

Methylene Blue Administration in Severe Systemic Inflammatory Response Syndrome (SIRS) after Thoracic Surgery

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A 66-year-old male patient developed significant pleural effusion on the right side six years after coronary bypass grafting and mitral valve replacement. After pleurocentesis, hemothorax developed and finally resulted in complete atelectasis of the right lung. Three weeks later, the patient was transferred to our department, and underwent a right lateral thoracotomy. The hematoma was removed and a complete decortication was performed. Four hours postoperatively the patient developed severe SIRS with beginning multiorgan failure. Even extremely high doses of norepinephrine could not raise the systemic vascular resistance. Single intravenous administration of methylene blue led to significant and permanent improvement of the hemodynamic status. (Ann Thorac Cardiovasc Surg 2002; 8: 306–10)

Key words: methylene blue, systemic inflammatory response syndrome (SIRS), thoracic surgery, vasoactive therapy

Introduction

Response to injury is usually appropriate in degree and is self-limited. In more severe injury, response may persist inappropriately, leading to severe systemic inflammatory response syndrome (SIRS), multiorgan dysfunction (MOD) and possibly to multiorgan failure (MOF). In the case of SIRS there are more than one of the following physiologic changes in absence of other known causes for such abnormalities: (1) a body temperature of $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, (2) a heart beat rate of $>90 \text{ min}^{-1}$, (3) tachypnea $>20 \text{ breaths} \cdot \text{min}^{-1}$ or hyperventilation, as indicated by a $\text{PaCO}_2 <4.3 \text{ kPa}$, (4) an alteration of the white blood body count (WBC) of $>12.000 \text{ cells} \cdot \text{mm}^{-3}$, $<4.000 \text{ cells} \cdot \text{mm}^{-3}$, or the presence of $>10\%$ immature neutrophils.¹⁾ The biochemical processes inducing SIRS are still unclear. Therefore, in

exception of some questionably successful efforts with administration of anticytokines and plasmapheresis, the therapy in case of SIRS has been mostly symptomatic. The most important symptom which has to be treated primarily is circulatory failure with low systemic vascular resistance (SVR) and consequently low mean arterial pressure. This significant fall of arterial pressure results in a reduction of organ system perfusion, which may lead to MOD and MOF with high mortality rates, ranging from 30-80% depending on the number of failed organs.²⁾

The classic symptomatic therapy consists of volume infusion and intravenous administration of catecholamines in order to maintain an adequate cardiac output. The low vascular resistance is treated by a vasoconstrictor agent (e.g., norepinephrine) to achieve mean arterial pressures of at least 60 mmHg. We present the case of a patient after thoracic surgery, in which norepinephrine therapy was not effective, whereas administration of methylene blue resulted in a rapid and long lasting improvement of systemic hemodynamics.

Case Report

A 66-year-old male patient was admitted to a peripheral

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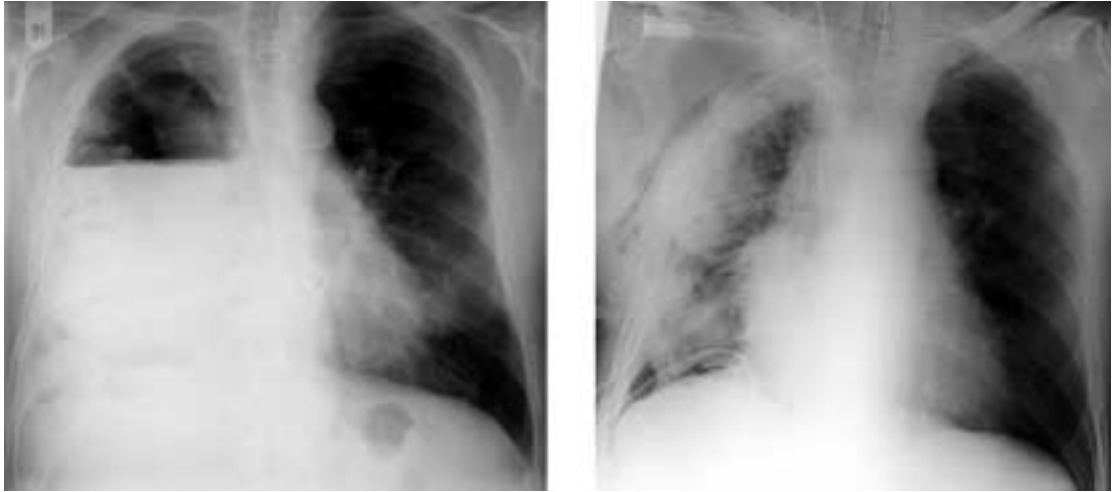


