METHYLENE BLUE IN PATIENTS WITH SEVERE PULMONARY HYPERTENSION To the Editor:

We read with great interest the recent article by Grubb and colleagues.¹ Apart from the successful reversal of postcardiopulmonary bypass vasoplegia with the use of a single dose (1 mg/kg) followed by continuous infusion of 0.5 mg/kg/hour intravenous methylene blue, achieving hemodynamic stability during a third-time redo sternotomy for heart transplantation in a 60-year-old man, the authors reported the role of methylene blue as a causative agent of serotonin syndrome in a patient receiving selective serotonin reuptake inhibitor medication.

We entirely agree with their opinion and would like to add a brief comment related to our experience in the treatment of anaphylaxis secondary to protamine administration after cardiac surgery. The patient was a 70-year-old woman undergoing aortic valve replacement for severe aortic stenosis with moderated left ventricular dysfunction and normal pulmonary pressure. Her past medical history included hypertension and smoking (10 pack-years) and she denied having allergy to fish proteins. Her medications included furosemide and enalapril. The operation was carried out through a median sternotomy with antegrade cold blood cardioplegia. Operative findings revealed a small, heavily calcified aortic annulus. After extensive decalcification a No. 19 bioprosthesis (Mitroflow; Sorin Group Inc, Vancouver, Canada) was implanted. The weaning from cardiopulmonary bypass was uneventful with a low dose of vasoconstrictor support. Protamine infusion was accompanied by refractory hypotension, despite the use of high doses of epinephrine and norepinephrine. The administration of 1% methylene blue (2 mg/kg during a time period of 20 minutes) and the discontinuation of protamine

were highly effective to restore a normal hemodynamic status, and to taper down progressively the vasoconstrictor agents. The postoperative course was unremarkable. According to the literature, this is the third report describing the successful use of methylene blue in dramatic anaphylaxis secondary to protamine administration after cardiac surgery.^{2,3}

We have only 1 question for Grubb and colleagues, who apparently have bigger experience with methylene blue in vasoplegic syndrome. What is your opinion about infusing methylene blue in patients with known severe pulmonary hypertension undergoing cardiac surgery and experiencing catecholamine-refractory vasoplegic syndrome? In vitro and in vivo studies suggest that resting pulmonary vascular tone and endothelium-dependent pulmonary vasodilatation are mediated by changes in vascular smooth muscle concentrations of cyclic guanosine 3',5' monophosphate.^{3,4} Methylene blue is a potent guanylate cyclase inhibitor. And by reducing the effect of nitric oxide⁵ it can cause a significant increase in pulmonary arterial pressure, especially in patients with severe pulmonary hypertension and cause a detrimental effect on gas exchange.

We congratulate Grubb and colleagues on the survival of their patient and the dissemination of important information concerning the caution of using methylene blue in patients with vasoplegic syndrome who are receiving antidepressant therapy; moreover, we want to add a warning against the use of methylene blue in patients with severe pulmonary hypertension.

Jamil Hajj-Chahine, MD
Christophe Jayle, MD, PhD
Pierre Corbi, MD, PhD
Department of Cardiothoracic Surgery
University Hospital of Poitiers
Poitiers, France

References

1. Grubb KJ, Kennedy JL, Bergin JD, Groves DS, Kern JA. The role of methylene blue in serotonin syndrome following cardiac transplantation: a case report and review of the literature. *J Thorac Cardiovasc Surg.* 2012;144:e113-6.
2. Del Duca D, Sheth SS, Clarke AE, Lachapelle KJ, Ergina PL. Use of methylene blue for catecholamine-refractory vasoplegia from protamine and aprotinin. *Ann Thorac Surg.* 2009;87:640-2.
3. Viaro F, Dalio MB, Evora PR. 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.
4. Fineman JR, Crowley MR, Heymann MA, Soifer SJ. In vivo attenuation of endothelium-dependent pulmonary vasodilation by methylene blue. *J Appl Physiol.* 1991;71:735-41.
5. Leyh RG, Kofidis T, Strüder M, Fischer S, Knobloch K, Wachsmann B, et al. Methylene blue: the drug of choice for catecholamine-refractory vasoplegia after cardiopulmonary bypass? *J Thorac Cardiovasc Surg.* 2003;125:1426-31.

<http://dx.doi.org/10.1016/j.jtcvs.2012.11.091>

Reply to the Editor:

Hajj-Chahine and colleagues¹ describe an interesting case of a protamine reaction resulting in hypotension unresponsive to vasopressor therapy. Methylene blue 1%, dosed 2 mg/kg during a period of 20 minutes, resulted in normal hemodynamics. The case highlights yet another example of the use of methylene blue for the treatment of vasoplegic syndrome.

In regard to Hajj-Chahine and colleagues' inquiry, in patients with known severe pulmonary hypertension (PH) and vasoplegic syndrome undergoing cardiac surgery, there is certainly concern for worsening PH due to a reduction of endogenous nitric oxide with the potential for right ventricular failure. We have not had this experience, although we are aware of the possibility. We certainly would caution against using methylene blue in patients with severe PH.

The comments regarding the use of methylene blue for the treatment of vasoplegia offered by Evora² are appreciated. We agree, methylene blue clearly can be beneficial for