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Role of Milrinone in Septic Myocardial Depression

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Abstract

At present, myocardial depression (MD) in septic shock (SS) is more frequently recognized. In 1984, Parker et al. published 20 patients with SS where 50

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1 INTRODUCTION

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2 I. INTRODUCTION

At present, myocardial depression (MD) in septic shock (SS) is more frequently recognized. In 1984, Parker et al. published 20 patients with SS where 50% of them showed a left ventricular ejection fraction (LVEF) less than 40% 1 . It was not until 2006 that it became more widely accepted that some degree of MD was present in this kind of patients 2 . However, the prevalence has been variable depending on the evaluation method, either through cardiac output (CO), measurement of troponins, B type Natriuretic Peptide or by echocardiography [2][3][4] .

In 2008 Vieillard-Baron et al. studied 67 patients with SS without a history of heart disease with transesophageal echocardiography. They estimated a mean incidence of MD greater than 60%, which manifests itself in the first 48 hours of evolution and recovers between seven and ten days after the onset of SS 5 .

3 Jardin et al. evaluated patients in SS

echocardiographically and demonstrated to have normal end-diastolic volume but decreased stroke volume (SV), and those who survived developed more marked abnormalities in ventricular function at symptom onset, recovering LVEF once SS was overcome 6 .

In 1985 the presence of a circulating myocardial depressant factor was confirmed by Parrillo et al. through the demonstration that the serum obtained during the acute phase of patients with SS was able to decrease the shortening rate of cardiomyocytes of rats in vitro, while the serum of patients non-septics restored its function 7 . Today it is known that interleukins 1 (IL-1), IL-2, IL-6 and TNF-? behave as circulating myocardial depressants factors **??** . There is also evidence of activation of apoptotic pathways that impair cardiomyocyte mitochondrial function. Likewise, there is adhesion of activated leukocytes to the cardiomyocyte via intercellular adhesion molecules that induce dysfunction and ultimately death of the cardiomyocyte 9,10 .

On the other hand, the myofibrils show a decreased sensitivity to calcium, probably explained by I-troponin phosphorylation at the site where it combines with calcium 11 . In addition, it is recognized that MD is associated with increased intracellular nitric oxide (NO), which plays an indirect role through the formation of peroxynitrite, whose inhibition produces improvement in MD 12 .

Given the above, it is postulated that MD could be explained both due to intra and extracardiac factors, ruling out the hypothesis associated exclusively with hypoperfusion, since that coronary blood flow in SS is preserved 13 .

The use of inotropic agents in the management of the SS should induce improvement in left ventricular performance, increased mixed venous oxygen saturation/central venous oxygen saturation (SvO2/ScvO2) and reduction of serum lactate levels. Dobutamine (DBT) remains the drug recommended by the Surviving Sepsis Campaign to treat septic MD 14 . However, the ?1-agonist agents may be less effective when there is down regulation of such receptors, oxidation of catecholamines by increased oxidative stress, and London Journal of

Medical and Health Research inhibition of G protein associated with the ?1-adrenergic receptor that prevents the activation of adenylate cyclase 15 .

Tachyarrhythmias and increased myocardial O 2 consumption (VO 2), especially in patients in SS with low left ventricular filling pressures have been described 16 . On the other hand, Kumar et al. demonstrated that DBT increases LVEF more than 10% only in 35% of these patients 17 .

Milrinone (MN), being an inhibitor of the phosphodiesterase III, exerts an inotropic effect increasing cAMP in the cytosol of the cardiomyocytes; however, due to its systemic vasodilatory effect it has not been widely recommended in septic MD 18,19 .

Our group carried out a study where the impact of starting MN infusion in 72 patients with SS was evaluated. Pulse contour cardiac output (PiCCO system) to monitorizing the cardiovascular performance was used **??**0 . Improved in cardiac output (CO) and metabolic parameters (ScvO2, v-a CO2 difference, arterial lactic acid and base excess) were observed.

It is worth mentioning that the increase in CO was not due to a reduction in systemic vascular resistance (SVR) or improvement in preload (intrathoracic blood volume [ITBV]), which supports that the optimization of CO most likely it was due to an improvement in myocardial contractility. All events previously described occurred in absentia of hypotension and without the need to withdraw the infusion of MN **??**0 . 21 .

There are doubts regarding the additive effect of MN and DBT. Sakai et al., in rats with sepsis induced by cecal ligation and puncture (CLP) and a control group, demonstrating that the levels of cAMP were significantly elevated in both groups in response to MN, but with DBT only occurred in the control group (operated without cecal ligation and puncture) 22 .

