The Hemodynamic Effects of Methylene Blue When Administered at the Onset of Cardiopulmonary Bypass

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Hypotension occurs during cardiopulmonary bypass (CPB), in part because of induction of the inflammatory response, for which nitric oxide and guanylate cyclase play a central role. In this study we examined the hemodynamic effects of methylene blue (MB), an inhibitor of guanylate cyclase, administered during cardiopulmonary bypass (CPB) to patients taking angiotensin-converting enzyme inhibitors. Thirty patients undergoing cardiac surgery were randomized to receive either MB (3 mg/kg) or saline (S) after institution of CPB and cardioplegic arrest. CPB was managed similarly for all study patients. Hemodynamic data were assessed before, during, and after CPB. The use of vasopressors was recorded. All study patients experienced a similar reduction in mean arterial blood pressure (MAP) and systemic vascular resistance (SVR) with the onset of CPB and cardioplegic arrest. MB increased MAP and SVR and this effect lasted for 40 minutes. The saline group demonstrated a persistently reduced MAP and SVR throughout CPB. The saline group received phenylephrine more frequently during CPB, and more norepinephrine after CPB to maintain a desirable MAP. The MB group recorded significantly lower serum lactate levels despite equal or greater MAP and SVR. In conclusion, administration of MB after institution of CPB for patients taking angiotensin-converting enzyme inhibitors increased MAP and SVR and reduced the need for vasopressors. Furthermore, serum lactate levels were lower in MB patients, suggesting more favorable tissue perfusion.

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Systemic blood pressure and vascular resistance decline with the onset of cardiopulmonary bypass (CPB), in part as the result of acute hemodilution, the administration of calcium-binding citrate in the cardioplegia, and the onset of a systemic inflammatory response. The latter is associated with increased nitric oxide (NO) activity, and, for a minority of patients, may result in a "vasoplegic syndrome" for which conventional treatments with IV fluid and vasoconstrictors are less effective (1–8).

Methylene blue, a commonly used tissue marker, is, normally, hemodynamically inert. However, for a variety of clinical scenarios associated with an inflammatory response, methylene blue results in increases of systemic blood pressure, systemic vascular resistance (SVR), and myocardial contractility (9–15). The purpose of this study was to assess the effects of methylene blue on systemic hemodynamics during and immediately after CPB in the subgroup of patients taking angiotensin-converting enzyme inhibitors (ACEi), a known risk factor for significant and persistent reductions in systemic blood pressure and vascular resistances (3,4,16,17). We hypothesize that the administration of methylene blue will reduce both the incidence and severity of hypotension during CPB, and the need for vasoconstrictor medications.

METHODS

After obtaining permission from the hospital IRB, Food and Drug Administration approval to administer methylene blue for an "off-label" purpose, and written informed consent, 30 patients taking ACEIs within 24 h before elective heart surgery requiring CPB were randomized to receive either methylene blue or saline (S) during CPB. Patients taking ACEi were chosen because they are at increased risk to require vasoconstrictors during CPB (3,4,16,17). All regularly prescribed medications were continued until and including the morning of surgery.

Exclusion criteria included emergency surgeries, patients requiring vasoconstrictors and/or inotropic medications before heart surgery, patients with renal insufficiency (serum creatinine $\geq$1.8 mg/dL), hepatic disease (increase of liver function tests), or evidence of acid/base abnormalities based on preoperative laboratory data (pH $<$7.35 or TCO_2 $<$22 meq/dL), pregnant patients, women of childbearing potential, patients with history of hypersensitivity to methylene blue, and patients with known G6PD deficiency.

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Before the start of anesthetic care, patients were randomized to receive either methylene blue or the equivalent volume of saline. Because of the color of methylene blue, the known effect on measurement of oxygen saturation by light reflection techniques, and the alteration in the urine color, caregivers could not be blinded as to randomization groups.

