Reversal of severe vasoplegia with single-dose methylene blue after heart transplantation

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Low vascular resistance after cardiopulmonary bypass occurs fairly frequently.[1,3] In the early postoperative phase after heart transplantation, decrease of blood pressure might be aggravated by the effects of antigen release from the donor organ and acute inflammatory response. Decrease of systemic resistance in patients after cardiac transplantation may lead to significant organ hypoperfusion and is usually treated with vasoconstrictors. We report a case of a patient early after heart transplantation in a severe hyperdynamic state, including high cardiac output and low vascular resistance, who was successfully treated with a single dose of methylene blue.

Clinical Summary

A 55-year-old man with congestive heart failure (cardiac index, 1.8 $L \cdot min^{-1} \cdot m^{-2}$) with an automatic implantable cardioverter defibrillator device underwent orthotopic bicaval cardiac transplantation and explantation of the automatic implantable cardioverter defibrillator device. The underlying disease was a dilative cardiomyopathy with a history of myocarditis. Preoperative evaluation revealed impaired left ventricular systolic function (ejection fraction, 20%) and moderate pulmonary hypertension (mean pulmonary artery pressure, 28 mm Hg). The patient was on a program of furosemide, spironolactone, amiodarone, metoprolol, captopril, and digitoxin preoperatively. His clinical status reached New York Heart Association class IV. Blood pressure was 100/60 mm Hg preoperatively.

Cold ischemia time was 158 minutes, and aortic clamp time was 31 minutes. The patient was separated from cardiopulmonary bypass without problems after a reperfusion time of 60 minutes. Thereafter, his blood pressure progressively sagged. The central venous pressure was 10 mm Hg, and the hemoglobin level was 8.1 g/dL. Blood loss was negligible, and oxygen tension was 375 mm Hg on an inspired oxygen fraction of 1.0 at transfer to the intensive care unit. Online hemodynamic monitoring revealed a cardiac output of 11.2 L/min and a systemic vascular resistance of 480 dynes $\cdot s^{-1} \cdot cm^{-5}$ under norepinephrine infusion at a rate of 0.37 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Over the course of 4 hours, the requirement for norepinephrine to maintain a systolic blood pressure above 100 mm Hg escalated to 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Methylene blue was given intravenously (2 mg/kg body weight) over 30 minutes, resulting in an immediate rise in blood pressure. One hour after administration, norepinephrine requirements decreased to 0.22 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and 6 hours later, norepinephrine could be discontinued. Figure 1 demonstrates the norepinephrine requirements over time, together with pulmonary artery pressure, mean arterial pressure, and central venous pressure recordings. No additional methylene blue was necessary, and minimal intravenous doses of epinephrine were administered after the second postoperative day, according to our regular strategy after heart transplantation.

Hemodynamic status remained stable over the next days. Fever did not occur, and no signs of an inflammatory response, such as high leukocyte counts and C-reactive protein, could be documented. Creatine kinase levels peaked at 673 IU after 60 hours and creatine kinase MB levels peaked at 53 IU after 2 hours postoperatively and decreased gradually. Immunosuppression was started 6 hours after procedure with antithymocyte globulin (100 mg), which was administered daily for 3 consecutive days. Cyclosporine (INN: ciclosporin) was started on day 3 after transplant because of an initial increase of creatinine and urea serum levels. Urine was discolored, but its quantity was normal. Postoperative nonoliguric renal dysfunction persisted until day 10 after transplantation and resolved with medical treatment. Further laboratory findings, including pancreatic enzyme levels, blood cell counts, and coagulation factors remained within normal postoperative ranges. The first postoperative biopsy specimen was free of rejection. Cyclosporine blood levels were responsive on usual dose modifications. We do not have a reason to suspect any drug interaction of methylene blue with any of the usually administered post-transplantation medications. The patients' clinical condition is excellent 2 months after transplantation.

