

Twenty years of vasoplegic syndrome treatment in heart surgery. Methylene blue revised

Vinte anos de tratamento da síndrome vasoplégica em cirurgia cardíaca. Azul de metileno revisado

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Abstract

Objective: This study was conducted to reassess the concepts established over the past 20 years, in particular in the last 5 years, about the use of methylene blue in the treatment of vasoplegic syndrome in cardiac surgery.

Methods: A wide literature review was carried out using the data extracted from: MEDLINE, SCOPUS and ISI WEB OF SCIENCE.

Results: The reassessed and reaffirmed concepts were 1) MB is safe in the recommended doses (the lethal dose is 40 mg/kg); 2) MB does not cause endothelial dysfunction; 3) The MB effect appears in cases of NO up-regulation; 4) MB is not a vasoconstrictor, by blocking the cGMP pathway it releases the cAMP pathway, facilitating the norepinephrine vasoconstrictor effect; 5) The most used dosage is 2 mg/kg as IV bolus, followed by the same continuous infusion because plasma concentrations sharply decrease in the first 40 minutes; and 6) There is a possible “window of opportunity” for MB’s effectiveness. In the last five years, major challenges were: 1) Observations about side effects; 2) The need for prophylactic and therapeutic guidelines,

and; 3) The need for the establishment of the MB therapeutic window in humans.

Conclusion: MB action to treat vasoplegic syndrome is time-dependent. Therefore, the great challenge is the need, for the establishment the MB therapeutic window in humans. This would be the first step towards a systematic guideline to be followed by possible multicenter studies.

Descriptors: Methylene blue. Vasoplegic syndrome. Vasoplegia. Circulatory shock. Cardiac surgery. Nitric oxide.

Resumo

Objetivo: O presente estudo foi realizado com a finalidade de reavaliar conceitos estabelecidos em 20 anos, com ênfase nos últimos 5 anos, sobre a utilização do azul de metileno no tratamento da síndrome vasoplégica em cirurgia cardíaca.

Métodos: Foram considerados dados da literatura utilizando-se três bases de dados (MEDLINE, SCOPUS e ISI Web of Science).

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Abbreviations, acronyms & symbols	
ARDS	Acute respiratory distress syndrome
cAMP	Cyclic adenosine monophosphate
BBB	Blood-brain barrier
CPB	Cardiopulmonary bypass
GC	Guanylate cyclase
IE	Infective endocarditis
iNOS	Inducible nitric oxide synthase
LVAD	Left ventricular assist device
MB	Methylene blue
NO	Nitric oxide
RVEDP	Right ventricle end diastolic pressure
sGC	Soluble guanylate cyclase
VHS	Valvular heart surgery
VS	Vasoplegic syndrome

Resultados: Os conceitos reavaliados e reafirmados foram:

1) Nas doses recomendadas o AM é seguro (a dose letal é de 40 mg/kg); 2) O AM não causa disfunção endotelial; 3) O

efeito do AM só aparece em caso de supra nivelamento do NO; 4) O AM não é um vasoconstritor, pelo bloqueio da via GMPc ele libera a via do AMPc, facilitando o efeito vasoconstritor da norepinefrina; 5) A dosagem mais utilizada é de 2 mg/kg, como bolus EV, seguida de infusão contínua porque as concentrações plasmáticas decaem fortemente nos primeiros 40 minutos, e; 6) Existe uma “janela de oportunidade” precoce para efetividade do AM. Nos últimos cinco anos, os principais desafios foram: 1) Observações de efeitos colaterais; 2) A necessidade de diretrizes, e; 3) A necessidade da determinação de uma janela terapêutica para o uso do AM em humanos.

Conclusão: O efeito do AM no tratamento da SV é dependente do tempo, portanto, o grande desafio atual é a necessidade do estabelecimento da janela terapêutica do AM em humanos. Esse seria o primeiro passo para a sistematização de uma diretriz a ser seguida por possíveis estudos multicêntricos.

Descritores: Azul de metileno. Síndrome vasoplégica. Vasoplegia. Choque circulatório. Cirurgia cardíaca. Óxido nítrico.

