Dobutamine vs Milrinone in Heart Failure with Preserved Ejection Fraction: How do We Choose?

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Heart failure (HF) occurs when the heart cannot pump sufficient blood to meet tissue needs and/or does so at the expense of high filling pressures, clinically manifesting itself through signs and symptoms of congestion and/or low cardiac output.

Decompensation is frequently observed in the condition's natural history. Approximately 20% of HF exacerbations occur in low cardiac output syndrome, with cardiogenic shock being the most severe presentation. When there is evidence of poor organ perfusion, inotropes are fundamental pharmacological support, with dobutamine and milrinone being the most commonly used drugs.

Dobutamine is a synthetic catecholamine that acts as a β1 and β2 receptor agonist, while milrinone is a phosphodiesterase 3 inhibitor that acts as an inotropic and vasodilator.[1] Although there are important pharmacokinetic and pharmacodynamic differences between these medications, there is little evidence in the literature about which is best in HF with reduced ejection fraction (HFrEF).

The hemodynamic effect of milrinone was compared to that of dobutamine in 14 patients with severe HF and low cardiac output (defined as pulmonary capillary pressure > 15 mmHg and cardiac index < 2.5 l/min/m^2). The drugs produced a similar increase in cardiac index and right ventricular (RV) ejection, with a reduction in RV end-systolic volume. However, the improved RV performance in the milrinone group can be partially explained by reduced pulmonary artery pressure (RV afterload reduction), which did not appear to be an important mechanism in the dobutamine contractility response.[2] Thus, it would seem that milrinone is a better choice in patients with significant RV afterload (pulmonary hypertension).

In the OPTIME-CHF study, 949 patients admitted for decompensated HF were randomized to placebo or milrinone for 48 to 72 hours. Among patients with ischemic etiology, milrinone increased the rate of death or prolonged hospitalization and/or re-hospitalization for HF within 60 days compared to placebo. The opposite was observed in patients with non-ischemic HF.[3] However, these results are subject to criticism since there was no standardized definition of ischemic vs non-ischemic HF, inotropes were prescribed without pre-established criteria, the ischemic HF group had worse results than the non-ischemic group (denoting greater severity and worse prognosis in this etiology), no comparison was made with another inotropic agent in the ischemic group (eg, dobutamine), and the results were derived from post hoc analysis. Although this study showed that inotropes may be associated with increased mortality, especially in ischemic etiology, this effect cannot be attributed exclusively to milrinone.

A 2001 retrospective analysis of 329 patients with advanced HF seen at the Cleveland Clinic (Cleveland, OH, USA), 82% of whom received dobutamine and 18% of whom received milrinone, found no significant in-hospital mortality differences between the groups, although nitroprusside was needed less often for clinical compensation in the milrinone group (40% vs 18%, p < 0.01). On the other hand, cost analysis showed that dobutamine was less expensive per patient than milrinone: USD 45 (standard deviation [SD], USD 10) vs USD 1855 (SD, USD 350)(p < 0.0001).[4] These results plus the cost-effectiveness analysis favor the choice of dobutamine, since there was no disadvantage in terms of mortality.

While waiting for a transplant, inotropes are often needed for long periods. In such a setting, there are conflicting results between dobutamine and milrinone. One study found no difference in hemodynamic changes, death, the need for additional vasodilators/inotropes, or the need for mechanical circulatory assistance before transplantation.[5] However, another study found that patients who received milrinone less frequently needed mechanical ventricular assistance or an intra-aortic balloon as a bridge to transplantation, although they found no difference in mortality between the groups.[6] In other studies, milrinone was associated with a higher survival rate among patients on the waiting list for heart transplantation.[7] This wait is often long and covers a group of patients with advanced HF in Interagency Registry for Mechanically Assisted Circulatory Support profiles 2 and 3. A number of factors must be considered in this patient profile. First, since dobutamine is associated with an increased chance of tachyphylaxis and eosinophilic myocarditis, milrinone should be preferred. Second, the hemodynamic profile is variable, comprising patients with: a) pulmonary hypertension and RV dysfunction, for whom milrinone can be a compensation strategy until transplantation, since reducing pulmonary hypertension

