# Role of Milrinone in Septic Myocardial Depression

*Vinko Tomicic & Ivania Tomicic*

## 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 patients2. 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 echocardiography2-4.

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 SS5.

*Keywords:* NA

*Classification:* NLM Code: WG 205

*Language:* English

Great Britain Journals Press

LJP Copyright ID: 392884

London Journal of Medical and Health Research

Volume 23 | Issue 4 | Compilation 1.0

# Role of Milrinone in Septic Myocardial Depression

Vinko Tomicic[α] & Ivania Tomicic[σ]

*Author* α: Unidad de Pacientes Críticos Hospital Regional de Antofagasta, Chile.
α: Profesor of Surgery, Facultad de Medicina y Odontología, Universidad de Antofagasta, Chile.
σ: Medical Student, Facultad de Medicina y Odontología, Universidad de Antofagasta, Chile.

## 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[2-4].

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].

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-α behave as circulating myocardial depressants factors[8].

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 β1-agonist agents may be less effective when there is down regulation of such receptors, oxidation of catecholamines by increased oxidative stress, and

inhibition of G protein associated with the β1-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[20]. Improved in cardiac output (CO) and metabolic parameters (ScvO2, v-a CO2 difference, arterial lactic acid and base excess) were observed.

Table: Hemodynamic and metabolic parameters before and after start MN infusion

| Parameters | Before MN | After MN | *p* |
|---|---|---|---|
| Cardiac Index | 3.1 ± 1.0 | 3.3 ± 1.1 | 0.003 |
| v-a CO2 difference | 7.6 ± 3.3 | 6.0 ± 3.6 | 0.03 |
| Lactic acid | 18.75 ± 14.87 | 13.1 ± 9.1 | 0.01 |
| ScvO2 | 71.1 ± 10.3 | 76.1 ± 7.3 | 0.004 |
| Urine output | 1070 ± 946 | 1490 ± 1243 | 0.0003 |
| SVR | 1931 ± 999 | 1753 ± 917 | 0.13 |
| ITBVI [NV: 850-1000] | 865 ± 181 | 902 ± 237 | 0.23 |

Table: MN: milrinone; $ScvO_2$: central venous oxygen saturation; SVR: systemic vascular resistance; ITBVI: intrathoracic blood volumen Index (PiCCO system), NV: normal value; values are expressed as mean ± standard deviation.

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[20]. Table

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 [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

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 (β2 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)[20].

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[20].

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 β 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

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$^2$).

## REFERENCES


1. Parker MM, Shelhamer JH, Bacharach SL, green MV, natanson CH, Fredericket TM, et al. Profound but reversible myocardial depression in patients with septic shock. Ann Intern Med 1984; 100(4): 483-440.
2. Maeder M, Fehr T, Rickli H, Ammann P. Sepsis associated myocardial dysfunction: Diagnostic and prognostic impact of Cardiac Troponins and Natriuretic Peptides. Chest 2006; 129(5): 1349-1366.
3. Vieillard-Baron A, Prin S, Chergui K, Dubourg O, Jardin F. Hemodynamic Instability in Sepsis. Bedside Assessment by Doppler Echocardiography. Am J Respir Crit Care Med 2003; 168(11): 1270-1276.
4. Antonucci E, Fiaccadori E, Donadello K, Taccone FS, Franchi F, Scolletta S. Myocardial depression in sepsis: from pathogenesis to clinical manifestations and treatment. J Crit Care 2014; 29: 500-511.
5. Vieillard-Baron A, Caille V, Charron C, Belliard G, Page B. Actual incidence of global left ventricular hypokinesia in adult septic shock. Crit Care Med 2008; 36: 1701-1706.
6. Jardin F, Fourme T, Page B, Loubières Y, Vieillard-Baron A, Beauchet A, et al. Persistent preload defect in severe sepsis despite fluid loading: A longitudinal echocardiographic study in patients with septic shock. Chest 1999; 116(5): 1354-1359.
7. Parrillo JE, Burch C, Shelhamer JH, Parker MM, Natanson C, Schuette W. 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 Clin Invest 1985; 76: 1539-1553.
8. Maass DL, White J, Horton JW. IL-1beta and IL-6 act synergistically with TNF-alpha to alter cardiac contractile function after burn trauma. Shock 2002; 18(4): 360-366.
9. Walley KR. New Approaches to Modifying Inotropy in Sepsis-Induced Myocardial Dysfunction. Critical Care Medicine. 2017; 45(4): 754-756.
10. Davani EY, Boyd JH, Dorscheid DR, et al: Cardiac ICAM-1 mediates leukocyte-dependent decreased ventricular contractility in endotoxemic mice. Cardiovasc Res 2006; 72:134–142
11. Price S, Anning PB, Mitchell JA and Evans TW. Myocardial dysfunction in sepsis: mechanisms and therapeutic implications. European Heart Journal 1999; 20: 715-724.
12. Steendijk P. The role of nitric oxide signaling in sepsis-induced myocardial dysfunction. Crit Care Med 2006; 34(1): 255-257.
13. Cunnion RE, Schaer GL, Parker MM, Natanson C, Parrillo JE. The coronary circulation in human septic shock. Circulation 1986; 73(4): 637-644.
14. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: Critical Care Medicine 2021; 49(11): e1063-e1143.
15. Böhm M, Kirchmayr R, Gierschik P, Erdmann E. Increase of myocardial inhibitory G-proteins in catecholamine refractory septic shock or in septic multiorgan failure. Am J Med 1995; 98: 183-186.
16. Jindal N, Hollenberg SM, Dellinger RP. Pharmacologic issues in the management of septic shock. Crit Care Clin 2000; 16: 233-249.
17. Krishnagopalan S, Kumar A, Parrillo JE, Kumar A. Myocardial dysfunction in the patient with sepsis. Current opinion in critical care 2002; 8(5): 376-388.
18. Lindgren S, Almqvist P, Arvidsson D, Montgomery A, Andersson KE, Haglund U. Lack of beneficial effects of milrinone in severe septic shock Circ Shock. 1990; 31(4): 365-375.
19. Wilkman E, Kaukonen KM, Pettila V, Kuitunen A, Varpula M. Association between inotrope treatment and 90-day mortality in patients with septic shock. Acta Anaesthesiol Scand. 2013; 57(4): 431-442.

