *Chest* 2002;122:1061–6.
3. Horrow JC. Protamine: a review of its toxicity. *Anesth Analg* 1985;64:348–61.

4. Gupta SK, Veith FJ, Ascer E, et al. Anaphylactoid reactions to protamine: an often lethal complication in insulin-dependant diabetic patients undergoing vascular surgery. *J Vasc Surg* 1989;9:342-50.
5. Pearson PJ, Evora PRB, Ayrançioğlu K, Schaff HV. Protamine releases endothelium-derived relaxing factor from systemic arteries: a possible mechanism of hypotension during heparin neutralization. *Circulation* 1992;86:289-94.
6. Dietrich W, Ebell A, Busley R, Boulesteix AL. Aprotinin and anaphylaxis: analysis of 12,403 exposures to aprotinin in cardiac surgery. *Ann Thorac Surg* 2007;84:1144-50.
7. Mangano DT, Tudor IC, Dietzel C. The risk associated with aprotinin in cardiac surgery. *N Engl J Med* 2006;354:353-65.
8. Daemen-Gubbels CRGH, Groeneveld PHP, Groeneveld ABJ, van Kamp GJ, Bronsveld W, Thijs LG. Methylene blue increases myocardial function in septic shock. *Crit Care Med* 1995;23:1363-70.

Early Constrictive Epicarditis After Coronary Artery Bypass Surgery

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A patient with constrictive pericarditis early after coronary bypass surgery is presented. At reoperation a dense inflammatory process was encountered on the epicardial surface of the heart with minimal pericardial thickening. Crosshatching of the epicardial scar tissue produced an immediate and durable clinical response.

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Constrictive pericarditis impairs filling of cardiac chambers, resulting in venous congestion and diminished cardiac output. The visceral pericardium, or epicardium, contributes variably to this process. We present a patient with postoperative constrictive physiology early after coronary artery bypass surgery. At the time of reoperation, the patient was found to have pronounced constrictive epicarditis.

A 62-year-old man underwent coronary artery bypass surgery for severe three-vessel disease. The operation was uneventful and no pericardial abnormalities were noted. He was discharged on day 4 and had an unremarkable early postoperative recovery. At week 6 he began experiencing exertional dyspnea. Echocardiography showed normal ventricular contraction with early septal collapse and diminished respiratory variation of the inferior vena cava. Contrast enhanced computed tomography of the chest was unremarkable except for small bilateral pleural effusions, a small pericardial effu-

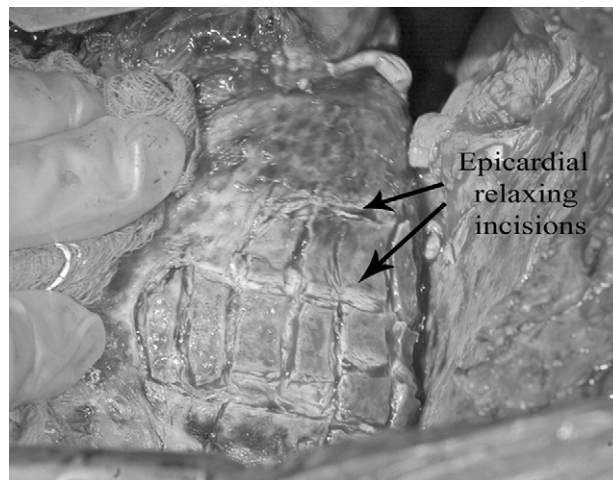


Fig 1. Diaphragmatic surface of the heart showing thickened epicardium that has been sharply incised. This process encapsulated a large portion of the left and right ventricles.

sion, and normal postoperative changes. No pericardial thickening was evident on computed tomography. Despite intravenous diuretic therapy and a short course of intravenous steroids, the patient experienced worsening dyspnea and continued to gain weight. Cardiac catheterization revealed equalization of left and right ventricular diastolic pressures, a central venous pressure of 19 mm Hg, and a cardiac index of $1.73 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$. All three grafts were widely patent.

The patient was taken to the operating room for presumed constrictive pericarditis. A reoperative median sternotomy was performed. The pericardium, which was left open at the original operation, was minimally thickened. On cardiopulmonary bypass the heart was freed from the surrounding pericardium, which was then resected anteriorly from phrenic to phrenic. The epicardium, in contrast to the pericardium, was globally thickened. As the epicardium was sharply incised, there was notable expansion of the underlying myocardium. This process was repeated along the diaphragmatic and lateral surfaces of the heart creating a crosshatch or waffle pattern (Fig 1). At the conclusion of the case, hemodynamic measurements were improved with central venous pressure decreasing from 19 to 9 mm Hg, and his cardiac index increased to $3.5 \text{ L/min}^{-1}/\text{m}^{-2}$. The fibrous pericardium submitted to pathology was read as mild chronic inflammation and was measured to be approximately 1-mm thick. Since being discharged, the patient has resumed normal activity, including jogging.

Comment

Constrictive pericarditis classically involves a thickened, noncompliant pericardium. Early filling is normal, but abruptly ceases when the volume limitation imposed by the pericardium is reached. Impaired filling causes symptoms of heart failure despite normal myocardial contraction. This disease may be idiopathic, but it is also

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