Induction of anesthesia consisted of thiopental (2–3 mg/kg), pancuronium (0.15 mg/kg), and fentanyl (5–10 μg/kg). Administration of benzodiazepines was at the discretion of the attending anesthesiologist. Maintenance of anesthesia was accomplished using fentanyl, pancuronium, isoflurane (0.3% to 1%) in an oxygen/air mixture. Normocarbia (Pco_2 35–45 mm Hg) and a normal pH (7.35–7.45) were maintained throughout the surgical procedure. All patients had standard invasive and noninvasive monitoring.

CPB consisted of a closed system membrane oxygenator with centrifugal pumps with normothermic perfusate at 37°C and cold cardioplegic arrest as previously described (18,19). CPB was managed with a systemic flow rate of 2.5 L/min/m^2. Hematocrit (Hct) was maintained above 18% during cardiopulmonary bypass and then >23% after separation from CPB. An IV infusion of phenylephrine or inhaled isoflurane was administered to sustain a mean arterial blood pressure (MAP) more than 55 mm Hg and less than 80 mm Hg. All patients received between 0.25% and 0.5% inspired isoflurane during CPB for amnesia. Phenylephrine was administered using an infusion pump (6201 Infusion Pump; FloGard Deerfield IL) to allow titration and quantification of the total dose administered. Separation from CPB was achieved according to divisional routine management, which included MAP >55 mm Hg and a cardiac index ≥2.5 L/min/m^2. The choice of vasoactive medications was left to the discretion of the attending anesthesiologist.

After the onset of CPB, the initial dose of cardioplegia, and a period of stabilization (5 min), 3 mg/kg of methylene blue or its equivalent volume of saline was administered via the central venous catheter. Relative to other investigations, a larger dose of methylene blue was empirically chosen in the present study to account for the increase volume of distribution when the patient's blood was mixed into the CPB circuit (9–15,20). Because of the light absorption properties of methylene blue and the technique by which oximetry is continuously monitored during CPB, it was expected that mixed venous saturation (Svo_2) would decline after the administration of the study drug.

The patient's chart was reviewed for the following data: age, gender, body surface area, preoperative medications, presence of hypertension, presence of left ventricular hypertrophy, and assessment of ventricular and valve function (both based on preoperative transthoracic echocardiography), and presentation or history of congestive heart failure, myocardial infarction, and syncope. Surgical data collected included use of antifibrinolytics (aprotinin or aminocaproic acid), surgical procedure, times for aortic cross-clamp (AoXCl) and CPB.

Hemodynamic and laboratory data were obtained for the first 60 min of CPB. Pre-CPB hemodynamic data included heart rate, MAP, right atrial pressure, mean pulmonary pressure, pulmonary capillary wedge pressure, and cardiac output (CO). CO was obtained with a thermodilution technique using room temperature dextrose solution and made in triplicate during brief periods of apnea and averaged. SVR and pulmonary vascular resistance were calculated. Data obtained during CPB included MAP, right atrial pressure, and systemic flows (CO during CPB). Data during CPB were obtained at the following points:

PreDrug: Before the administration of the study drug, and after a 5-min period of stabilization after the institution of CPB and cardioplegic arrest.

PostDrug: 10 min after the administration of the study drug.

PostDrug20: 20 min after the administration of the study drug.

PostDrug40: 40 min after the administration of the study drug.

PostDrug60: 60 min after the administration of the study drug.

These times were selected so that hemodynamic data would be obtained approximately 5–10 min after the administration of the preceding dose of cardioplegia. The use of phenylephrine and its total dose during this time period of CPB were recorded. The use of inotropes, vasopressors, and vasodilators after CPB was also recorded.