INTRODUCTION

The vasoplegic syndrome (VS) concepts are a valuable Brazilian contribution to cardiac surgery. Gomes^[1-3] described the syndrome and the MB treatment was proposed by Evora et al.^[4-8]. VS is a constellation of signs and symptoms: hypotension, high cardiac index, low systemic vascular resistance, low filling pressures, diffuse bleeding tendency, and sustained hypotension despite the use of high doses of vasoconstrictor amines. There is experimental and clinical evidence to show that the pathophysiology of VS is associated with endothelial dysfunction caused by systemic inflammation. The most important mediator is nitric oxide (NO) produced from L-arginine by polymorphonuclear blood cells. NO release is dependent on the expression of inducible nitric oxide synthase (iNOS). It has been demonstrated along the years, that the blockade of NO synthesis is associated with prohibitive morbidity and mortality by microcirculation impairment. This has led to the proposition of using MB, a blocking of soluble guanylate cyclase (sGC), an enzyme whose expression is related to the formation of cGMP, which is the final messenger of the NO pathway responsible for vasoplegia.

Although MB has been used for over 20 years in the treatment of VS, there are few quality clinical studies that would allow the treatment to become a protocol. Three studies involving a higher number of patients deserve to be cited: 1) In 2003, Leyh et al.^[9] reported, in Germany, 54 cases of cardiac surgery patients not carrying bacterial endocarditis who had been treated with MB, with over 90% of the patients responding to the treatment. 2) Levin et al.^[10-12], in Argentina,

reported the incidence of 8.8% of VS in 638 patients. Among the 56 vasoplegic patients randomly receiving MB or placebo, there was no mortality in the group treated with MB, and it was possible to discontinue vasoconstrictors in a short period time, with less consequential morbidity and mortality. In contrast, in the placebo group two deaths occurred and the use of amines lasted in average 48 hours, with a higher incidence of respiratory and renal problems. 3) From the prevention point of view, Ozal et al.^[13], in Turkey, showed in a prospective and randomized study that MB was associated to with lower incidence of vasoplegia and amines use.

In 2009, targeting MB for VS treatment in heart surgery, we published a personal statement including fifteen years of questions, answers, doubts and certainties. Some observations can be applied to VS: 1) MB is safe in the recommended doses (the lethal dose is 40 mg/kg). 2) The use of MB does not cause endothelial dysfunction. 3) The MB effect appears in cases of NO up-regulation. 4) MB is not a vasoconstrictor, by blocking the cGMP pathway it releases the cAMP pathway, facilitating the epinephrine vasoconstrictor effect. 5) It is possible that MB acts through this “crosstalk” mechanism and its use as a drug of first choice may not be right. 6) The most used dosage is 2 mg/kg as IV bolus followed by the same continuous infusion because the plasma concentrations sharply decrease in the first 40 minutes. 7) Although there are no definitive multicentric studies, the MB used to treat heart surgery VS, at the present time, is the best, safest and cheapest option. 8) But there is a possible 'window of opportunity' for the MB's effectiveness^[14].

The above observations, drawn from 15 years, of use of MB, were presented in the introduction of this text as a

reaffirmation of concepts. However, the ultimate aims will be centered in the subsequent five years (2009-2014).

The relevant literature review (1994-2008) will be updated, emphasizing that the great majority of the articles are letters and case reports as well as and some excellent reviews. Most of the present discussion is based on our letters motivated against the concept that MB is a rescue and not a first line therapy. This study was carried out to critically examine the use of MB in treating cardiac surgery VS, based on literature data and 20 years of clinical and experimental experience, highlighting what has been going in the last 5 years. It was presented on the 22nd Annual Meeting of the Asian Society for Cardiovascular and Thoracic Surgery (Istanbul – April 2014).

The text will discuss the following points that address why the use of MB to treat cardiac surgery VS remains questionable: 1) Observations about side effects; 2) Restrictions in using MB in cases of pulmonary hypertension and acute respiratory distress syndrome (ARDS); 3) The need for prophylactic and therapeutic guidelines, and; 4) The need for the establishment of the MB therapeutic window in humans.