This phenomenon is attributed to the fact that the effect of DBT is affected in CLP rats because of cAMP phosphate hydrolysis due to up-regulation of phosphodiesterase IV (PDE-IV), without observing changes in the activity of ß1 receptors 22 .

Wang et al, studied three groups of patients with SS: standard care, milrinone, and group London Journal of Medical and Health Research esmolol-milrinone. The benefits observed with the association of esmolol-MN are attributed to the reduction of heart rate and the release of catecholamines induced by esmolol, which optimizes the left ventricular end diastolic volume. Surprisingly, the group MN plus esmolol improved 28 days survival 23 .

Schmittinger et al. analyzed 40 patients with SS and MD without previous heart disease, using MN plus enteral Metoprolol and concluded that this combination is viable in these patients 24 .

In SS, regulation of vasomotor tone is due to the synthesis of vasoconstrictor and vasodilators molecules. The main vasodilator is nitric oxide (NO) whose production is increased by the greater expression of oxide inducible nitric synthase (i-NOS) 25 . In this vasodilation stage it is difficult to introduce inodilating agents that decrease vasomotor tone such as DBT (?2 effect) and MN 26 .

Although MN causes more hypotension and reduced SVR than DBT, our results suggest that MN, as an isolated inotrope, could benefit patients with SS who are euvolemic and supported by noradrenaline (NAD) **??**0 .

About 38% of patients with SS develop early septic MD (primary hypokinesia) and 21% will develop it in the next 24 to 48 hours, probably due to the increase in afterload induced by NAD (secondary hypokinesia). Consequently, the use of inotropic agents, by improving the contractility, may maintain or increase systemic blood pressure 4 .

Therefore, dobutamine and MN can trigger arrhythmias due to intracellular calcium overload and myocardial ischemia secondary to imbalance between delivery and VO 2 . Its use is also associated with increased mortality, emphasizing the importance of limiting the use, especially if they are administered in a combined manner 27 .

Despite these disadvantages, many patients are unable to restore their organ functions without inotropic support.

In our study, the patients who used NAD and MN, 17.2% developed atrial fibrillation (AF), while in the group that used DBT+MN+NAD a 26.6% developed AF, without reaching significant differences **??**0 .

If we compare DBT with MN, the first one produces greater stimulation of myocardial contractility, while MN produces greater vasodilation and reduction of left ventricular filling pressures. 28 In addition, MN reduces pulmonary vascular resistance (PVR) more significantly than DBT, showing advantages in right ventricular dysfunction, such as in cases of pulmonary SS (primary Acute Respiratory Distress Syndrome) that evolve with elevated PVR due to hypoxic pulmonary vasoconstriction.

The association of MN to conventional treatment with DBT, dopamine and/or nitroprusside has been shown to have additive effects, improving ventricular ejection parameters. Colucci et. al, using intracoronary infusion of MN to avoid the peripheral effects of the drug, demonstrated an improvement in contractility in patients who were receiving dobutamine simultaneously, through a significant increase in dP/dt (coefficient between delta pressure and delta time of the arterial curve) with the combination of both drugs 29 .

Meissner, studied the hemodynamic effects of DBT and MN administered in isolation and in combination, noticing that the combined administration produced more SV increase 30 .

Poelaert et. al, with echocardiogram in 25 patients with SS identified 3 subgroups: (1) with preserved systolic function, (2) with diastolic dysfunction and (3) global failure 31 .

Levosimendan favors the rate of diastolic relaxation (lusitropic effect) and MN by reducing the cAMP

degradation also benefits ventricular filling, effect that is not observed with the ? adrenergics agents 32,33 . Notwithstanding the foregoing, levosimendan is not superior to dobutamine as inotropic drug in SS 34,36 .

In summary, a significant percentage of patients with SS evolved with MD. These patients required the inclusion of inotropes agents such as DBT and/or milrinone and in case of refractory London Journal of Medical and Health Research 29 hypotension, they required epinephrine 37 . In our study it was observed that MN is a safe alternative as an adjuvant to treat SS with MD in patients who are adequately resuscitated (ITBV index: normal values: 850-1000 ml/min/M 2
). [1] [2]

Figure 1:

Liet

et al., randomly studied injection-induced septic shock with pseudomonas in rabbits. One group received MN and the other placebo. MAP

and cardiac index (CI) were measured every 30 minutes (PiCCO system) demonstrating a progressive fall of CI in the group without MN. No fall of MAP in the treated group was observed

Figure 2: Table Liet

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[London Journal of Medical and Health Research] , *London Journal of Medical and Health Research*

[Tomicic et al. ()] , V Tomicic , J Gerrero , Endotelio , Sepsis . *Med Intensiva* 2005. 29 (3) p. .