20. Tomicic V, Zouein L, Espinoza J, Ugarte S. Milrinone role in treatment of septic shock Crit Care 2015; 19 (1): p154.
21. Liet J-M, Jacqueline C, Orsonneau JL, Gras-LeGuen Ch, Potel G, Rozé J-Ch. The effects of milrinone on hemodynamics in an experimental septic shock model. Pediatr Crit Care Med 2005; 6: 195-199.
22. Sakai M, Suzuki T, Tomita K, Yamashita S, Palikhe S, Hattori K, et al. Diminished Responsiveness to Dobutamine as an Inotrope in Mice with Cecal Ligation and Puncture Induced Sepsis: Attribution to Phospho-diesterase 4 Up-regulation. Am J Physiol Heart Circ Physiol. 2017; 312(6): H1224-H1237.
23. Wang Z, Wu Q, Nie X, Guo J, Yang C. Combination Therapy with Milrinone and Esmolol for Heart Protection in Patients with Severe Sepsis: A Prospective Randomized Trial. Clin Drug Investig 2015; 35(11): 707-716.
24. Schmittinger CA, Dünser MW, Haller M, Ulmer H, Luckner G, Torgersen C, et al. Combined milrinone and enteral metoprolol therapy in patients with septic myocardial depression. Critical Care 2008, 12: R99.
25. Tomicic V, Gerrero J. Endotelio y Sepsis. Med Intensiva 2005; 29(3): 142-150.
26. Jentzer JC, Coons JC, Link CB, Schmidhofer M. Pharmacotherapy Update on the Use of Vasopressors and Inotropes in the Intensive Care Unit. Journal of Cardiovascular Pharmacology and Therapeutics 2015; 20(3): 249-260.
27. Ossinen J, Harjola VP, Siirila-Waris K, Lassus J, Melin J, Peuhkurinen K, et al. The use of more tan one inotrope in acute heart failure is associated with increased mortality: a multi-centre observational study. Acute Cardiac Care 2008; 10(4): 209-213.
28. Colucci WS, Wright RF, Jaski BE, Fifer MA, Braunwald E. Milrinone and dobutamine in severe heart failure: Differing hemodynamic effects and individual patient responsiveness. Circulation 1986; 73(s3): III175-III183.
29. Colucci WS, Denniss AR, Leatherman GF, Quigg RJ, Gauthier DF. 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. J Clin Invest. 1988; 81(4): 1103-1110.
30. Meissner A, Herrmann G, Gerdesmeyer L, Simon R. Additive effects of milrinone and dobutamine in severe heart failure. Z Kardiol. 1992; 81(5): 266-271.
31. Poelaert J, Declerck C, Vogelaers D, Colardyn F, Visser CA. Left ventricular systolic and diastolic function in septic shock. Intensive Care Med 1997; 23(5): 553-560.
32. Barraud D, Faivre V, Damy T, Welschbillig S, Gayat E, Heymes C et al. Levosimendan restores both systolic and diastolic cardiac performance in lipopolysaccharide treated rabbits: Comparison with dobutamine and milrinone. Crit Care Med 2007; 35: 1376-1382.
33. Geraci SA. Pharmacologic approach in patients with heart failure. In: Chernow B (ed). The Pharmacologic Approach to the Critically ill Patient. Williams and Wilkins, 1994; page 80-94.
34. Chang W, Xie JF, Xu JY, Yang Y. Effect of levosimendán on mortality in severe sepsis and septic shock: a meta-analysis of randomised trials. BMJ Open 2018; 8(3): e019338. doi: 10.1136/bmjopen-2017-019338.
35. Feng F, Chen Y, Li M, Yuan JJ, Chang XN, Dong CM. Levosimendan does not reduce the mortality of critically ill adult patients with sepsis and septic shock: A meta analysis. Chin Med J (Engl). 2019 May 20; 132(10): 1212-1217.
36. Meng JB, Hu MH, Lai ZZ, JI CL, Xu XJ, Zhang G, Tian S. Levosimendan Versus Dobutamine in Myocardial Injury Patients with Septic Shock: A Randomized Controlled Trial. Med Sci Monit. 2016 May 3; 22: 1486-1496.
37. Deep A, Goonasekera CD, Wang Y, Brierley J. Evolution of haemodynamics and outcome of fluid-refractory septic shock in children. Intensive Care Med. 2013; 39: 1602-1609.