Laboratory data included arterial blood gas analysis (Pao_2, $Paco_2$, pH), Hct, lactate, ionized calcium (Cai), methemoglobin levels, and Svo_2 measured during CPB. Blood samples were analyzed using the GEM premier 3000 Blood Gas/Electrolyte Analyzer (model 5700; Instrumentation Laboratory; Lexington, MA). $Svo_2$was measured using the BioTrend Oxygen Saturation and Hematocrit System (Medtronic, Minneapolis, MN) using a dual wavelength light reflectance technique. Methemaglobin levels were measured using the Bayer Blood Gas Analyzer 865 (Bayer Pharmaceuticals, Tarrytown NY). All measuring technologies were calibrated before each case as per the manufacturer's directions.

Chart documentation of nausea, vomiting, dizziness, cardiac ischemia by ST changes on telemetry, and rhythm disturbances was recorded.

Demographic variables are presented as number and percentage or mean and SD. Hemodynamic data are presented as the mean values and SD or occurrence and percentage. Demographic, presurgical, surgical, and hemodynamic variables were compared using Student's *t*-tests, analysis of variance, or Fisher's exact tests for categorical and continuous data. Univariate

Table 1. Preoperative Demographic Variables

	Methylene blue	Saline
Age (y)	69.8 (6.6)	68.4 (10.6)
BSA (m^2)	2.05 (0.21)	1.93 (0.12)
Weight (kg)	87.7 (18.5)	81.9 (8.1)
Sex (M/F)	12/3	11/4
Surgical procedure (*n*)		
AVR/Aorta	1	1
AVR	2	1
AVR/CABG	2	2
CABG	6	6
MVR/CABG	3	3
MVR	1	2
ACE inhibitor (*n*)		
Captopril	2	3
Enalapril	3	2
Fosinopril	2	1
Lisinopril	8	9
Beta blocker (*n*)	10	9
Ca channel block (*n*)	5	3
Diuretic (*n*)	6	3
LVEF (%; SD)	44 (15)	50 (11)
Number ≤40% (n (%))	7 (47)	6 (40)
Hypertension (*n*)	15	15
CHF (*n*)	9	7
Diabetes (*n*)	6	5
Tobacco/COPD/asthma (*n*)	13	11

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$: when compared with saline group.

BSA = body surface area; AVR = aortic valve replacement; CABG = coronary artery bypass grafting; MVR = mitral valve replacement; ACE = angiotensin converting enzyme; Ca = calcium; LVEF = left ventricular ejection fraction; CHF = congestive heart failure; COPD = chronic obstruction lung disease.

analyses were performed to assess the impact of perioperative variables on hemodynamic changes. *P* values <0.05 was considered as statistically significant. SAS v.8.2 (SAS Institute Inc., Cary, NC) was used for the statistical analysis.

RESULTS

Thirty patients were randomized to receive either methylene blue or saline. Data were obtained immediately before, during the initial 60 min of, and after separation from CPB.

Demographic and surgical variables (Tables 1 and 2) were not significantly different between the two study groups. Preoperative medications, cardiovascular functions, and anesthetic technique were similar. There were no significant differences with regard to the type of surgical procedures, time on CPB, or aortic cross-clamp time. A similar amount of blood was transfused to patients in both groups and Hcts were similar. Other than the administration of methylene blue, no other preoperative or operative variables were found to predict hemodynamic changes during CPB (Tables 3 and 4).

Administrations of aprotinin and aminocaproic acid were similar between the two study groups. Neither drug was associated with hemodynamic data when assessed for all study patients, or within each study group.

Hemodynamic and laboratory data are presented in Tables 3 and 4. Baseline data, defined as pre CPB and Pre Drug, were similar between the two study groups (Table 3). Both groups demonstrated similar reductions in SVR, MAP, ionized calcium, and Hct with the onset of CPB. Immediately after administration of the methylene blue, the MAP was significantly increased from predrug levels (53.7 mm Hg to 63.0 mm Hg; $P < 0.001$) (Table 4 and Fig. 1) and was significantly more than the MAP in the saline group (methylene blue 63.0 mm Hg versus saline 55.0 mm Hg; $P < 0.05$), despite a greater use of phenylephrine for the latter (Table 3). The use of phenylephrine during CPB was significantly increased in the saline group at all time points during CPB (Table 3). Lactate levels were significantly reduced in the methylene blue group compared with the saline group at all time periods during CPB after the administration of the study drug (Table 3).

