aorta, the most logical explanation may be related to the rather short half-life (<10 seconds) of adenosine in blood because of the very effective uptake by the red cells.¹¹

The second article on which we would like to comment, by Ross and associates, is titled "Hypothermic Retrograde Venous Perfusion With Adenosine Cools the Spinal Cord and Reduces the Risk of Paraplegia After Thoracic Aortic Clamping" (*J Thorac Cardiovasc Surg* 2000;119:588-95).

1. Although apparently no statistically significant difference was reported between the adenosine group (III: Tarlov score 4.7 ± 0.2) and the plain saline solution group (II: Tarlov score 3.8 ± 0.4), no explanation is offered regarding the neurologic recovery in group III, which seems to us significantly better ($P < .002$).

2. Somatosensory evoked potentials (SSEPs) ceased significantly faster in the groups receiving regional infusion of hypothermic solution (II and III) than in the normothermic ischemia group (I), corroborating in the spinal cord a widely known observation in the nonischemic brain (the electroencephalogram becomes a straight line below 24°C-25°C) that hypothermia markedly decreases all neural activity, transmission included. However, no differences were observed between groups II and III ($P = .86$ according to our analysis of the presented data). The authors' conclusion that electrical silence is the major determinant of protection seems not to be substantiated by the significantly different neurologic outcomes in two groups, in which SSEPs ceased within comparable times after hypothermic perfusion.

3. The lesser amplitude of the postreperfusion returned SSEP of group III (85% vs 90% of group II; whether differences would be statistically significant could not be calculated since no SDs are provided) was not unexpected, and the better neurologic outcome can be explained by the same comments (inhibitory effects of adenosine/taurine) made for the previous article.

Tadaomi-A. Miyamoto, MD
Research Department
Kokura Memorial Hospital
Kitakyushu, Japan
Koho-J. Miyamoto, MD, PhD
Assistant Professor
II Department of Physiology
University of the Ryukyus
School of Medicine
Okinawa, Japan

REFERENCES

- Miyamoto, TA, Miyamoto KJ, Ohno N. Objective assessment of CNS function within 6 hours of spinal cord ischemia in rabbits. *J Anesth* 1998;12:189-94.
- Schubert P, Kreutzberg GW. Cerebral protection by adenosine. *Acta Neurochir Suppl Wien* 1993;57:80-8.
- Fredholm BB. Adenosine receptors in the central nervous system. *News Physiol Sci (NIPS)* 1995;10:122-8.
- Madelian V, Silliman S, Shain W. Adenosine stimulates cAMP-mediated taurine release from LRM55 glial cells. *J Neurosci Res* 1988;20:176-81.
- Wright CE, Tallan HH, Lin YY, Gaull GE. Taurine: biological update. *Annu Rev Biochem* 1986;55:427-53.
- Huxtable RJ. Taurine in the central nervous system and the mammalian actions of taurine. *Prog Neurobiol* 1989;22:471-533.
- Aruoma OI, Halliwell B, Hoey BM, Butler J. The antioxidant action of taurine, hypotaurine and their metabolic precursors. *Biochem J* 1988;256:251-5.
- Miyamoto TA, Miyamoto KJ. Effects of adenosine on taurine release in the central nervous system. *J Jpn Physiol Soc* 1996;46(Suppl):179.
- Miyamoto TA, Miyamoto KJ. Does adenosine release taurine in A1 receptors rich hippocampus? *J Anesth* 1999;13:94-8.
- Milei J, Ferreira R, Llesuy S, Forcada P, Covarrubias J, Boveris A. Reduction of reperfusion injury with preoperative rapid intravenous infusion of taurine during myocardial revascularization. *Am Heart J* 1992;123:339-45.
- Sollevi A. Cardiovascular effects of adenosine in man: possible clinical implications. *Prog Neurobiol* 1986;27:319-49.

12/8/104341

doi:10.1067/mtc.2000.104341

Should methylene blue be the drug of choice to treat vasoplegias caused by cardiopulmonary bypass and anaphylactic shock?

To the Editor:

Yiu, Robin, and Pattison¹ presented a rapid reversal of refractory hypotension with methylene blue after cardiopulmonary bypass (CPB). I would like to reinforce this kind of therapeutic approach, not only for low systemic vascular resistance (SVR) after CPB, but also for other types of vasoplegias, including anaphylactic shock.

My colleagues and I² reported the restoration of SVR with the use of methylene blue in 6 patients after cardiac surgery with and without CPB. In the immediate postoperative period, all patients had tachycardia, oliguria, good peripheral perfusion, and important systemic arterial hypotension not responsive to large doses of infused catecholamines. Hemodynamic analysis, done by the thermodilution technique (Swan-Ganz; Baxter Healthcare Corp, Santa Ana, Calif), showed a profile compatible with systemic inflammatory response syndrome, with a mean SVR index of $868 \text{ dina} \cdot \text{s} \cdot \text{cm}^5$. Methylene blue was administered to block the action of nitric oxide inhibiting the soluble guanylate cyclase at doses of 1.5 mg/kg during 1 hour of intravenous infusion. The systemic vascular tone restoration (SVR index = $1693 \text{ dina} \cdot \text{s} \cdot \text{cm}^5$ with normal arterial pressure and clinical performance) was effective and fast, showing methylene blue as a pharmacologic tool that improves the morbidity and mortality in systemic inflammatory response syndrome. Methylene blue did not affect cardiac output or pulmonary vascular resistance in those patients. This clinical experience was started in 1994 with the use of methylene blue in desperate situations in the operating room and early hours of the postoperative period. Since the presentation of these hemodynamic data, methylene blue has been widely used in Brazil.² Trying to find cause-effect clues, we identified some

isolated data³: (1) Most of the events were observed during or after CPB. (2) Many cases were associated with the use of the curare alcuronium. (3) Some cases were observed under usual anesthesia with etomidate, fentanyl, pancuronium, and diazepam. (4) Some cases were clearly associated with protamine infusion. (5) At least in one case the vasodilatation was induced after heparin infusion. (6) The vasoplegia was also observed in noncardiac operations. (7) Our impression was that the syndrome happened periodically. (8) Many patients had diabetes. (9) Many patients were previously using the calcium antagonist diltiazem. To these observations we can add the possible effects of the angiotensin-converting enzyme inhibitors as suggested by Tuman and associates⁴ and mentioned by Yiu, Robin, and Pattison.¹

