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Is the cyclic GMP system underestimated by intensive care and emergency teams?

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Summary At present, the clinical management inflammatory vasoplegia associated to sepsis or anaphylaxis is symptomatic. Volume is expanded by means of administration of fluids, and low blood pressure is managed by means of administration of positive inotropes and vasoconstrictors. This therapeutic approach is mainly associated to the cyclic AMP (cAMP) and, many times the circulatory shock is refractory to high amines concentrations. However, beside of cAMP-dependent vasoreactivity mechanisms there are other two known vasoplegia involved mechanisms: cyclic GMP (cGMP) and hyperpolarization that is less clinically considered. Also, it is possible to speculate about 'probable vasopressin deficiency'. Methylene blue (MB) is the most useful and clinically safe cGMP blocker. We propose a decision tree for diagnosis and institution of this therapeutical approach many times underestimate by intensive care and emergency teams.

Introduction

The endogenous vascular relaxing factor, nitric oxide (NO), is a major pathophysiological determinant of the distributive shock related vasodilatation cascade and decreased systemic vascular resistance. Irreversible hemorrhagic and septic shocks, as well as anaphylactic, SIRS and ischemia reperfusion injury associated shocks seem to involve NO overproduction that, in practical terms, abolishes catecholamine induced vascular vasoconstriction while promoting myocardial depression. As a result, a usually lethal hypotensive state ensues as part of a process known as 'vasoplegic endothelium dysfunction' [1].

Considering that NO vasodilatation is cyclic GMP mediated, some logical therapeutical options evolved: (a) Nonspecific NO synthesis inhibition by

Abbreviations: cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine 3′, 5′monophosphate; iNOS, inducible nitric oxide synthase; L-NMMA, NG-monomethyl-*L*-arginine; MB, methylene blue; NO, nitric oxide; NOS, nitric oxide synthase; OLT, orthotopic liver transplantation; SIRS, systemic inflammatory response syndrome.

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L-arginine analogs; (b) Nonspecific corticoid and/or aminoguanidine induced iNOS- inhibition; (c) guanylyl cyclase inhibition by methylene blue (MB). As unspecific NO synthesis inhibition/blockade may cause adverse hemodynamic effects as well as tissue necrosis and increased mortality, the third option, i.e., MB guanylyl cyclase inhibition treatment is seem as more rational and safer.

This text supports the latter therapeutic view based on our clinical experience and critically reviews the specialized literature, on the assumption that the cGMP system seems still underestimated. When one addresses the question: 'What can we do when circulatory shock becomes refractory to the classical therapeutic measures including fluid administration, inotropes and vasoconstrictors?'. Responses to this question are presently limited to the accumulated evidence regarding three vasoconstrictive cAMP-independent mechanisms herein mentioned as 'known mechanisms': (1) cGMP/NO-dependent vasoconstriction; (2) vasopressin administration; (3) hyperpolarization-dependent vasoconstriction (Fig. 1). Another frequently asked question is: 'Why these therapeutic alternatives do not always work?' We believe that there are, at least, five aspects pertaining to this inquiry: (1) Nonconsideration of the existing 'guidelines' or 'evidence based medicine' regarding the accepted available treatment options; (2) lack of knowledge of different vasodilatation mechanisms; (3) the possibility of ensuing crosstalk among the different vasodilatation mechanisms; (4) the soluble guanylyl cyclase enzymatic dynamics and; (5) the common use of MB administration as a 'rescue or ultimate' therapeutic attempt.

We also suggest the reader to explore a review by Kilbourn, Traber and Szabo, published in 1997 [2] and a more recent one, authored by us, in 2006 [3]. Both were seminal to the hypothesis elaboration herein presented.

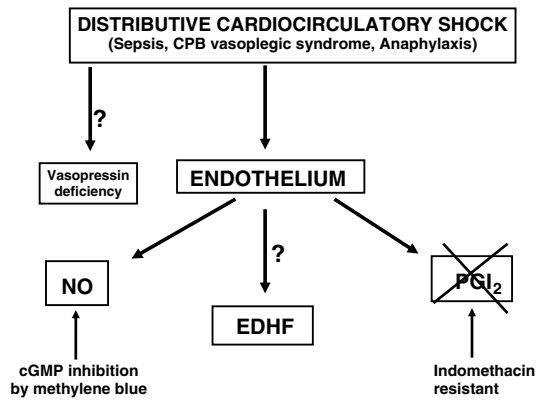

Figure 1 Cardiocirculatory shock mechanisms of vasodilatation.

The NO/cGMP system therapeutic targeting

Nitric oxide stimulates soluble guanilyl cyclase to increase cyclic guanosine 3′,5′ monophosphate (cGMP) production, leading to smooth muscle relaxation. This most important vasodilatation mechanism occurring in sepsis, cardiac surgery vasoplegic syndrome, anaphylaxis, transplanted liver reperfusion and cardiogenic shock secondary to myocardium injury is not reversed by vasoconstrictor amines. NOS inhibitors, on the other hand, are not currently in clinical use due to their lack of specificity with consequent risk of generalized tissue necrosis. For these reasons, it seems more reasonable to use MB as a therapeutic agent, in the aforementioned shock related vasoplegic states. This drug does not interfere with NOS, and has played a longstanding beneficial role in many other clinical conditions. As a potent guanylyl cyclase inhibitor, it blocks the increase in cyclic GMP levels, and, consequently, prevents vascular smooth muscle NO endothelium-dependent relaxation.

Published data about MB clinical use, usually refer to the safety of using 2—3 mg/kg doses, and, sometimes, even higher doses of 6—7 mg/kg. However, there are also reports of MB as capable of causing restlessness, anxiety, reversible paresthesia and a blue—gray skin discoloration that may be confused with cyanosis. Higher doses may be associated with dyspepsia and a persistent mouth burning sensation over 24 h. Green colored urine and vomiting, as well as chest pain and other minor symptoms can also occur and this raises concern regarding eventual deleterious side effects to the coronary circulation as well as a potential risk to coronary heart disease patients. On the other hand, not withstanding the potential for cardiac ischemia [3], in a possibly lethal emergency situation of severe hypotension unresponsive to amine administration, there seems to be no other choice but trying it. Schreiber [4] wrote a suggestive editorial named 'Methylene blue: NO panacea' based on five pediatric septic patients not responsive to MB [5]. He reinforces the danger of generalized NO syntheses blockage, but call attention to the fact that MB can help in raising arterial blood pressure, although tissue capillary perfusion may not ameliorate.

We agree with this universal concept, and based on our 15 year clinical experience with the drug [3,6—8] and our experimental findings, in porcine