Although both study groups demonstrated a similar and significant reduction in MAP and SVR after the onset of CPB, administration of methylene blue was associated with a significantly larger percent increase (16–21%) in both measures of afterload for up to 40 minutes compared to PreDrug measures (Table 3 and 4; Fig. 1). In contrast, both MAP and SVR in saline group remained depressed throughout CPB when compared to the PreDrug data (Table 3).

All patients were successfully weaned from CPB. There were no differences in the use of amrinone, nitroglycerin, epinephrine, or dopamine. However, fewer patients in the methylene blue group required norepinephrine to maintain MAP (methylene blue 6/15 (40%) versus saline 11/15 (73%); $P < 0.05$).

There were no pre-specified complications or adverse events associated with the administration of methylene blue. Although Svo_2 was significantly lower for the first 20 min after the administration of methylene blue, the systemic arterial oxygen tensions (Pao_2) were not significantly different (Table 3). Measured pH and Pco_2 were also similar between the two groups (Table 3).

DISCUSSION

The results of the present study show that administration of methylene blue during CPB results in improved hemodynamics when compared with the saline group, which required greater use of vasopressor to maintain hemodynamics. The greater use of vasoactive drugs for saline group likely contributed to the recording of similar MAP and SVR between the two study groups. The lower lactate levels in patients receiving methylene blue suggests that methylene blue increases vascular tone without compromising global tissue perfusion. By contrast, the use of phenylephrine was associated with increased systemic lactate levels, a finding previously reported (21).

Methylene blue is an inhibitor of guanylate cyclase and thereby reduces cyclic guanosine monophosphate (cGMP) production (22–29). By contrast, NO activates

Table 2. Perioperative Variables

	Methylene blue	Saline
Hematocrit (%)		
Pre CPB	38.7 (5.1)	38.9 (4.5)
Pre Drug	19.7 (3.3)	19.8 (2.6)
Post Drug	21.2 (2.8)	21.6 (3.7)
Post 20 Minutes	21.4 (3.6)	22.5 (1.9)
Post 40 Minutes	22.1 (4.0)	23.2 (1.9)
Post 60 Minutes	22.3 (2.9)	23.5 (2.0)
Post CPB	25.6 (2.1)	24.5 (2.3)
Transfusion (units/pt)	1.3 (1)	1.5 (1.0)
Anesthetic		
Fentanyl		
Pre CPB total	725 (249)	686 (355)
μg/kg	8.4 (2.5)	8.3 (4.0)
Post CPB total	242 (243)	206 (247)
μg/kg	2.8 (2.6)	2.6 (3.3)
Isoflurane (%)		
Pre CPB	0.5	0.5
Pre Drug	0.33 (0.12)	0.38 (0.20)
Post Drug	0.35 (0.13)	0.38 (0.25)
Post 20 Minutes	0.33 (0.12)	0.37 (0.20)
Post 40 Minutes	0.35 (0.13)	0.37 (0.24)
Post 60 Minutes	0.34 (0.13)	0.40 (0.27)
Pre CPB vasoactive (*n*)		
Nitroglycerin	4	5
Norepinephrine	1	2
Aprotinin/aminocaproic acid (*n*)	8/7	8/7
Peak Met Hb	0.65 (0.12)*	0.52 (0.18)
Phenylephrine CPB (*n*)		
Total (mL/patient)	1.8 (4.3)***	25.2 (21.0)
Post Drug	0 (0%)***	12/15 (80%)
CPB 20 min	0 (0%)***	11/15 (73%)
CPB 40 min	1/15 (7%)*	8/15 (53%)
COB 60 min	1/15 (7%)**	9/15 (60%)
Adverse events		
Nausea/vomiting	4 (26.7%)	5 (33.3%)
Dizziness	1 (6.7%)	0
Rhythm abnormalities		
Atrial	5 (33.3%)	5 (33.3%)
Ventricular	0	0
Cardiac ischemia	0	0

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$: When compared with Saline group.