Fig. 1. Chest X-ray in a patient with hemopneumothorax at the right side before (a) and after (b) thoracic surgery.

a | b

hospital with clinical signs of left ventricular failure. Six years previously he had undergone coronary bypass grafting and mitral valve replacement due to a severe coronary artery disease and mitral valve stenosis. An atrial fibrillation had been treated with digoxin and phenprocoumon for approximately 15 years. Additionally the patient had a history of mild pulmonary hypertension and chronic renal insufficiency. There were no signs of acute myocardial infarction or ischemia. A trans-thoracic echocardiography revealed a normal function of MVR without vegetation and no thrombosis. The chest X-ray showed significant pleural effusion on the right side (Fig. 1a). After stopping anticoagulation with phenprocoumon (Quick 62%) and beginning of continuous intravenous heparin administration, pleurocentesis was performed. This procedure was followed by development of a massive hemopneumothorax, due to prolonged prothrombin time (49 s). A chest tube was inserted, but the hematoma could not be drained entirely. The hematoma could not be evacuated. Due to respiratory deterioration and unsuccessful drainage a computed tomography scan of the chest was performed. This showed a complete atelectasis of the right lung and a massive and partially organized hematoma in the right pleural cavity. For surgery the patient was transferred to our department. A right lateral thoracotomy was performed and more than 3 l mostly organized hematoma were removed. The right lung was completely collapsed and complete decortication performed (Fig. 1b). After

surgery the patient was transferred to our intensive care unit in a stable hemodynamic condition with a low dose inotropic support. Mechanical ventilation (EVITA, Dräger Inc.) with biphasic airway pressure ventilation and inverse ratio was performed (pressure level 1: 24 mbar, pressure level 2: 8 mbar, 4 s: 2 s). Four hours postoperatively a rapid and significant fall of the arterial pressure developed. A Swan-Ganz catheter was placed. This revealed a low SVR of $430 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ and a high cardiac output (CO) of $8.9 \text{ l}\cdot\text{min}^{-1}$, mixed venous oxygen saturation (SvO₂) was 78%. A continuous intravenous administration of norepinephrine was started, and sufficient mean arterial blood pressures (MAP) of at least 65 mmHg could be achieved. A few hours later a new reduction of SVR ($279 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$) and MAP (46 mmHg) occurred, the mean heart beat rate was $120\text{--}134 \text{ min}^{-1}$, the central body temperature has shown an increase from 36.1 to 39.1°C. A respiratory rate of $26 \text{ breaths}\cdot\text{min}^{-1}$ was manifested. In this time the WBC increased from 9.800 to $20.200 \text{ cells}\cdot\text{mm}^{-3}$ and decreased within two days to $11.200 \text{ cells}\cdot\text{mm}^{-3}$. The blood lactate concentration had risen to $18 \text{ mg}\cdot\text{dL}^{-1}$. In order to achieve an adequate coronary and organ system perfusion, the administration rate of norepinephrine was raised up to $165 \text{ }\mu\text{g}\cdot\text{min}^{-1}$, resulting in elevation of SVR to $408 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$, and MAP to 70 mmHg. Acute renal failure made a continuous veno-venous hemodiafiltration (CVVHDF) necessary.

After a new fall of SVR and MAP 30 minutes later in spite of maximal doses of catecholamines, an intravenous



Fig. 2. Registration of blood pressure in a patient with severe SIRS before and after administration of 2 mg*kg⁻¹ methylene blue.