METHODS

A wide review of literature and the authors' documented observations over a period of 20 years was carried out using the data extracted from: MEDLINE, SCOPUS and ISI WEB OF SCIENCE. The following combinations of key words

were adopted: 1) “Methylene blue and heart surgery” or; 2) “Methylene blue and cardiac surgery”. This combination of MB with rather generic keywords was intentional in the sense obtaining a wider view of the subject.

RESULTS

The previous fifteen years bibliographical survey (1994 - 2009) on the therapeutic use of MB, based on MEDLINE and SCOPUS database searches, revealed a total of 58 publications directly related to VS in cardiac surgery. Approximately 30 more publications were added on the last five years (2010 - 2014).

Concerning the number of publications, there are about 70 publications, showing an increasing trend in the number of publications and citations (Figure 1).

Concerning the type of articles, there is prevalence of article reports (50-70%), reviews (21%), and letters (11-18%) (Figure 2).

The country of origin of the publications is shown on Figure 3.

DISCUSSION

It is crucial to emphasize the increasing number of citations. The prevalence of articles kept to the profile (case reports, letters, and reviews). Regarding the country of origin of the publications, Brazil has been the sixth place in the last five years, dropping four positions in the rank.

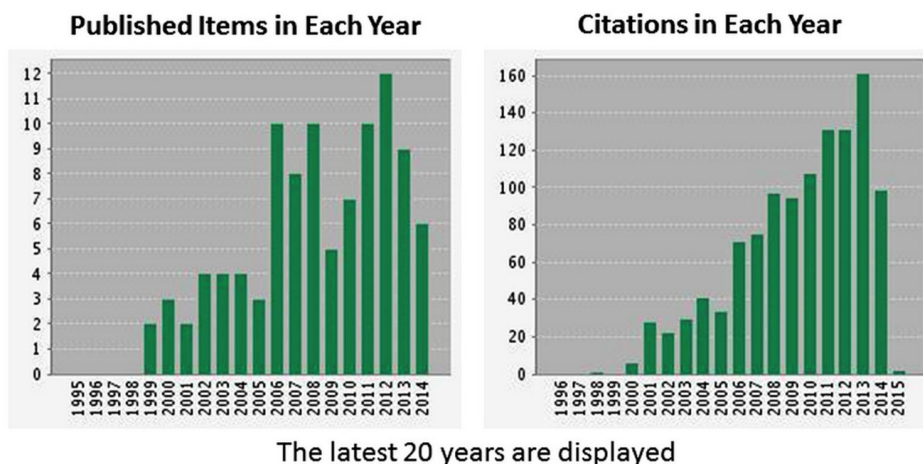


Fig. 1 - Published items and citations per year.

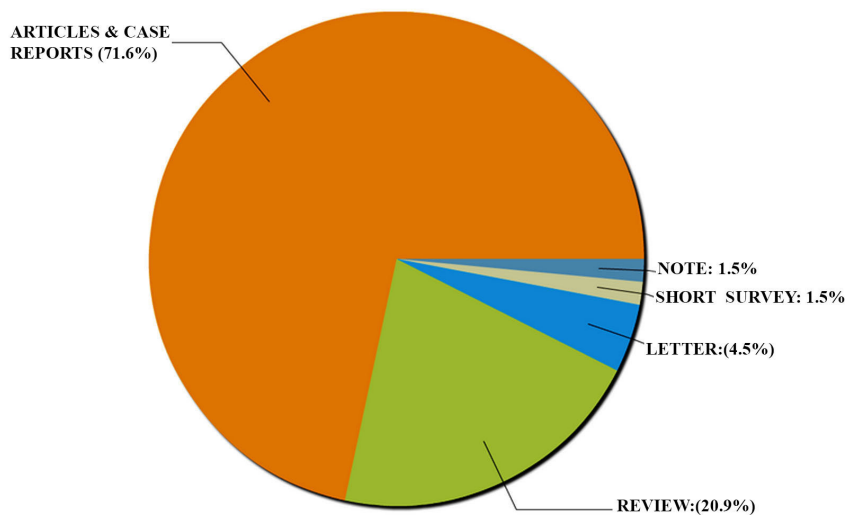


Fig. 2 - Types of articles.