CPB = cardiopulmonary bypass; Met Hb = methemaglobin.

guanylate cyclase, which increases cGMP, causing vascular smooth muscle relaxation and cardiac depression (23,24). Data suggest that methylene blue may compete with NO for binding to the heme moiety of guanylate cyclase, thereby reducing the enzyme's activity and resultant hemodynamic effects (22–29). The hemodynamic benefits of methylene blue have been reported across different clinical scenarios including cardiac surgical patients, patients with sepsis, and patients undergoing liver transplantation (10–14,22–24). When administered alone in the perfused rat heart, methylene blue causes coronary vasodilation, suggesting that methylene blue may not be a direct vasoconstrictor but more likely counters the hemodynamic effects of NO (30).

Investigators have cited the role of inflammation with its multiple components as a cause of decreased SVR and MAP during CPB. (1–8,21,31,32). A final common pathway involves NO induction and its activation of guanylate cyclase. For the majority of patients, reductions of SVR/MAP during CPB are easily managed with increases in systemic blood flow, optimization of metabolic parameters, and low dose infusions of vasopressors such as phenylephrine or norepinephrine. Although vasopressors have been associated with increases in systemic lactate levels, this is usually transient and improves within hours after separation from CPB (21). However, 5% to 44% of patients experience "vasoplegic syndrome" in the perioperative period, requiring prolonged administration of vasoactive medication (33,34). Vasoplegia syndrome is defined as hypotension (mBP < 50 mm Hg or SBP <85 mm Hg), decreased SVR (<600–800 dynes · s · cm^2 or SVRI < 1800 dyne · s · cm^5/m^2), normal to high systemic flows (CI >2.5 L · min · m^2), normal or reduced central filling pressures (CVP <10 mm Hg; PCWP <10 mm Hg), and an increasing

Table 3. Hemodynamic and Metabolic Measurements Obtained Prior to, After the Onset of, and After Separation from Cardiopulmonary Bypass (CPB)[a]