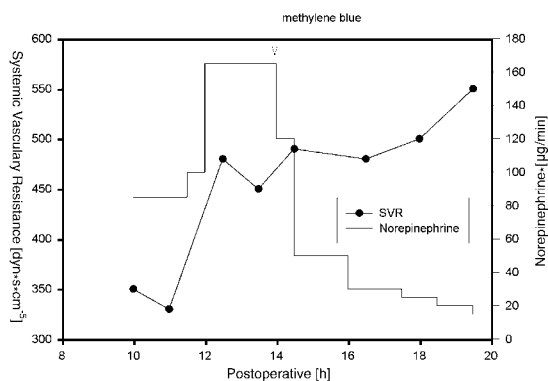


Fig. 3. Development of systemic vascular resistance and dose of norepinephrine after single dose of 2 mg*kg⁻¹ methylene blue.

administration of methylene blue in a dosage of 2 mg*kg⁻¹ body weight over 15 minutes was started. Shortly after injection hemodynamic stabilization was achieved. Norepinephrine dosage could be reduced (Fig. 2) and hemodynamic parameters remained stable (SVR: 471-486 dyn*s*cm⁻⁵, MAP 68-70 mmHg (Fig. 3). The effect was permanent and the reduction of norepinephrine dose could be continued (Table 1). Hemodynamic improvement was

followed by the onset of diuresis after 48 h of CVVHDF. Lactate concentration fell from a maximum of 18 mg*dL⁻¹ to 6 mg*dL⁻¹ within seven hours. After 72 hours all inotropic and vasoactive drugs could be stopped and the patient showed a complete hemodynamic recovery. Side effects were not observed. All the microbial cultures from blood and endotracheal samples obtained from our patient were negative, and there were no signs of an infectious focus.

Discussion

The surgical trauma associated with the (partial) reexpansion of the right lung, which had been compressed and atelectatic for more than 10 days is the most probable cause of a massive release of mediators from the altered lung tissue and the following severe SIRS. Via receptor regulated mechanisms different neurotransmitters (e.g., acetylcholine, adenosinetriphosphate and substance P), hemostasis regulating factors (e.g., adenosinediphosphate, serotonin, bradykinin and thrombin) and biogenic amines (e.g., norepinephrine and histamine) induce synthesis and release of two endothelial autocoïdes: endothelium derived relaxant factor (nitric

Table 1. Hemodynamic changes and laboratory data after thoracic surgery in a patient with severe SIRS

Time [h]	MAP [mmHg]	PAP (mean) [mmHg]	CVP [mmHg]	CO [$l \cdot \text{min}^{-1}$]	PCWP [mmHg]	SVR [$\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$]	PVR [$\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$]	SvO ₂ [%]	Lactate [$\text{mg} \cdot \text{dL}^{-1}$]	NE [$\mu\text{g} \cdot \text{min}^{-1}$]	E [$\mu\text{g} \cdot \text{min}^{-1}$]
1	68		24						1.3	0	3
2	54		20						1.5	0	3
3	54	19	19	8.1	16	385	123	61	1.9	5	10
4	55	14	14	7.4	17	378	119		3.8	10	5
5	48	12	12	8.6	16	334	114		8	10	5
6	48	18	18						10	10	5
7	45	19	18						11.2	10	3
8	47	21	18	8.7	17	340	125		12.2	10	3
9	48	26	20						14	40	3
10	46	28	19	10	18	350	120	65	14.9	85	3
11	46	32	17	9.5	18	330	100		16.1	140	3
12	50	31	16			410	140		17	165	0
13	64	35	20	9.6	19	480	175		18	165	0
14	78	37	23	9.8		450	145		17	120	0
15	72	43	24	9.3	19	490	170	78	16	50	0
16	69	38	19						14	50	0
17	67	38	17	8.2		480	160		13.4	30	0
18	61	26	16	8		500	160		7	25	0
19	62	33	14						6.5	25	0
20	63	39	16	7.5		550	150	67	6	15	0

Time, hours after end of surgery; MAP, mean arterial blood pressure; PAP, pulmonary arterial pressure; CVP, central venous pressure; CO, cardiac output; PCWP, pulmonary wedge pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; SvO₂, mixed-venous oxygen saturation; NE, norepinephrine; E, epinephrine

oxide, NO) and prostacyclin (PGI₂). NO stimulates the soluble guanylate cyclase in smooth muscle cells directly. This results in an increase of cyclic GMP (cGMP) level followed by vasodilation.^{3,4)} The biogenic amines (e.g., serotonin, histamine and norepinephrine) have either an endothelium-dependent (NO-mediated) dilating or a direct (endothelium-independent) constricting effect on vessels. The end response is a result of the interaction of these two contradictory effects. A dysfunction of this balanced system by an overproduction and massive release of mediators results in an excessive vasodilation and clinical manifestation of SIRS. The clinical SIRS-criteria was in this case fulfilled (consensus conference¹⁾).