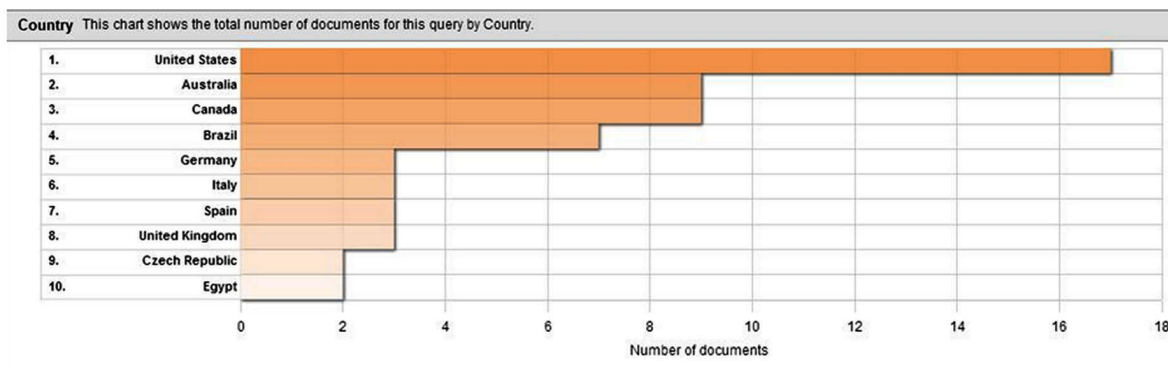


Fig. 3 - Country of origin of publications.

Conceptual aspects

One problem still present when describing VS is the lack of consistency in its definition. There is neither a clear definition, nor a single biomarker, and even the determination of nitrite/nitrate (NO_x) failed to characterize the syndrome^[15].

At present, clinical management of inflammatory vasoplegia associated to sepsis or anaphylaxis is symptomatic. Volume is expanded by administration of fluids, and low blood pressure is managed by administering positive inotropes and vasoconstrictors. This therapeutic approach is mainly associated with cyclic AMP (cAMP) and, many times the circulatory shock is refractory to high amines concentrations.

Methylene blue side effects (binomial efficiency/safety)

Methylene blue administration may also result in worsening of arterial oxygenation. The pathophysiology thought to be responsible for this finding is that MB leads to systemic vasoconstriction as well as pulmonary vasoconstriction. Impaired gas exchange in the lung and pulmonary hypertension are caused by this pulmonary vasoconstriction. The adverse pulmonary effects of MB may limit its use in patients with adult respiratory distress syndrome. In addition, high-doses of MB may also result in mesenteric bed constriction and compromise blood flow in mesenteric vessels^[16].

More recently, MB has been shown to cause a serotonin

syndrome reaction in patients who are concomitantly taking serotonergic agents such as serotonin reuptake inhibitors. This is attributable to an inhibitory action of MB on monoamine oxidase.

MB's monoamine oxidase-inhibiting property and its ability to display anxiolytic and antidepressant activity are likely the reason it was used to treat neuropsychiatric illnesses as early as 1989. The syndrome only occurs in a small percentage of patients and it is treatable with benzodiazepines and supportive care. Its incidence is less impeditive than the risk of untreated vasoplegia and potential end-organ injury and graft loss^[17].

Weiner et al.^[18] hypothesized that patients with vasoplegia who were treated with MB were more likely to show increased postoperative morbidity and mortality. A multiple logistic regression model demonstrated that receiving MB was an independent predictor of in-hospital mortality. A propensity score matching the association with morbidity was also seen, but the relationship with mortality was not found. The study identified the use of MB treatment was independently associated with poor outcomes. The authors concluded that, while further studies are required, a thorough risk-benefit analysis should be applied before using MB and, perhaps, it should be relegated to rescue use and not as first-line therapy^[18].