[Parrillo et al. ()] 'A circulating myocardial depressant substance in humans with septic shock: septic shock patients with reduced ejection fraction have a circulating factor that depresses in vitro myocardial cell performance'. J E Parrillo , C Burch , J H Shelhamer , M M Parker , C Natanson , W Schuette . *J Clin Invest* 1985. 76 p. .

[Vieillard-Baron et al. ()] 'Actual incidence of global left ventricular hypokinesia in adult septic shock'. A Vieillard-Baron , V Caille , C Charron , G Belliard , B Page . *Crit Care Med* 2008. 36 p. .

[Meissner et al. ()] 'Additive effects of milrinone and dobutamine in severe heart failure'. A Meissner , G Herrmann , L Gerdesmeyer , R Simon . *Z Kardiol* 1992. 81 (5) p. .

[Wilkman et al. ()] 'Association between inotrope treatment and 90-day mortality in patients with septic shock'. E Wilkman , K M Kaukonen , V Pettila , A Kuitunen , M Varpula . *Acta Anaesthesiol Scand* 2013. 57 (4) p. .

[Davani et al. ()] 'Cardiac ICAM-1 mediates leukocytedependent decreased ventricular contractility in endotoxemic mice'. E Y Davani , J H Boyd , D R Dorscheid . *Cardiovasc Res* 2006. 72 p. .

[Wang et al. ()] 'Combination Therapy with Milrinone and Esmolol for Heart Protection in Patients with Severe Sepsis: A Prospective Randomized Trial'. Z Wang , Q Wu , X Nie , J Guo , C Yang . *Clin Drug Investig* 2015. 35 (11) p. .

[Schmittinger et al. ()] 'Combined milrinone and enteral metoprolol therapy in patients with septic myocardial depression'. C A Schmittinger , M W Dünser , M Haller , H Ulmer , G Luckner , C Torgersen . *Critical Care* 2008. 12 p. 99.

[Sakai et al. ()] 'Diminished Responsiveness to Dobutamine as an Inotrope in Mice with Cecal Ligation and Puncture Induced Sepsis: Attribution to Phosphodiesterase 4 Up-regulation'. M Sakai , T Suzuki , K Tomita , S Yamashita , S Palikhe , K Hattori . *Am J Physiol Heart Circ Physiol* 2017. 312 (6) p. .

[Chang et al. ()] 'Effect of levosimendán on mortality in severe sepsis and septic shock: a meta-analysis of randomised trials'. W Chang , J F Xie , J Y Xu , Y Yang . 10.1136/bmjopen-2017-019338. *BMJ Open* 2018. 8 (3) p. 19338.

[Deep et al. ()] 'Evolution of haemodynamics and outcome of fluid-refractory septic shock in children'. A Deep , C D Goonasekera , Y Wang , J Brierley . *Intensive Care Med* 2013. 39 p. .

[Vieillard-Baron et al. ()] 'Hemodynamic Instability in Sepsis. Bedside Assessment by Doppler Echocardiography'. A Vieillard-Baron , S Prin , K Chergui , O Dubourg , F Jardin . *Am J Respir Crit Care Med* 2003. 168 (11) p. .

[Maass et al. ()] 'IL-1beta and IL-6 act synergistically with TNF-alpha to alter cardiac contractile function after burn trauma'. D L Maass , J White , J W Horton . *Shock* 2002. 18 (4) p. .

[Böhm et al. ()] 'Increase of myocardial inhibitory Gproteins in catecholamine refractory septic shock or in septic multiorgan failure'. M Böhm , R Kirchmayr , P Gierschik , E Erdmann . *Am J Med* 1995. 98 p. .

[Colucci et al. ()] 'Intracoronary infusion of dobutamine to patients with and without severe congestive heart failure. Dose-response relationships, correlation with circulating catecholamines, and effect of phosphodiesterase inhibition'. W S Colucci , A R Denniss , G F Leatherman , R J Quigg , D F Gauthier . *J Clin Invest* 1988. 81 (4) p. .

[Lindgren et al. ()] *Lack of beneficial effects of milrinone in severe septic shock Circ Shock*, S Lindgren , P Almqvist , D Arvidsson , A Montgomery , K E Andersson , U Haglund . 1990. 31 p. .

[Poelaert et al. ()] 'Left ventricular systolic and diastolic function in septic shock'. J Poelaert , C Declerck , D Vogelaers , F Colardyn , C A Visser . *Intensive Care Med* 1997. 23 (5) p. .

[Feng et al. (2019)] 'Levosimendan does not reduce the mortality of critically ill adult patients with sepsis and septic shock: A meta analysis'. F Feng , Y Chen , M Li , J J Yuan , X N Chang , C M Dong . *Chin Med J (Engl)* 2019 May 20. 132 (10) p. .

