Methylene blue: The drug of choice for catecholamine-refractory vasoplegia after cardiopulmonary bypass?

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Objectives: Vasoplegia is a frequent complication after cardiopulmonary bypass that often requires the application of norepinephrine. In a number of cases, however, vasoplegia is refractory to norepinephrine. The guanylate cyclase inhibitor methylene blue could be an attractive treatment alternative in such cases. This study examines the results of methylene blue therapy for norepinephrine-refractory vasoplegia after cardiopulmonary bypass.

Methods: A total of 54 patients with norepinephrine-refractory vasoplegia after cardiopulmonary bypass were treated with methylene blue (2 mg/kg) administered intravenously through a period of 20 minutes. The effects on hemodynamics, norepinephrine dosage, and clinical outcome were evaluated.

Results: Three patients (5.6%) died during the hospital stay. A clinically relevant increase in systemic vascular resistance and a decrease in norepinephrine dosage were observed in 51 patients within 1 hour after methylene blue infusion. Four patients (7.4%) had no response to methylene blue. No adverse effects related to methylene blue were observed.

Conclusions: A single dose of methylene blue seems to be a potent approach to norepinephrine-refractory vasoplegia after cardiopulmonary bypass for most patients, with no obvious side effects. Guanylate cyclase inhibitors could be a novel class of agents for the treatment of norepinephrine-refractory vasoplegia after cardiopulmonary bypass. A controlled clinical trial is now needed to evaluate the role of methylene blue in this situation.

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After surgery with cardiopulmonary bypass (CPB) support, low peripheral vascular resistance may result in high vasopressor requirements to maintain sufficient mean arterial blood pressure. The underlying mechanisms that regulate the decreased vascular tone are unclear and remain a subject of intense research and debate.¹⁻⁹ The reported incidence of a hyperdynamic state with low systemic vascular resistance (SVR) is as great as 10% among all patients after cardiac surgical intervention with CPB support.⁶ In most cases low-dose norepinephrine application is sufficient to restore adequate SVR. In some cases, however, prolonged vasoplegia is resistant to norepinephrine. These patients have been treated with the intravenous application of vasopressin, as shown by Argenziano and colleagues.¹⁰ However, this approach has not been validated.

Recently, several cases have been described in the literature by us and by others in which the guanylate cyclase inhibitor methylene blue (MB) was successfully administered intravenously to reverse norepinephrine-resistant vasoplegia after CPB.¹¹⁻¹⁴ The available data have been obtained from anecdotal case observations only, however, and the effect of MB has not been examined in larger cohorts. Here we report our experience with the use of MB for norepinephrine-refractory post-CPB vasoplegia in a cohort of 54 patients.

Material and Methods

Patients

Between October 2000 and October 2001, a total of 1111 various operation with CPB support were performed. In 4.8% of these cases ($n = 54/1111$), norepinephrine-refractory systemic vasoplegia developed. Norepinephrine-refractory systemic vasoplegia was defined as a mean arterial blood pressure lower than 60 mm Hg, a cardiac output greater than 4.0 L/min, low SVR ($<600 \text{ dyne} \cdot \text{s} \cdot \text{cm}^{-5}$) under intravenous norepinephrine infusion ($\geq 0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). These 54 patients (41 [76%] male, mean age 56.7 ± 15.1 years) received the guanylate cyclase inhibitor MB in addition to norepinephrine for restoration of mean systemic blood pressure. Patients with active endocarditis were excluded from the cohort. No other medications were applied to treat low SVR, including vasopressin, phenylephrine hydrochloride, or corticosteroids.

Anesthesia, CPB, and Surgery

Anesthesia was induced with etomidate (0.3 mg/kg) and sufentanil (0.8 $\mu\text{g}/\text{kg}$) and maintained with continuous administration of sufentanil and propofol during surgery. Pancuronium bromide was used for neuromuscular blockade. In all cases Stöckert™ roller pumps (Stöckert Instrumente GmbH, Munich, Germany) and membrane oxygenators (Minpech; BioCor, LLC, Yardley, Pa) primed with 1000 mL Ringer solution, 300 mL 5% glucose, and 40 mL 8.4% sodium bicarbonate were used for CPB.

A nonpulsatile pump flow was maintained at $2.4 \text{ L} \cdot \text{min} \cdot \text{m}^{-2}$ with a perfusion pressure of 60 to 80 mm Hg. CPB was initiated at moderate hypothermia (30°C - 32°C). For cardioplegia, St Thomas solution or intermittent cold blood cardioplegia was used. Initial heparinization was accomplished with 300 IU/kg body weight and was supplemented as required to maintain an activated clotting time longer than 400 seconds. All procedures were performed with the use of aprotinin according to the Hammersmith protocol.¹⁵ The intraoperative variables and operations performed are depicted in Table 1.

