(A23187), which causes receptor-independent nitric oxide release.

A single dose of IV MB (2 mg/kg, 20-minute infusion time), as used by Leyh and coworkers, was our first option in 1995.² We are frequently asked about dose, infusion, and route (venous or arterial). Many colleagues tell us that they only observed a transient effect using a 1 or 2 mg/kg IV bolus. In our opinion, the IV MB bolus is a rescue treatment. It is important to maintain a continuous infusion. In some cases, we use a continuous infusion for more than 48 or 72 hours. Because the lethal doses of MB are well known (40 mg/kg), it is possible to use higher doses if necessary. In regard to the infusion route, in at least 1 anecdotal case, we observed a catastrophic reaction to protamine without response to norepinephrine or an IV MB bolus of 2 mg/kg. CPB was again established with high flow, but we were unable to increase the mean arterial pressure even with norepinephrine infusion. The situation was controlled only by using MB infusion in the CPB arterial line again. Grayling and Deakin³ presented this approach using MB during CPB to treat valve endocarditis in a case of ongoing septicemia.

In Argentina, Levin and colleagues⁴ performed a prospective, randomized study including 638 patients who underwent cardiac surgery, 56 (8.8%) of whom fulfilled the vasoplegic postoperative criteria. The overall mortality was 27 patients (4.2%), 6 (10.7%) of whom were in the vasoplegic syndrome group and 21 (3.6%) of whom were in the control group ($P = .02$). The 56 patients with vasoplegic syndrome were randomized to IV MB (1.5 mg/kg, 1-hour infusion time) (28 patients) or placebo (28 patients). The general and surgical characteristics of these 2 populations were quite similar. There were no deaths in the MB group and 6 deaths (21.4%) in the placebo group. The MB resolution vasoplegia time course was approximately 2 hours in all cases. In those treated only with vasopressors (8/28 patients, 28.6%), vasoplegia persisted for more than 48 hours.

Since Gomes and colleagues⁵ described vasoplegic syndrome, we speculate, as surgeons in undeveloped countries, whether the vasoplegia was caused by some failure in CPB material or drug quality control.

MB is increasingly used, for example in liver transplantation. As there are few papers about its use in cardiac surgery it is

possible that cardiac surgical teams do not consider vasoplegic syndrome to be a catastrophic and unexpected problem, and it may be underestimated.

Paulo Roberto B. Evora, MD, PhD^a

Ricardo L. Levin, MD^b

Laboratory of Cardiovascular Surgical

Research and Endothelium Function

Ribeirão Preto Medical School

University of São Paulo and CECORP-

Ribeirão Preto Specialized

Heart and Lung Center

Ribeirão Preto, SP, Brazil^a

Division of Cardiovascular Surgery

Navy Hospital

French Hospital

Swiss-Argentine Clinic

Argentine Institute of Diagnosis and Treatment

and Santa Isabel Clinic

Buenos Aires, Argentina^b

References

1. Leyh RG, Kofidis T, Struber M, Fischer S, Knobloch K, Wachsmann B, et al. Methylene blue: the drug of choice for catecholamine-3 refractory vasoplegia after cardiopulmonary bypass? *J Thorac Cardiovasc Surg.* 2003;125:1426-31.
2. Evora PR, Ribeiro PJ, de Andrade JC. Methylene blue administration in SIRS after cardiac operations. *Ann Thorac Surg.* 1997;63:1212-3.
3. Grayling M, Deakin CD. Methylene blue during cardiopulmonary bypass to treat refractory hypotension in septic endocarditis. *J Thorac Cardiovasc Surg.* 2003;125:426-7.
4. Levin RL, Degrange MA, Bilbao J, et al. Síndrome vasoplejico en postoperatorio de cirugía cardíaca. Reducción de la mortalidad mediante el empleo de azul de metileno. *Rev Argent Cardiol.* 2001;69:524-9.
5. Gomes WJ, Carvalho AC, Palma JH, et al. Vasoplegic syndrome: a new dilemma. *J Thorac Cardiovasc Surg.* 1994;107:942-3. doi:10.1016/j.jtcvs.2003.09.046

Reply to the Editor:

The results from the studies performed by Evora and colleagues^{1,2} encouraged us to use methylene blue (MB) as a rescue treatment in catecholamine refractory vasoplegia after cardiopulmonary bypass (CPB).³ We used an intravenous MB dose of 2 mg/kg as an infusion with a positive effect in 92% of our patients. We selected this dose because the majority of MB side effects obviously do not occur when a dose of MB of 2 mg/kg or less is administered.⁴⁻⁶ We have no experience with continuous MB infusion for more than 48

hours. Continuous MB infusion could be an option for patients not responding to a single dose of MB. However, more scientific evidence is mandatory to define the role of MB in the treatment of catecholamine refractory vasoplegia after CPB (eg, multicenter, prospective, and randomized studies). Even more important is a better understanding of the mechanism triggering vasoplegia after CPB to avoid this potentially lethal complication, because a preoperative selection process to identify patients prone to vasoplegia after CPB could result in prophylactic treatment with guanylate cyclase inhibitors.

R. G. Leyh, MD

T. Kofidis, MD

M. Struber, MD

S. Fischer, MD, MSc

K. Knobloch, MD

B. Wachsmann, MS

C. Hagl, MD

A. R. Simon, MD

A. Haverich, MD

Hannover Medical School

Division of Thoracic and Cardiac Surgery

Hannover, Germany

References

1. Evora PR. Should methylene blue be the drug of choice to treat vasoplegias caused by cardiopulmonary bypass and anaphylactic shock? *J Thorac Cardiovasc Surg.* 2000;119:632-4.
2. Evora PR, Ribeiro PJ, Andrade JC. Methylene blue administration in SIRS after cardiac operation. *Ann Thorac Surg.* 1997;63:1212-3.
3. Leyh RG, Kofidis T, Struber M, Fischer S, Knobloch K, Hagl C, et al. Methylene blue: the drug of choice for catecholamine-refractory vasoplegia following cardiopulmonary bypass? *J Thorac Cardiovasc Surg.* 2003;6:1426-31.
4. Cheng X, Pang CC. Pressor and vasoconstrictor effects of methylene blue in endotoxaemic rats. *Naunyn Schmiedeberg's Arch Pharmacol.* 1998;357:648-53.
5. Zhang H, Rogiers P, Preiser JC, Spapen H, Manikis P, Metz G, et al. Effects of methylene blue on oxygen availability and regional blood flow during endotoxic shock. *Crit Care Med.* 1995;23:1711-21.
6. Weingartner R, Oliveira E, Oliveira ES, Sant'Anna UL, Oliveira RP, Azambuja LA, et al. Blockade of the action of nitric oxide in human septic shock increases systemic vascular resistance and has detrimental effects on pulmonary function after a short infusion of methylene blue. *Braz J Med Biol Res.* 1999;32:1505-13.

doi:10.1016/j.jtcvs.2003.09.047