[Barraud et al. ()] 'Levosimendan restores both systolic and diastolic cardiac performance in lipopolysaccharide treated rabbits: Comparison with dobutamine and milrinone'. D Barraud , V Faivre , T Damy , S Welschbillig , E Gayat , C Heymes . *Crit Care Med* 2007. 35 p. .

[Meng et al. (2016)] 'Levosimendan Versus Dobutamine in Myocardial Injury Patients with Septic Shock: A Randomized Controlled Trial'. J B Meng , M H Hu , Z Z Lai , J I Cl , X J Xu , G Zhang , S Tian . *Med Sci Monit* 2016 May 3. 22 p. .

[Colucci et al. ()] 'Milrinone and dobutamine in severe heart failure: Differing hemodynamic effects and individual patient responsiveness'. W S Colucci , R F Wright , B E Jaski , M A Fifer , E Braunwald . *Circulation* 1986. 73 (3) p. .

[Tomicic et al. ()] 'Milrinone role in treatment of septic shock'. V Tomicic , L Zouein , J Espinoza , S Ugarte . *London Journal of Medical and Health Research* 2015. 20 (1) p. 154. (Crit Care)

[Antonucci et al. ()] 'Myocardial depression in sepsis: from pathogenesis to clinical manifestations and treatment'. E Antonucci , E Fiaccadori , K Donadello , F S Taccone , F Franchi , S Scolletta . *J Crit Care* 2014. 29 p. .

[Price et al. ()] 'Myocardial dysfunction in sepsis: mechanisms and therapeutic implications'. S Price , P B Anning , J A Mitchell , T W Evans . *European Heart Journal* 1999. 20 p. .

[Krishnagopalan et al. ()] 'Myocardial dysfunction in the patient with sepsis'. S Krishnagopalan , A Kumar , J E Parrillo , A Kumar . *Current opinion in critical care* 2002. 8 (5) p. .

[Walley ()] 'New Approaches to Modifying Inotropy in Sepsis-Induced Myocardial Dysfunction'. K R Walley . *Critical Care Medicine* 2017. 45 (4) p. .

[Jardin et al. ()] 'Persistent preload defect in severe sepsis despite fluid loading: A longitudinal echocardiographic study in patients with septic shock'. F Jardin , T Fourme , B Page , Y Loubières , A Vieillard-Baron , A Beauchet . *Chest* 1999. 116 (5) p. .

[Geraci ()] 'Pharmacologic approach in patients with heart failure'. S A Geraci . *The Pharmacologic Approach to the Critically ill Patient*, B Chernow (ed.) 1994. Williams and Wilkins. p. .

[Jindal et al. ()] 'Pharmacologic issues in the management of septic shock'. N Jindal , S M Hollenberg , R P Dellinger . *Crit Care Clin* 2000. 16 p. .

[Jentzer et al. ()] 'Pharmacotherapy Update on the Use of Vasopressors and Inotropes in the Intensive Care Unit'. J C Jentzer , J C Coons , C B Link , M Schmidhofer . *Journal of Cardiovascular Pharmacology and Therapeutics* 2015. 20 (3) p. .

[Parker et al. ()] 'Profound but reversible myocardial depression in patients with septic shock'. M M Parker , J H Shelhamer , S L Bacharach , M V Green , C H Fredericket , TM . *Ann Intern Med* 1984. 100 (4) p. .

[Maeder et al. ()] 'Sepsis associated myocardial dysfunction: Diagnostic and prognostic impact of Cardiac Troponins and Natriuretic Peptides'. M Maeder , T Fehr , H Rickli , P Ammann . *Chest* 2006. 129 (5) p. .

[Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock Critical Care Medicine ()] 'Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock'. *Critical Care Medicine* 2021. 49 (11) p. .

[Cunnion et al. ()] 'The coronary circulation in human septic shock'. R E Cunnion , G L Schaer , M M Parker , C Natanson , J E Parrillo . *Circulation* 1986. 73 (4) p. .

[Liet et al. ()] 'The effects of milrinone on hemodynamics in an experimental septic shock model'. J-M Liet , Jacqueline C Orsonneau , JL , Gras-Leguen Ch , G Potel , J-Ch Rozé . *Pediatr Crit Care Med* 2005. 6 p. .

[Steendijk ()] 'The role of nitric oxide signaling in sepsis-induced myocardial dysfunction'. P Steendijk . *Crit Care Med* 2006. 34 (1) p. .

[Ossinen et al. ()] 'The use of more tan one inotrope in acute heart failure is associated with increased mortality: a multicentre observational study'. J Ossinen , V P Harjola , K Siirila-Waris , J Lassus , J Melin , K Peuhkurinen . *Acute Cardiac Care* 2008. 10 (4) p. .