Postoperative Treatment

In cases of postoperative hemodynamic instability despite adequate fluid substitution, a thermodilution catheter was inserted and norepinephrine infusion was initiated according to the cardiac output and SVR. If hemodynamic instability in patients with high-output circulatory failure persisted despite norepinephrine infusion ($\geq 0.4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and fluid substitution, a single dose of MB (2 mg/kg) was administered intravenously (infusion time of 20 minutes).

TABLE 1. Intraoperative variables and surgical procedures

Bypass time (min, mean $\pm$ SD)	167 $\pm$ 80
Aortic crossclamp time (min, mean $\pm$ SD)	94 $\pm$ 77
Temperature ($^\circ\text{C}$, mean $\pm$ SD)	30.5 $\pm$ 1.7
Surgical procedures (No.)	
Coronary artery bypass grafting	15
Reoperative coronary artery bypass grafting	1
Coronary artery bypass grafting with valve surgery	4
Aortic valve surgery	3
Mitral valve surgery	6
Tricuspid valve surgery	1
Double valve surgery	6
Heart transplantation	7
Double-lung transplantation	2
Left ventricular assist device placement	3
Miscellaneous	6

Hemodynamic Measures

Mean arterial pressure, mean pulmonary arterial pressure, mean right atrial pressure, mean left atrial pressure, and cardiac output were recorded, and the SVR was calculated according to a standard formula. All measurements and calculations were performed immediately before MB infusion and 1, 6, and 12 hours thereafter.

Postoperative Follow-up

Complete postoperative follow-up was obtained in all cases. As a gross evaluation of pulmonary function the duration of mechanical ventilation and the ratio of Pao_2 to inspired oxygen fraction were determined before MB infusion and 1, 6, and 12 hours thereafter. For evaluation of organ function, routine laboratory indices, including serum concentrations of creatinine, aspartate aminotransferase, alanine aminotransferase, and lactate, were assessed before MB administration and 1, 6, 12, 24, and 48 hours thereafter.

Statistical Analysis

Continuous variables are expressed as mean $\pm$ SD unless otherwise indicated. The Friedmann test was used for comparisons of means within the group. Intragroup comparisons of values at sequential time points at different times were done with the Wilcoxon test for nonnormally distributed data. Statistical calculations were performed with the SPSS software package for Windows (SPSS Inc, Chicago, Ill).

Results

MB was administered 136 ± 48 minutes after surgery and 51 ± 28 minutes after initiation of norepinephrine infusion to stabilize the hemodynamic situation. In all cases MB infusion was initiated when a norepinephrine dosage of at least $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ was reached. Hemodynamic measures are depicted in Table 2. Immediately after MB infusion, clinically significant increases in mean arterial pressure and SVR combined with a significant decrease in norepinephrine dosage (before MB vs. 1 hour after MB $P < .001$, before MB vs. 6 hours after MB $P < .001$, before MB vs. 12 hours after MB $P < .001$) were seen in 92.4% of patients (Figure 1). The cardiac output decreased after MB

Figure 1. Persistent increase in mean arterial pressure (mAP) (before vs. 1 hour after MB $P = .02$, before vs. 6 hours after MB $P = .02$, before vs. 12 hours after MB $P = .02$) and clinically significant increase in SVR (before vs. 1 hour after MB $P < .001$, before vs. 6 hours after MB $P < .001$, before vs. 12 hours after MB $P < .001$) combined with significant decrease in norepinephrine dosage (before vs. 1 hour after MB $P < .001$, before vs. 6 hours after MB $P < .001$, before vs. 12 hours after MB $P < .001$) were observed after single intravenous dose of MB.

TABLE 2. Hemodynamic data

Variable	Time points				P values		
	Before MB	1 h after MB	6 h after MB	12 h after MB	Before vs. 1 h after MB	Before vs. 6 h after MB	Before vs. 12 h after MB
Mean arterial pressure (mm Hg)	68 ± 9	72 ± 12	71 ± 9	73 ± 10	.02	.02	.02
Mean pulmonary artery pressure (mm Hg)	23 ± 6	24 ± 7	25 ± 5	24 ± 8	>.1	>.1	>.1
Mean right atrial pressure (mm Hg)	14 ± 4	14 ± 4	15 ± 4	15 ± 5	>.1	>.1	>.1
Mean left atrial pressure (mm Hg)	11 ± 4	10 ± 3	12 ± 5	10 ± 5	.09	.08	.09
Cardiac output (L/min)	7.6 ± 3.1	6.5 ± 2.8	6.1 ± 2.4	5.8 ± 1.9	<.001	<.001	<.001
SVR (dyne · s · cm ⁻⁵)	547 ± 108	766 ± 194	796 ± 153	876 ± 184	<.001	<.001	<.001

infusion in parallel with the increase in SVR. Mean pulmonary arterial pressure, mean right atrial pressure, and mean left atrial pressure did not change with time after MB infusion. Data from patients who did not have a response to MB are depicted in Table 3.