It is remarkable that the risks are taking into more consideration than the lifesaving benefits. As to the safety and ethical aspects of MB's clinical use, it can be affirmed that in recommended doses it is a safe drug (the lethal dose is 40 mg/kg). The accumulation of clinical experience has tested the binomial efficiency/safety. These results show that intravenous infusion of MB seems to be safe. The findings support clinical trials where MB was used to treat VS after coronary artery bypass grafting with CPB on inflammatory response syndrome patients - SIRS and anaphylaxis. These results are not unexpected, especially when analyzed in healthy animals, in which hemodynamics present fine, but not total regulation under the control of NO. In these conditions, no action is expected when there is inhibition of guanylate cyclase by MB.

Methylene blue injection in a non VS carrier individual does not have hemodynamic effects in normal conditions. The MB effect appears only in the case of NO supra-regulation, and thus, spasm occurrence in coronary arterial grafts is unlikely. The risk of vasospasm and thrombosis of these grafts require confirmation *in vivo*. The perception of safety is fully grounded in data set in studies in healthy animals that received MB *in vivo*. Although ischemic events were not evidenced in the ECG monitoring, normal endothelium-dependent and endothelium-independent vascular reactivity was determined by *in vitro* studies. With a wide safety range, these data support the assumption that, unlike the NO (L-NAME) synthesis inhibition, the injection *in vivo* does not cause endothelial dysfunction^[4,14,19].

Methylene blue and endocarditis

Infective endocarditis is a life-threatening condition that occasionally necessitates emergency valve replacement. Patients with an ongoing systemic inflammatory response as a result of infective endocarditis and those who require CPB for emergency valve replacement may demonstrate resistant hypotension related to vasoplegia. It has a spectrum of clinical presentation and is associated with a systemic inflammatory response and the release of nitric oxide. Hemodynamically, it is characterized by arterial vasodilation, high cardiac output despite myocardial depression, and a decreased sensitivity of the heart and peripheral vessels to sympathomimetic agents.

Grayling et al.^[20] described the first case of methylene blue used in the CPB prime and in the context of refractory hypotension in a patient undergoing valve replacement surgery for infective endocarditis, suggesting that methylene blue should be added to the CPB prime (2 mg/kg), and as a continuous infusion (0.25-2 mg/kg × h) to ameliorate the hypotension.

In a prospective, randomized, controlled, open-label, pilot study to evaluate the effects of continuous infusion of methylene blue (MB), on hemodynamics and organ functions in human septic shock, Kirov et al.^[21] concluded that, in human septic shock, continuously infused MB counteracts myocardial depression, maintains oxygen transport, and reduces concurrent adrenergic support. Infusion of MB appears to have no significant adverse effects on the selected organ function variables.

Ozal et al.^[13] prospectively studied whether preoperative MB administration would prevent vasoplegic syndrome in these high-risk patients. Angiotensin-converting enzyme inhibitors, calcium channel blockers, and preoperative intravenous heparin use are independent risk factors for cardiac surgery VS. They did not include septic endocarditis as a risk factor. The results suggested that preoperative MB administration reduces the incidence and severity of vasoplegic syndrome in high-risk patients, thus ensuring adequate systemic vascular resistance in both operative and postoperative periods and shortening both intensive care unit and hospital stays. This report may be the first suggestion of the prophylactic use of MB prior to CPB.

The accentuated NO release that is induced by the systemic inflammatory response associated with infective endocarditis (IE) and cardiopulmonary bypass (CPB) may result in catecholamine refractory hypotension (vasoplegia) and increased transfusion requirement due to platelet inhibition. Cho et al.^[22] aimed to evaluate the effect of prophylactic MB administration before CPB on vasopressor and transfusion requirements in patients with IE undergoing valvular heart surgery (VHS). Forty-two adult patients were randomly assigned to receive 2 mg/kg of MB (MB group, n=21) or saline (control group, n=21) for 20 min before the initiation of CPB. According Cho et al.^[22], "the primary end points were comparisons of vasopressor requirements serially assessed after