We also have used methylene blue to treat anaphylaxis. Our cumulative clinical experience includes 6 patients. The causes were iodinate radiographic contrast material (5 patients) and penicillin (1 patient). The traditional treatments (high doses of epinephrine and corticosteroids) failed to reverse the cardiocirculatory collapse, urticaria, and angioedema. Four patients were treated by a bolus infusion of 4% methylene blue, 1.5 mg/kg (120 mg), followed by continuous infusion of another 120 mg diluted in 5% glucose in water. The infusion was administered as a bolus because of the severity of shock. Two patients received only continuous infusion during 30 to 40 minutes. The anaphylactic manifestations were completely reversed in 10 to 15 minutes. In 1 patient we observed nodal cardiac rhythm over 1 minute during the infusion of the dye, which reversed spontaneously. One hypertensive patient had angina pectoris during infusion, without any electrocardiographic manifestation, and did not require coronary vasodilators to reverse the symptoms. We obtained the hemodynamic registers of 2 patients who had anaphylactic shock caused by radiographic contrast material in the cardiovascular catheterization laboratory. Cumulative experience would indicate that this dye is the treatment of choice or an alternative to the treatment of distributive circulatory shock. I am reporting, probably, the first experience treating anaphylaxis in human beings with methylene blue, and it deserves wide circulation because it is a lifesaving choice.⁵

Nitric oxide stimulates soluble guanylate cyclase and activates the production of cyclic guanosine 3',5'-monophosphate (cGMP), resulting in relaxation. Inhibition of nitric oxide synthesis is not approved for clinical use because of the lack of specificity to the inducible form of nitric oxide synthase and its association with tissue necrosis. Methylene blue inhibits guanylate cyclase, avoiding the cGMP-dependent vasorelaxant effect of nitric oxide in the smooth muscle of the vessels. Also, thiazine dye is widely used in clinical medicine to reduce methemoglobin, to treat malaria, and to cleanse the urinary tract. Otherwise, methylene blue is not associated with tissue necrosis, as caused by nitric oxide synthase inhibition, and its lethal dose is more than 40 mg/kg, as shown experimentally in sheep. Myles, Leong, and Curry⁶ failed to identify an increase in nitric oxide release after, or as a consequence of, CPB on the basis of the

serum and urine nitrite/nitrate levels. Since methylene blue blocks the soluble guanylate cyclase, which is the final effect on the nitric oxide pathway, it is hard to determine a different cGMP-dependent mechanism, and the hypothesis of direct activation of this final common pathway of nitric oxide release is very improbable. I guess it is more logical to speculate on the existence of another non-nitric cGMP-dependent pathway, with different receptors and/or different G-proteins, or else a sensitization of vascular smooth muscle cells to the action of nitric oxide, as hypothesized by Yiu, Robin, and Pattison.¹

Paulo Roberto B. Evora, MD, PhD
Division of Experimental Surgery
Ribeirão Preto School of Medicine
University of São Paulo
Department of Surgery
UNAERP Medical School
Heart Hospital of Ribeirão Preto
Rua Rui Barbosa, 367, Ap 7
14015-120 Ribeirão Preto, SP, Brazil

REFERENCES

1. Yiu P, Robin J, Pattison CW. Reversal of refractory hypotension with single-dose methylene blue after coronary artery bypass surgery. *J Thorac Cardiovasc Surg* 1999;118:195-4.
2. Andrade JCS, Batista Filho ML, Evora PRB, et al. Methylene blue administration in the treatment of the vasoplegic syndrome after cardiac surgery. *Rev Bras Circ Cardiovasc* 1996;11:107-14.
3. Evora PRB, Ribeiro PJF, Andrade JCS. Methylene blue administration in SIRS after cardiac operations [letter/comment]. *Ann Thorac Surg* 1997;63:12-3.
4. Tuman KJ, McCarthy KJ, O'Connor CJ, Holm WE, Ivankovich AD. Angiotensin-converting enzyme inhibitors increase vasoconstrictor requirements after cardiopulmonary bypass. *Anesth Analg* 1995;80:473-9.
5. Evora PRB, Roselino CH, Schiavetto PM. Methylene blue in anaphylactic shock [letter]. *Ann Emerg Med* 1997;30:240.
6. Myles PS, Leong CK, Currey J. Endogenous nitric oxide and low systemic vascular resistance after cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 1997;11:571-4.

12/8/104472

doi:10.1067/mtc.2000.104472

Reply to the Editor:

We thank Evora for adding his experience with methylene blue. In most instances of low systemic vascular resistance (SVR) syndrome necessitating pharmacologic intervention, vasopressor therapy over a number of hours is limited. Thus whether methylene blue should be the drug of choice is speculative at this stage. Nevertheless, in cases in which first-line therapy has failed, the dramatic success and long-lasting effect of this drug that we found in our case, and that Evora and his colleagues presumably found as well, are certainly impressive. This leads us to propose that early use of methylene blue may halt the progression of low SVR even in patients responsive to norepinephrine and mitigate the need for a protracted course of vasoconstrictor use. A ran-