Putensen and Wrigge⁵⁾ showed that mechanical ventilation in patients with acute lung injury may encourage the development of SIRS, whereas SIRS can not be induced by an aggressive ventilation mode in patients without a preexisting lung injury. In the presented case the patient needed a quite aggressive ventilation mode after surgery. In combination with the preexisting lung injury this may result in an additional factor inducing SIRS. The most common therapy of low SVR consists in achieving and maintaining an adequate vasomotor tone by using the described direct effect of norepinephrine and volume

infusion.

Garcia-Fernandez et al.⁶⁾ showed that an early start of a continuous renal replacement therapy in patients with a SIRS results in a better outcome.

In the presented case this strategy was ineffective. Because of the continuous hemodynamic deterioration with consequently reduced organ system perfusion and a beginning MOF the patient was in a critical and life-threatening situation. An alternative strategy for achieving an adequate vascular resistance consists in reduction of cGMP level in vascular smooth muscle cells by inhibition of guanylate cyclase, which is stimulated by an excessive release of NO. Methylene blue is a strong inhibitor of guanylate cyclase, and it has been successfully used for treatment of low SVR in patients with SIRS after cardiopulmonary bypass⁷⁾ and septic shock.³⁾ Although this therapy is not causal as well, it describes an additional option to the classic therapy of high dose norepinephrine in similar critical cases. In this case of severe SIRS the administration of norepinephrine alone, even in the highest doses ($165 \mu\text{g} \cdot \text{min}^{-1}$), did not result in a normal range SVR. In the presented case refractory hypotension of MAP 40 mmHg and beginning cardiac failure, a single dose of methylene blue ($2 \text{ mg} \cdot \text{kg}^{-1}$) given intravenously

was remarkably effective, so that the norepinephrine administration rate could be reduced significantly within a short term of time. In spite of this significant norepinephrine reduction the SVR rose gradually resulting in cardiocirculatory stabilization. Decrease of lactate concentration within seven hours after methylene blue administration, could not be explained only by an improvement of tissue perfusion and consequently cellular oxygenation, but additionally due to the reductor properties of methylene blue itself.³⁾

Conclusion

Low SVR in severe SIRS after lung surgery and unsuccessful norepinephrine therapy attempt can be treated successfully by a guanilate cyclase inhibitor: methylene blue. A single dose infusion of methylene blue was remarkably effective, side effects were not observed. Further studies are required in order to define the exact criteria of indication, the optimum dose and administration time.

References

1. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; **20**: 864–74.
2. Baue AE, Durham R, Faist E. Systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), multiple organ failure (MOF): are we winning the battle? *Shock* 1998; **10**: 79–89.
3. Preiser JC, Lejeune P, Roman A, et al. Methylene blue administration in septic shock: a clinical trial. *Crit Care Med* 1995; **23**: 259–64 .
4. Ignarro LJ. Biological actions and properties of endothelium-derived nitric oxide formed and released from artery and vein. *Circ Res* 1989; **65**: 1–21.
5. Putensen C, Wrigge H. Ventilator-associated systemic inflammation in acute lung injury. *Intensive Care Med* 2000; **26**: 1411–3.
6. Garcia-Fernandez N, Lavilla FJ, Rocha E, Purroy A. Haemostatic changes in systemic inflammatory response syndrome during continuous renal replacement therapy. *J Nephrol* 2000; **13**: 282–9.
7. Yiu P, Robin J, Pattison W. Reversal of refractory hypotension with single-dose methylene blue after coronary bypass surgery. *J Thorac Cardiovasc Surg* 1999; **118**: 195–6.