	Pre CPB		CPB Pre Drug		CPB Post Drug		CPB 20 min		CPB 40 min		CPB 60 min		Post CPB	
Group	MeBlu	Sal	MeBlu	Sal	MeBlu	Sal	MeBlu	Sal	MeBlu	Sal	MeBlu	Sal	MeBlu	Sal
HR	70 (7)	69 (10)											88 (4) ††	89 (5) ††
MAP	81 (10)	80 (13)	54 (11)††	60 (11)††	63 (7)*##	55 (12)	60 (6)#	57 (9)	62 (8)*#	57 (7)	60 (8)	58 (8)	72 (4)†	71 (8)†
Flow	4.3 (1.0)	4.4 (0.8)	5.1 (0.4)†	4.9 (0.4)†	5.1 (0.4)	5.0 (0.5)	5.2 (0.5)	5.0 (0.5)	5.3 (0.5)	5.0 (0.5)	5.1 (0.4)	5.0 (0.6)	6.1 (1.7)††	5.6 (1.0)††
SVR	1440 (364)	1399 (438)	841 (187)†††	975 (200)††	986 (155)##	896 (249)	939 (116)#	928 (186)	952 (150)#	922 (167)	946 (116)	953 (207)	901 (238)†††	916 (204)†††
Phenyl	0	0	0	0	0***	12 (80)	0***	11 (73)	1 (7)*	8 (53)	1 (7)**	9 (60)		
Lactate	0.89 (0.2)	0.95 (0.31)	0.90 (0.25)	1.07 (0.29)	0.84 (0.27)**	1.30 (0.50)#	0.96 (0.38)***	1.65 (0.58)###	1.14 (0.63)*	1.71 (0.66)###	1.29 (0.67)*	1.85 (0.80)###	1.83 (1.43)†	2.25 (1.29)†††
Hct	33.9 (3.9)	33.9 (5.0)	19.7 (3.3)†††	19.8 (2.6)†††	21.2 (2.8)#	21.6 (3.7)	21.4 (3.6)#	22.5 (1.9)†††	22.1 (4.0)#	23.2 (1.9)###	22.3 (2.9)##	23.5 (2.0)	25.6 (2.1)†††	24.5 (2.3)†††
PH	7.43 (0.05)	7.41 (0.04)	7.42 (0.04)	7.39 (0.04)	7.37 (0.03)#	7.37 (0.03)	7.36 (0.03)#	7.39 (0.04)	7.38 (0.03)#	7.40 (0.03)	7.41 (0.05)	7.41 (0.03)	7.40 (0.02)†	7.39 (0.02)
$Paco_2$	39 (4)	41 (4)	40 (4)	41 (3)	44 (4)##	43 (4)	45 (4)*##	43 (4)	43 (2)#	41 (4)	41 (4)	40 (2)	40 (5)	42 (4)
Pao_2	281 (137)	290 (108)	274 (87)	290 (110)	182 (104)#	243 (99)#	226 (93)	238 (77)#	287 (79)	256 (65)	264 (71)	232 (67)	287 (110)	271 (104)
Svo_2			77 (6)	74 (5)	56 (13)***###	73 (4)	66 (7)***###	74 (4)	70 (5)##	73 (4)	71 (4)*#	74 (4)		
Cai	1.1 (0.1)	1.1 (0.1)††	0.9 (0.1)††	0.9 (0.1)†††	1.0 (0.1)#	0.9 (0.1)	1.0 (0.1)##	0.9 (0.1)#	1.0 (0.0)##	1.0 (0.1)##	1.0 (0.1)#	1.0 (0.1)##	1.2 (0.1)††	1.2 (0.1)†††

[a]Comparisons are made between methylene blue (MeBlu) and saline (Sal) groups at each time period. Comparisons are also made between time periods within each study group.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.005$; when compared with the Saline group: #$P < 0.5$; ##$P < 0.01$; ###$P < 0.001$; when compared with the Pre Drug value within each group.

†$P < 0.05$; ††$P < 0.01$; †††$P < 0.001$: when comparing with pre CPB.

HR = heart rate (beats/min); MAP = mean systemic blood pressure (mm Hg); Flow represents either cardiac output or arterial blood flow during cardiopulmonary bypass (CPB) (L/min); SVR = systemic vascular resistance (dynes/s/cm^5); Phenyl = phenylephrine (no. (%)); Lactate (); Hct = hematocrit (%); $Paco_2$ = arterial carbon dioxide (mm Hg); Pao_2 = arterial oxygen (mm Hg); Svo_2 = mixed venous oxygen saturation; Cai = ionized calcium (mEq/L)

need for vasopressor administration. For these patients additional therapies are necessary to maintain desired cardiovascular function and systemic organ perfusion. The mortality associated with vasoplegic syndrome typically ranges from 5%–10% (33,34). However, for patients who display vasoplegic syndrome for more than 48 hours, the mortality may be as high as 28.6% (15).

Risk factors for the development of vasoplegic syndrome include preoperative administration of ACEi, calcium channel blockers, IV heparin (35), and the presence of active endocarditis (21). Procedural risk factors include longer CPB times and systemic normothermic temperature management during CPB (34). The present study involved patients receiving ACEi scheduled for cardiac surgery requiring CPB managed with systemic normothermia. ACEi reduce angiotensin II levels and also the breakdown of endogenous bradykinin, which mediates their vasodilatory effects through the NO pathway. Metabolism of bradykinin occurs in the pulmonary system, which is bypassed during CPB, resulting in increased serum levels, which has been directly correlated with changes in MAP and SVR during CPB (3,17,31). The present study demonstrated increased MAP and SVR after administration of methylene blue for patients taking ACEi.