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minimizes the chance of postoperative RV dysfunction; b) arterial hypotension and vasopressor use, for whom dobutamine is the drug of choice due to its lower potential for vasodilation and arterial hypotension. Third, since the waiting time can last for months, for prolonged hospitalizations, in which drug costs can be a relevant factor, dobutamine would seem best. Finally, in patients with advanced HF, there is a progressive downregulation of beta-adrenergic receptors that can compromise the response to beta-adrenergic drugs,[8] making inotropes that act through other pathways interesting alternatives.

For initial cardiogenic shock treatment, neither dobutamine nor milrinone was found superior. However, there were significant differences in side effects, including a higher incidence of hypotension with milrinone and arrhythmias with dobutamine.[9] Thus, rather than efficacy, tolerance to adverse effects may be the deciding factor in selecting an inotropic agent.

In 2019, a meta-analysis was conducted of 11 studies published between 2001 and 2016 (23,056 patients) that compared dobutamine and milrinone. No significant differences were found between the groups regarding all-cause mortality, length of hospital stay, or significant arrhythmias in patients with decompensated HF and low output and/or cardiogenic shock. A major limitation in the interpretation of these results is that most of the included studies were observational cohorts, with only one randomized trial (36 patients).[10]

A recent double-blind randomized study, called DOREMI, compared dobutamine and milrinone in 192 patients with cardiogenic shock. The primary composite outcome of in-hospital all-cause mortality, resuscitated cardiac arrest, heart transplantation, ventricular assist devices, nonfatal acute myocardial infarction, stroke, or transient ischemic attack, and the need for renal replacement therapy did not differ significantly between the groups.[11]

Thus, most of the available scientific evidence does not support the use of one drug over another. Hence, the choice of inotropic agent must be based on the patient's clinical characteristics in conjunction with the peculiarities of each drug's action and the side effects that the patient can tolerate. A summary of the differences is provided in Table 1.

Although an association of the inotropes has been little studied, it is practiced in some clinical scenarios. Patients with low cardiac output who cannot regain organic perfusion with a single inotrope and who have not yet received mechanical circulatory assistance may benefit from an association of milrinone and dobutamine. Since these drugs act through different pathways and receptors, together they may have greater power to increase cardiac output and reduce filling pressures, as has been previously indicated.[12] This association is also frequently used following heart transplantation until complete recovery of myocardial contractility is achieved, especially in recipients with primary graft dysfunction.

Most evidence in the literature is from mechanistic studies describing hemodynamic parameters[2,13] or retrospective cohorts. Randomized controlled trials comparing these two inotropes in different settings are scarce. In general, for patients with low output there seems to be little difference between inotropic drugs. Thus, the best inotrope may be determined through consideration of the patient's hemodynamic parameters.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Bonatto MG.

Table 1 – Comparison between dobutamine and milrinone

Characteristics	Dobutamine	Milrinone
Mechanism of action	β1 and β2 receptor agonist	Phosphodiesterase 3 inhibitor
Dose	2.5-20 µg/kg/min	0.375-0.75 µg/kg/min
Inotropic effect (increased cardiac output)	Equal	Equal
Vasodilation (SVR reduction)	Lower	Higher
Reduction of pulmonary artery pressure (PVR reduction)	Lower	Higher
0_2 consumption	Higher	Lower
Tachycardia/arrhythmia	Higher	Lower
Hypotension	Lower	Higher
Influenced by beta-blockers or downregulation of beta receptors	Yes	No
Tachyphylaxis	Yes	No
Cost	Lower	Higher

SVR: systemic vascular resistance; PVR: pulmonary vascular resistance.

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Ethics approval and consent to participate

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