weaning from CPB and hemodynamic parameters serially recorded before and after CPB. The secondary endpoint was the comparison of transfusion requirements". The results of the study showed that "there were no significant differences in vasopressor requirements and hemodynamic parameters between the two groups. The mean number of units of packed erythrocytes, transfused per patient, was significantly less in the MB group. The numbers of patients transfused with fresh frozen plasma and platelet concentrates were lesser in the MB group". The authors concluded that in IE patients undergoing VHS, prophylactic MB administration before CPB did not confer significant benefits in terms of vasopressor requirements and hemodynamic parameters, but it was associated with a significant reduction in transfusion requirement^[22].

Taylor & Holtby^[23] have presented a case of refractory hypotension in a child with native mitral valve endocarditis with cerebral complications in whom MB was less effective than previously described. Although these authors seemed disappointed with the effect of the MB on blood pressure, we believe that their case had an impressive evolution despite its severity. We disagree that obvious clinical improvement using MB was not evident in this case since most of the pharmacologic support to the circulation was necessary for a short time. In our opinion, the controversy about the use of MB to treat similar cases arises when one uses MB merely as a "last-minute vasopressor". MB sometimes seems to work for this purpose and sometimes it does not, perhaps due the fact that, unlike many vasopressors, MB does not act through a membrane receptor. We believe that the pivotal action of MB is not exclusively the guanylyl cyclase blockage, resulting in a cGMP release decrease. This blockage also enhances the "crosstalk" between cyclic adenosine monophosphate (cAMP) and cGMP pathways, which facilitates the effect of the cAMP-dependent vasopressors. Many clinical reports in the medical literature, including sepsis treatment, substantiate that the guanylyl cyclase blockage seems to improve the effect of the vasopressors, shortening the length of pharmacologic cardiovascular support. Another quite advantageous effect of MB is its capacity to reduce vascular permeability.

We operated on a drug-addicted young man with native aortic valve endocarditis. The patient received a bileaflet valve prosthesis (St Jude Medical, Inc, St Paul, Minn). A high dose of norepinephrine was necessary to maintain a reasonable blood pressure during CPB. After weaning from CPB, he was hypotensive and had high cardiac output, low systemic vascular resistance, and pulmonary edema. The arterial oxygen saturation was below 80%, even though he was being ventilated with 100% oxygen and positive end-expiratory pressure. We started MB in a continuous infusion in a way quite similar to that used by Taylor & Holtby^[23], followed by a bolus of 3 mg/kg (in 100 mL of 5% glucose in water) twice a day. Even though the mean arterial pressure did not increase, even with norepinephrine, the cardiac output gradually

decreased, and the systemic vascular resistance increased. In addition, the rapid resolution of lung edema, improving arterial oxygen saturation, was astonishing^[19].

Methylene blue and heart transplant.

Grubb et al.^[17] reported a case of a 60-year-old male with history of nonischemic cardiomyopathy and end-stage heart failure who underwent placement of a left ventricular assist device (LVAD), replacement of a mechanical aortic valve with a porcine prosthesis complicated by multiple driveline infections. Heart transplantation was the last option. During the operation, the authors reported: "episodes of hypotension during the extensive lysis of adhesions for LVAD removal. Intermittent boluses of phenylephrine were administered to maintain a sufficient mean arterial pressure. Subsequently, a MB 1-mg/kg bolus followed by continuous infusion of 0.5 mg/kg per hour was administered. In the postoperative, the patient presented signals of serotonergic syndrome assumed as a consequence of the association of MB with antidepressants"^[17].

This report has two crucial points 1) the alert to the possibility of serotonergic syndrome triggered by the association of MB with antidepressants, and; 2) the routine use of MB to handle vasoplegia in the milieu of heart transplant. Kofidis et al.^[24] reported the first experience of vasoplegia treatment with MB after heart transplantation and pointed that this drug deserves attention because of its catecholamine-saving effect, thus preventing possible malperfusion. When searching MEDLINE, Kofidis's report is the only reference on the use of MB to treat vasoplegia associated to heart transplant.