The serum creatinine concentration and the pulmonary gas exchange, expressed as the ratio of P_{aO_2} to inspired oxygen fraction, remained unaffected by MB (Table 4). However, the serum aspartate aminotransferase and alanine aminotransferase concentrations, which were already increased before MB infusion, increased further during the next 48 hours after MB infusion. The serum lactate concentration decreased significantly within 12 hours after MB infusion (Table 4).

Three patients died during the hospital stay (5.6%). In a 51-year-old male patient with dilated cardiomyopathy and preoperative low cardiac output, a left ventricular assist device was implanted as a bridge to transplantation. This patient did not respond to MB and died of multiorgan failure on the third postoperative day. The second patient, a 71-year-old man, had norepinephrine-refractory vasoplegia develop after double valve replacement. After MB infusion, the SVR increased and the norepinephrine dosage could be reduced significantly. This patient had renal failure requiring hemodialysis develop and died of septic shock on the sixth postoperative day. The third patient was a 66-year-old man with unstable angina who underwent coronary artery bypass grafting. He was resuscitated 6 hours after the op-

TABLE 3. Data from patients without response to MB infusion

Case	Age (y)	Sex	Diagnosis	Operation	Bypass (min)	Aortic crossclamp (min)	Temperature (°C)	Outcome
1	51	Male	DCM	LVAD	183	143	28	Dead
2	66	Male	Unstable angina	CABG and LVAD	205	128	32	Dead
3	64	Male	AV and MV stenosis	AV and MV replacement	164	120	30	Alive
4	63	Male	DCM	Heart transplantation	115	—	30	Alive

DCM, Dilated cardiomyopathy; LVAD, left ventricular assist device; CABG, coronary artery bypass grafting; AV, aortic valve; MVR, mitral valve.

TABLE 4. Laboratory findings and gas exchange

Variable	Time points						P values				
	Before MB	1 h after MB	6 h after MB	12 h after MB	24 h after MB	48 h after MB	Before vs. 1 h after MB	Before vs. 6 h after MB	Before vs. 12 h after MB	Before vs. 24 h after MB	Before vs. 48 h after MB
Creatinine ($\mu\text{mol/L}$)	160 $\pm$ 107	163 $\pm$ 98	168 $\pm$ 106	172 $\pm$ 113	185 $\pm$ 116	169 $\pm$ 99	>.1	>.1	>.1	.06	>.1
Aspartate aminotransferase (U/L)	550 $\pm$ 240	749 $\pm$ 355	767 $\pm$ 420	890 $\pm$ 471	993 $\pm$ 502	764 $\pm$ 358	<.001	<.001	<.001	<.001	<.001
Alanine aminotransferase (U/L)	473 $\pm$ 194	505 $\pm$ 203	606 $\pm$ 276	609 $\pm$ 287	532 $\pm$ 314	508 $\pm$ 235	.08	<.001	<.001	.05	.08
Lactate (mmol/L)	6.4 $\pm$ 2.7	6.2 $\pm$ 2.5	5.8 $\pm$ 4.8	5.5 $\pm$ 4.1	3.6 $\pm$ 3.3	2.7 $\pm$ 1.9	>.1	p > 0.1	0.04	<.001	<.001
Po ₂ /inspired oxygen	1.44 $\pm$ 0.73	1.41 $\pm$ 0.55	1.8 $\pm$ 0.88	2.22 $\pm$ 0.51	—	—	.34	.04	.011	—	—

eration because of acute myocardial ischemia and was sent back to the operating room for additional coronary bypass grafting. He could not be weaned from CPB, and a left ventricular assist device was implanted. After the second operation, he had norepinephrine refractory vasoplegia develop that did not respond to MB. He died of multiorgan failure on the 12th postoperative day.

Six patients had coagulopathy develop. One of these patients underwent reexploration for excessive bleeding and died on the third postoperative day.

Four patients required renal dialysis (8%) during the postoperative course. Two of them died. Two of these patients were already receiving hemodialysis before the operation. The mean intensive care unit stay of all patients was 11 $\pm$ 8 days (range 1-42 days). The mean mechanical ventilation time was 212 $\pm$ 172 hours (range 14-794 hours). Most patients (82%, n = 44/54) required mechanical ventilation for more than 48 hours after the operation.

