

Possible advances in vasopressors and inotropes support in shock

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In a recent publication, Manolopoulos and colleagues (1) review the current use and advances in vasopressors and inotropes support in shock. Besides a concise pathophysiological review, the authors aimed “to describe recent advances (both experimental and clinical) that could hold a critical role for the near future regarding patient management.”

Over the last 25 years, I am convinced that the cGMP/NO pathway has been underestimated (2). The medical literature, currently available worldwide, suggests a lack of regulatory approval, cost considerations, and, thirdly, no prospective data trials supporting this approach.

In the absence of new drugs to block this pathway, I have been working with methylene blue. I am sure that trying to present my clinical and experimental experience, I am becoming obsessive, repetitive, and indeed this obsession should my uncountable “Letters to the Editor” be a critical target. However, when I read excellent texts as the doctor Manolopoulos presentation, I have to share my complementary opinion that blocking the nitric oxide pathway nowadays already has a critical role. Therefore, one more repetitive conceptual letter including well established key concepts (3,4) and a new approach to be considered for the distributive shock we defined as a “vasoplegic endothelium dysfunction.”

Since 1994, the blockade of guanylate cyclase by MB in distributive shock has been the study object in our Endothelial Function Laboratory. It has been used clinically by the Cardiovascular Surgery Group, both from the Ribeirão Preto Medical School of the University of São Paulo (FMRP-USP). We published personal statements

in 2009 and 2015, including twenty years of questions, answers, doubts, and certainties (3,4). Some observations can be considered. (I) MB is safe at the recommended doses (the lethal dose is 40 mg/kg). (II) The use of MB does not cause endothelial dysfunction. (III) The MB effect appears in cases of positive NO regulation. (IV) MB itself is not a vasoconstrictor, by blocking the cGMP pathway releases the cAMP pathway, facilitating the vasoconstrictor effect of epinephrine. (V) The MB may act through this mechanism of “crosstalk,” and its use as a first choice medication may not be correct. (VI) The most used dosage is 2 mg/kg in IV bolus, followed by the same continuous infusion, as plasma concentrations decrease markedly in the first 40 minutes. (VII) Although there are no definitive multicenter studies, the MB used in the treatment of VS cardiac surgery is currently the best, safest, and cheapest option. (VIII) However, there is possible precocious ‘window of opportunity’ for MB’s effectiveness.

We believe that there are at least five aspects to this investigation:

- (I) Lack of consideration of existing guidelines or evidence-based medicine about the accepted treatment options available;
- (II) The lack of more excellent knowledge of the different vasodilation mechanisms;
- (III) The possibility of interference between other vasodilation mechanisms;
- (IV) The enzymatic activity of soluble guanylyl cyclase (sGC);
- (V) The frequent use of MB as a therapeutic “rescue” or “final” attempt;

(VI) One “master” concept is that MB does not interfere with NOS and is considered a potent soluble guanylyl cyclase inhibitor is preventing vascular smooth muscle relaxation without directly affecting NO synthesis. However, NO synthase inhibitors are not currently in clinical use because of their lack of specificity in inhibiting the different NOS isoforms, with the consequent risk of generalized tissue necrosis and a higher death rate.

Nowadays, “broad-spectrum vasopressors” is the choice, considering the drugs associations with diverse pharmacological mechanisms (membrane receptors, endothelium-dependent mechanisms) (5), adopting “vasopressor support sparing strategies.” (6,7) and “microcirculation protection” avoiding or preventing high catecholamine doses (8). These protocols do not have to be considered as “rescue” therapy; by the contrary, it is essential that a precocious “window of opportunity. Search for novel vasopressor agents, such as synthetic human angiotensin II, which would increase blood pressure and reduce the need for high catecholamine vasopressors. Optimistically, if possible, seek new vasopressors that increase the arterial blood pressure without microcirculatory damage (7).

Regarding “broad spectrum vasopressors” patients with septic shock could be considered being initially put on multiple vasopressors with a different mechanism of action simultaneously while the vasopressor sensitivity is assessed and that vasopressor sensitivity could be assessed by sequential removal of vasopressors (moving on to vasopressor de-escalation). However, there are still major problems that need to be addressed: availability, familiarity, and safety profile. For one, there is currently no bedside test that predicts the blood pressure response to vasopressors. Secondly, not all of these vasopressors are currently available worldwide due to either a lack of regulatory approval or cost considerations. Thirdly, there are no prospective data supporting this approach.

I hope the presented concepts should complement the very good Manolopoulos and colleagues, review (1) and keep the subject an open discussion.

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Footnote

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