Doses of methylene blue range from 1.5 to 2.0 mg/kg, and in one case report was followed by a continuous infusion of 0.5 $mg \cdot kg^{-1} \cdot h^{-1}$. Initial hemodynamic benefits of methylene blue were demonstrated for patients with septic shock, those undergoing liver transplantation, and a for variety of cardiac surgical scenarios (9,10,12–15,36). For a patient with septic shock an initial dose of 2 mg/kg of methylene blue followed by an infusion for 6 hours resulted in improved MAP and SVR, reduced the need for vasoactive medications, and improved oxygen delivery for approximately 24 hours (36). During surgery for orthotopic liver transplantation, methylene blue improved systemic pressures, reduced the need for epinephrine, and was associated with reduced systemic lactate levels (11).

Three studies have evaluated the benefits of methylene blue for cardiac surgical patients who are at risk for or who have developed vasoplegic syndromes (10,14,15). When administered in the preoperative period, the perioperative benefits of methylene blue have included greater hemodynamic stability, less inotropic support (7/50 versus 25/50), less fluid administration, fewer blood transfusions, and shorter intensive care unit and hospital stays (14). Furthermore, when administered as a prophylactic, no patient receiving methylene blue experienced vasoplegic syndrome compared with 26% in the placebo group (14). In another study of 54 patients diagnosed with postoperative vasoplegic syndrome, methylene blue improved hemodynamics and reduced vasopressor requirements in 51 (92%) patients. This was associated

Table 4. Percentage Differences in Systemic Vascular Resistance (SVR) Among Different Time Periods as Listed Below[a]

	Time periods for which the SVR is compared						
	Pre CPB–Pre Drug	Pre Drug–Post Drug	Pre Drug–CPB 20	Pre Drug–CPB 40	Pre Drug–CPB 60	Pre Drug–Post CPB	Pre CPB–Post CPB
Methylene blue	−39.0 (15.5)	21.4 (27.2)**	16.4 (28.6)*	18.8 (33.3)*	12.4 (32.7)	9.3 (20.0)	−34.5 (19.7)
Saline	−25.6 (23.6)	−7.9 (18.3)	−3.2 (17.7)	−3.5 (16.6)	2.4 (24.4)	−3.4 (26.6)	−29.9 (23.8)
	Time periods for which the mBP is compared						
	Pre CPB–Pre Drug	Pre Drug–Post Drug	Pre Drug–CPB 20	Pre Drug–CPB 40	Pre Drug–CPB 60	Pre Drug–Post CPB	Pre CPB–Post CPB
Methylene Blue	−34.1 (10.8)	21.4 (27.2)**	17.8 (29.5)*	21.4 (31.5)*	14.0 (33.4)	41.3 (31.8)	−9.3 (11.6)
Saline	−23.9 (16.5)	−7.1 (17.3)	−2.3 (17.3)	−2.4 (16.5)	2.5 (23.0)	23.0 (29.2)	−9.2 (17.7)

[a]Changes were assessed by comparing the hemodynamic data measured prior to administration of the study drug to each time period. A negative value represents a reduction in SVR from either Prior to cardiopulmonary bypass (CPB), or prior to administration of the study drug (Pre Drug).

*$P < 0.05$; **$P < 0.005$: When compared with the changes seen in the saline group.

with a reduction in systemic lactate levels (10). In another postoperative study, 56 of 638 (8.8%) cardiac surgical patients were diagnosed with vasoplegic syndrome and these were randomized to receive 1.5 mg/kg of methylene blue or placebo (15). Compared with patients in the placebo group, those treated with methylene blue had less mortality (0% versus 21.4%), less renal failure (0% versus 14.3%), less respiratory failure (0% versus 14.3%), fewer incidences of supraventricular tachyarrhythmias (7% versus 28.6%), and reduced incidence of sepsis and multiorgan failure (0% versus 25%) (15). In the present study, a relatively larger dose of methylene blue (3 mg/kg) was given to high-risk patients (ACEi) after institution of CPB and decline in SVR and MAP. Consistent with previous data, methylene blue improved hemodynamics in association with lower serum lactate levels (10,14). Together these studies demonstrate a consistent benefit of methylene blue administered at three different times (preoperative, intraoperative, and postoperative) during the perioperative period.