To prevent morbidity and mortality associated with VS, Grubb et al.^[18] implemented an intraoperative protocol that includes administration of MB for VS resistant to vasopressor drugs". It is clear that they trusted the MB treatment since they concluded for its use while weighing the risks of serotonin syndrome^[25].

Methylene blue as rescue therapy

Blackler & Whaler^[26] reported a distributive shock case during an on pump coronary artery bypass grafting with no response to MB. A possible explanation, was given based on Fernandes academic thesis using a mouse sepsis model, that evidenced three eight-hour windows of guanylate cyclase (GC) activity^[27]. In the first eight hours, there was increased nitric oxide synthase (NOS) activity and GC upregulation. In the second eight hours, there was absence of GC expression and a downregulation of NOS. In the third eight hour window, there is an upregulation of GC and NOS. The authors emphasized two practical and educational fundamental aspects: 1) The disclosure in using the MB treatment considering the window opportunity, and; 2) The need for the establishment of this window in humans, perhaps choosing cGMP as biomarker since our attempt to use nitrite/nitrate, measured by chemiluminescence, was frustrating^[15]. In conclusion, MB use as a last

rescue therapeutic option is against the above mentioned concepts, and it is possible that MB does not act (second window), or acts too late (third window) when the circulatory shock is metabolically irreversible, presenting high lactate levels and intractable metabolic acidosis. It might be more sensible to consider MB not as a late rescue treatment, but as an adjuvant drug to be used precociously (window 1)^[28,29].

Methylene blue use in pulmonary hypertension and/or acute respiratory distress syndrome (ARDS)

The restriction to ARDS and pulmonary hypertension deserve some comments. Global NO blockade can contribute to an increase in pulmonary vascular resistance, which worsens the pulmonary hypertension that can be associated with sepsis. Trials that used high bolus doses of MB demonstrated an increase in pulmonary pressures, but this effect was absent in trials that used MB infusions. Some researchers have thus suggested that infusions at low doses should be always used for this reason. Simultaneous treatment with inhaled NO might also be considered for this side effect of NO inhibition. There is also evidence that MB attenuates the inhibition of mitochondrial function as well as decreases acute lung injury in sepsis. In addition, Evgenov et al.^[30,31] demonstrated that MB reduces the increments in pulmonary capillary pressure, lung lymph flow, protein clearance, and pulmonary hypertension and edema in endotoxemic sheep. Raikhelkar et al.^[32] report a case of the use of MB in a patient with acute right ventricular failure and vasoplegic shock after surgical pulmonary embolectomy. The authors discussed, based on the medical literature, that studies have reported MB to increase pulmonary artery pressures and pulmonary vascular resistance. These elevations in pulmonary vascular indices were noted to be clinically and statistically insignificant. One may argue this small increase may exacerbate RV dysfunction in susceptible individuals. This aspect of administration of MB has not been systematically studied. The authors feel the benefits of augmentation of MAP and coronary perfusion may offset small increases in the right ventricle end diastolic pressure (RVEDP)^[32].

Methylene blue neuroprotection and cardiac arrest

Cerebral edema, increased blood-brain barrier (BBB) permeability and neurologic injury, are observed early in ischemia induced by cardiac arrest. Upregulation of NO synthase (NOS) is associated with increased production of NO that induces breakdown of the BBB. It has been suggested that pretreatment with pharmacological agents that reduce NO excess or oxidative stress might reduce disruption of BBB permeability caused by ischemia/reperfusion injury. MB, a nontoxic dye and also a scavenger, recently proved to be a potential aid in resuscitation from cardiac arrest by attenuating oxidative, inflammatory, myocardial and neurologic injury^[33-35].

Experimental investigations have proven the cardioprotective and neuroprotective effects of MB in a porcine

model of experimental cardiac arrest. The main physiological effects during reperfusion include systemic circulation stabilization without significantly increasing total peripheral resistance and moderately increasing cerebral cortical blood flow; a reduction of lipid peroxidation and inflammation, and less anoxic brain and heart tissue damage^[34,35].