Discussion

Decrease of vascular tone after cardiac transplantation is believed to occur because of (1) general inflammatory response to cardiopulmonary bypass[1] and (2) release of antigens from graft tissue, which activate host immune mechanisms that become operative in the early reperfusion phase.[1,3] An adequate blood pressure, however, is required for sufficient organ perfusion and undisturbed graft function during the early postoperative time. Vasoplegia at this stage can be severe and refractory to conservative therapy and fluid administration. After orthotopic heart transplantation, loss of

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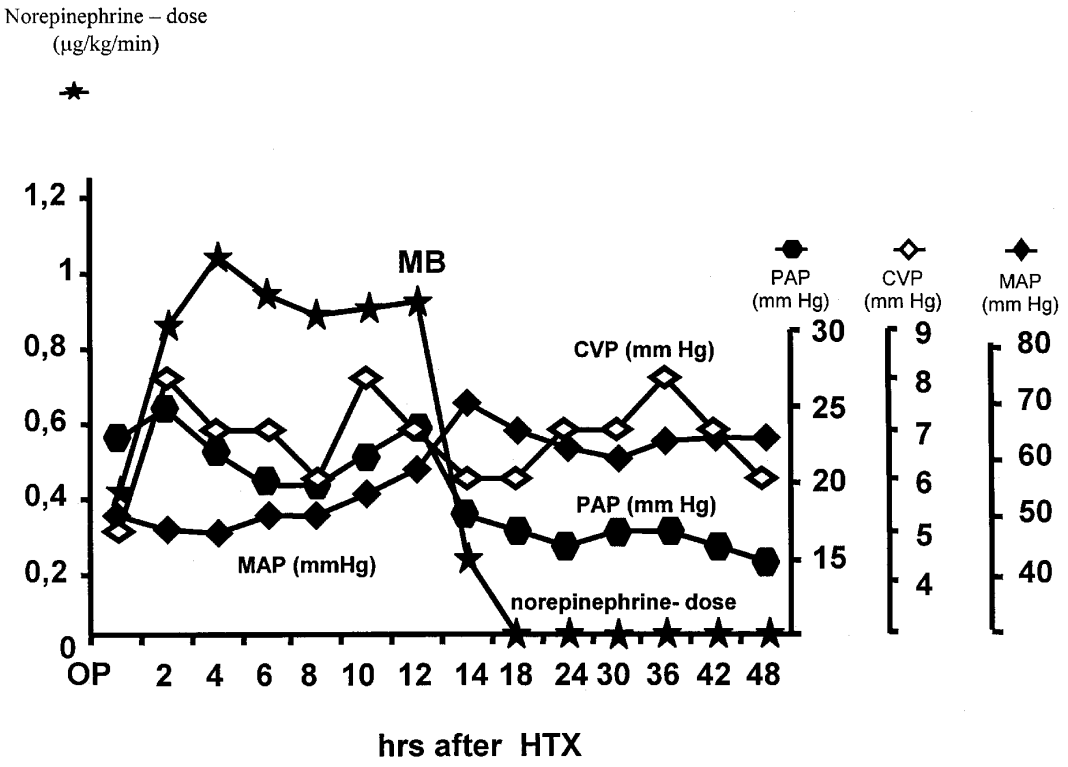

Figure 1. Administration of methylene blue results in an immediate fall of norepinephrine requirements and a consequent rise of blood pressure. Mean pulmonary artery pressure curve descends parallel to withdrawal of norepinephrine.

peripheral vascular resistance may become life-threatening with respect to the limitations of right-sided heart function. The underlying mechanism is believed to be increased nitric oxide synthesis, which in turn stimulates guanylate cyclase and activates the production of cyclic guanosine 3´,5´ monophosphate (cGMP), resulting in vascular relaxation.[4] Methylene blue inhibits guanylate cyclase, avoiding the cGMP-dependent vasorelaxant effect of nitric oxide in the smooth muscle of the vessels. Myles and colleagues[4] failed to identify an increase in nitric oxide release after CPB by means of analysis of urine nitrite-nitrate levels. Evora and colleagues[2] speculate on the existence of a distinct, nonnitric, cGMP-dependent pathway with different receptors, different G proteins, or both, or else a sensitization of vascular smooth muscle cells to the action of nitric oxide, as hypothesized by Yiu and colleagues.[3] On the basis of this theoretic background, methylene blue has also been administered to treat sepsis and anaphylactic shock.[2,5]

To our knowledge, we report the first experience of vasoplegia treatment with methylene blue after heart transplantation and believe that this drug deserves our attention because of its catecholamine-saving effect, thus preventing possible malperfusion. The postoperative course of our patient after orthotopic heart transplantation did not differ from others in which methylene blue was not used, except from the impressive shortening of norepinephrine administration, volume saving, and decrease of monitoring requirements in the intensive care unit. We did not identify any adverse drug interactions with immunosuppressive drugs or significant organ malfunction. Further studies are necessary to identify possible mechanisms and side effects of the use of methylene blue after cardiac operations.

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