Discussion

We have shown the intravenous application of MB to be highly effective in the treatment of norepinephrine-refractory vasoplegia after CPB, with no relevant side effects. According to the literature, MB has chiefly been used to treat patients with septic shock and low peripheral vascular resistance.^{16,17} The effectiveness of MB in cardiac surgery

has only been described in anecdotal case reports by us and others.¹¹⁻¹⁴ To our knowledge, this is the first large-scale investigation with postoperative human subjects in which severe vasoplegia after CPB was treated with MB.

A few adverse effects of MB in the treatment of norepinephrine-refractory vasoplegia have been described, such as cardiac arrhythmias; coronary vasoconstriction; decreases in cardiac output, renal blood flow, and mesenteric blood flow; increases in pulmonary vascular pressure and resistance; and deterioration in gas exchange. However, most of these side effects are dose dependent and do not occur when a dose of MB no greater than 2 mg/kg is administered.¹⁸⁻²¹ In our patients none of the mentioned side effects were observed. In contrast, we found a significant decrease in arterial serum lactate concentration within 24 hours after MB infusion, underlining the restoration of normal peripheral blood flow after MB infusion. Although we noticed significant increases in serum levels of aspartate aminotransferase and alanine aminotransferase after application of MB, it remains a matter of speculation whether this increase is related to the application of the drug or is an effect of the accompanying high norepinephrine dosage. Several reports have demonstrated that norepinephrine-refractory vasoplegia alone is associated with a higher postoperative morbidity.²²⁻²⁴ Furthermore, the duration of norepinephrine-refractory vasoplegia may be an important factor influencing the

outcome. Gomes and coworkers²⁴ showed in a small series of patients that norepinephrine-refractory vasoplegia persisting longer than 36 to 48 hours is associated with increases in morbidity and mortality. Thus an aggressive and fast treatment of postoperative norepinephrine-refractory vasoplegia is mandatory to reduce postoperative morbidity and mortality. Four of our patients had no response to MB, and 2 of them died. The reason could not be elucidated from our data and remains a matter of speculation. However, a persistent release of proinflammatory mediators as a result of placement of a left ventricular assist device system could explain this phenomenon in 2 of the 4 who had no response.

The underlying mechanisms that are involved in the regulation of post-CPB vasoplegia are a matter of controversy but may be related to the activation of an inflammatory response.¹⁻⁹ The favorable effect of MB demonstrated in this study suggests that refractory vasoplegia after CPB may reflect a dysregulation of nitric oxide synthesis and vascular smooth muscle cell guanylate cyclase activation. In recent studies an increase in nitric oxide release after CPB could not be demonstrated.^{7,25} Therefore it can be hypothesized that the CPB-triggered release of proinflammatory mediators may act through the induction of the final common pathway of nitric oxide, which is the activation of the guanylate cyclase, leading to vasodilation, as shown by Wu and coworkers.²⁶ This group showed that the hyporesponsiveness to norepinephrine in a hypercirculatory state is due to the activation of the soluble guanylate cyclase, which in part is mediated by nitric oxide. Even more supportive of the hypothesis that post CPB vasodilation is nitric oxide independent is the finding described by Beasley and McGuiggin²⁷ and Schmidt²⁸ that interleukin 1 and oxygen free radicals may activate the soluble guanylate cyclase leading to vascular hyporeactivity in the absence of nitric oxide. Because cytokines and free radicals are produced during CPB, a nitric oxide-independent activation of the guanylate cyclase could be an initiator of refractory vasoplegia after CPB.

This was an observational study with no control group. However, an immediate increase in SVR and an immediate clinically significant decrease in norepinephrine dosage were observed in 92% of our patients after a single dose of MB, with no side effects related to the drug. Thus we were reluctant to withhold this new treatment modality from patients with norepinephrine-refractory vasoplegia after CPB, because the only alternative for these patients is the maintenance or even increase of the norepinephrine dosage, with the known side effect of reduced microperfusion of the visceral organs.

In conclusion, the inhibition of the soluble guanylate cyclase elicited by nitric oxide or any endothelially soluble guanylate cyclase activating factor (eg, interleukin 1, atrial natriuretic peptide, and bradykinin) could be a novel ap-

proach in the treatment of norepinephrine-refractory vasoplegia after CPB. We recommend the use of MB in such cases. For final judgment of this novel concept, however, a prospective randomized study is desirable. Furthermore, the effects of MB in the treatment of norepinephrine-refractory vasoplegia after CPB should be compared with those of other agents, such as vasopressin.

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