One intriguing investigation studied the effects of cardiac arrest and CPR on BBB permeability and consequent neurological injury. In addition, this investigation studied the MB effects on the maintenance of BBB integrity, and NO release in the cerebral cortex. In a piglet model of 12 minutes of cardiac arrest, the authors demonstrated a time-dependent increase of necrotic neurons, caused by ischemia and reperfusion. Moreover, the immunohistochemistry analysis indicated less blood brain barrier disruption in the animals receiving MB, evidenced by decreased albumin leakage, water content and potassium, and less neuronal injury^[34,35]. Similarly, MB treatment reduced nitrite/nitrate ratio, iNOS expression, and nNOS expression. In summary, MB markedly reduced BBB disruption and subsequent neurologic injury. In addition to these cerebral morphologic effects, the exposure to MB was associated with a decrease of NO as measured by nitrate/nitrite content and partial inhibition of NOS activity^[34,35].

Induced mild hypothermia and administration of MB proved to have neuroprotective effects in CPR. However, induction of hypothermia is time consuming. A study was conducted to determine if the MB administered during CPR can enhance the neuroprotective effect of hypothermia. A piglet model of cardiac arrest with variable duration of CPR showed that the neuroprotective effect of MB in combination with hypothermia was significantly greater than the delayed hypothermia alone^[36].

Effects of MB in cardiac arrest and CPR were investigated. A pig model of cardiac arrest, comparing 12 min without CPR and 8 min of CPR, was employed to assess the addition of MB to a hypertonic saline-dextran solution. Hemodynamic variables were slightly improved at 15 min, and MB, co-administered with a hypertonic-hyperoncotic solution, increased 4-hr survival, reducing neurologic injury^[36].

MB could be used in association with hypertonic sodium chloride, but it precipitates. However, an alternative mixture of MB in hypertonic sodium lactate was developed and investigated, using the same piglet model, during and after CPR. This association could be used against reperfusion injury during experimental cardiac arrest, presenting similar effects as MB plus hypertonic saline-dextran^[36].

There are no publications considering MB, VS and neuroprotection, but the above concepts would be relevant considering brain protection in cardiac surgery.

CONCLUSION

In summary, as already mentioned, there are 2 opposing concepts: (1) The use of MB as rescue therapy to treat vaso-

plegic syndrome, and (2) the use of MB as an early adjuvant drug (window 1). Methylene blue use as a final rescue therapeutic option is against the above-mentioned concepts. There is the possibility that MB does not act (second window) or acts too late (third window) when circulatory shock is metabolically irreversible, presenting high lactate levels and uncontrollable metabolic acidosis. Regardless of the strong limitations, pointed out by Weiner et al.^[18], it would be more sensible to consider MB, not as a late rescue treatment, but as an adjuvant drug to be used early (window 1), not just dismissing its action. Perhaps, an easier concept to understand than the “Window of Opportunity” definition is that MB’s action to treat vasoplegic syndrome is time-dependent.

Many authors are reluctant to recommend early use MB given the unusually limited level of evidence at this time, and the potential adverse effects, encouraging trials that systematically collect data to help address these issues. As emergency situations involving risk of death, circulatory collapse does not permit prospective randomized studies. Although there are no definitive multicenter studies, the use of MB to treat VS, at the present time, is the most rational, safest, and cheapest option.

The data from this extended review leaves the impression that the number and quality of publications do not reflect the frequency at which MB is used in clinical practice. Therefore, it the difficulty of conducting multicenter studies is implied. The disclosure and possible consecration of this therapy will be passed on as verbal information and depending on the increase of publications, in studies based on evidence. In the literature data and medical practice set, there is still certainty that the soluble guanylate cyclase blockage in distributive shock control remains underestimated.

Authors' roles & responsibilities	
PRBE	Main author
LAJ	Final approval of the manuscript
CAF	Final approval of the manuscript
ACM	Final approval of the manuscript
SB	Final approval of the manuscript
AJR	Final approval of the manuscript
ASF	Final approval of the manuscript
WVAV	Final approval of the manuscript

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