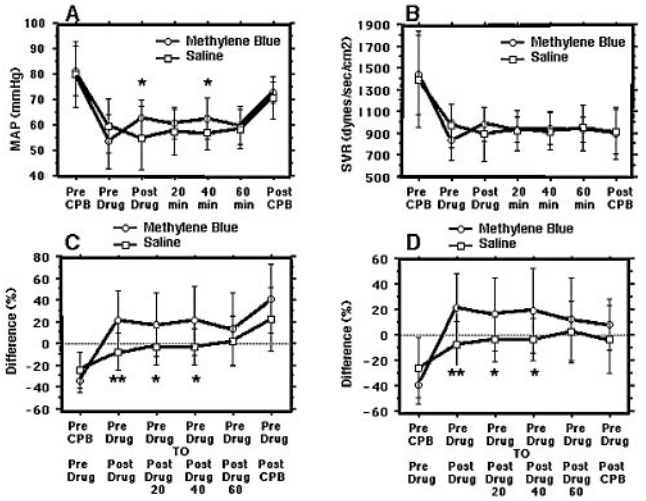

Figure 1. In conjunction with Tables 3 and 4, these graphs highlight the mean changes and SD (error bars) of hemodynamics during the study period. Panels A and B show the mean systemic blood pressure (MAP; mm Hg) and systemic vascular resistance (SVR; dynes/s/cm^5) at different time periods. Panels C and D show the percent differences (%) of MAP and SVR among different time periods. Although the first data point in panels C and D compare pre-cardiopulmonary bypass (pre CPB) hemodynamics with those after institution of CPB but before administration of the study drug (preDrug), the remaining data points compare the preDrug data to that obtained at various time points thereafter as described in Methods. These included 10, 20, 40, and 60 min after the administration of the study drug and then after separation from CPB. Actual data are recorded in Tables 3 and 4 * $P < 0.05$; ** $P < 0.005$.

The small sample size of the current study limits conclusions regarding the safety of methylene blue. However, our results in conjunction with other studies suggest that methylene blue can be administered with relatively few adverse effects. To the best of our knowledge, methylene blue has not been associated with significant compromise of pulmonary function, which may be of concern considering the beneficial effects of NO on pulmonary vascular tissues and gas exchange (36,37). With regard to the present study, during which hemodynamic data were recorded during CPB, gas exchange was achieved through the CPB circuit. However, no dysfunction was noted during the post CPB period, nor has this been reported in previous studies (9,10,12–15,20). Although such considerations are beyond the scope of this manuscript, these data either suggest that the mechanism of methylene blue is more complex, and/or that other chemical mediators affect pulmonary function and gas exchange (38,39).

The administration of aprotinin, aminocaproic acid, anesthetic medications, and the management of anemia were not controlled for in the present study. Although no significant differences were noted between groups in the present study, this study was not powered to discern such differences in these factors.

Although the statistical analysis did not demonstrate an impact of preoperative demographic variables on the study's outcome, these were not specifically controlled for, and therefore we may not be able to make definitive claims that these variables, which may have an impact on the inflammatory system (e.g., use of antifibrinolytics, or left ventricular ejection

fraction), could not have affected the results. Furthermore, the present study did not measure systemic catecholamines nor assays of inflammatory mediators to further define the impact of these chemicals on the data obtained.

In conclusion, methylene blue improved hemodynamics during CPB and reduced the need for vasopressors during and after CPB. In conjunction, systemic lactate levels were reduced, suggesting that methylene blue improves systemic organ blood flow and tissue perfusion. Methylene blue is a useful adjunct for treating hypotension during CPB for patients receiving preoperative ACEi.

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