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THERAPEUTIC DECISION IN ACUTE HEART FAILURE: INOTROPIC AGENTS OR VASODILATOR DRUGS?

INSUFICIÊNCIA CARDÍACA AGUDA (ICA) – DECISÃO TERAPÊUTICA: INOTRÓPICOS OU VASODILATADORES?

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ABSTRACT

Acute heart failure is the leading cause of hospitalization in patients over 65 years of age and is accompanied by high hospital mortality rates. In its therapeutic approach, rapid diagnosis and prompt characterization of the hemodynamic profile based on clinical signs of congestion and low cardiac output are mandatory so that we can provide intravenous drug therapy for rapid symptom relief to restore adequate organ perfusion and reduce the risk of death. Drugs to be used alone or in combination are represented by intravenous furosemide in intermittent infusion and continue to depend on the degree of pulmonary and/or systemic congestion, vasodilator drugs, and inotropic agents. Vasodilator drugs, such as sodium nitroprusside and intravenous nitroglycerin, are often added to diuretics for the treatment of acute cardiac insufficiency with hemodynamic profile B, promoting faster hemodynamic stability and prompt relief of dyspnea. Sodium nitroprusside is preferable in patients with hemodynamic profile B with high peripheral vascular resistance and severe pulmonary congestion. Nitroglycerin is preferable in patients with ischemic heart disease or acute coronary insufficiency associated with heart failure (HF). Positive inotropic agents are indicated in patients with acute HF and evidence of low cardiac output (hemodynamic profile C) to ensure improvement in tissue perfusion by increasing cardiac output, especially in patients with hypotension and worsening renal function. The association of inotropes and vasodilators should be considered when there is a combination of low cardiac output and significant increase in pulmonary and/or systemic vascular resistance.

Keywords: Heart Failure; Diuretics; Inotropes; Vasodilators agents.

RESUMO

A insuficiência cardíaca aguda é a principal causa de hospitalização em pacientes acima de 65 anos, além de possuir altos índices de mortalidade hospitalar. Na sua abordagem terapêutica é mandatório um diagnóstico rápido e pronta caracterização do perfil hemodinâmico, baseando-se nos sinais clínicos de congestão e baixo débito cardíaco, para que possamos instituir a terapêutica com drogas endovenosas para alívio rápido dos sintomas, restabelecer a perfusão adequada dos órgãos e reduzir o risco de morte. As drogas a serem administradas de forma isolada ou em combinação são representadas pela furosemida endovenosa em infusão intermitente e contínua, dependendo do grau de congestão pulmonar e/ou sistêmica, as drogas vasodilatadoras e os agentes inotrópicos. As drogas vasodilatadoras, como o nitroprussiato de sódio e a nitroglicerina via endovenosa são, frequentemente, adicionadas aos diuréticos para o tratamento da insuficiência cardíaca aguda com perfil hemodinâmico B, promovendo estabilidade hemodinâmica mais rápida e pronto alívio da dispneia. O nitroprussiato de sódio é preferível nos pacientes com IC perfil B com níveis elevados de resistência vascular periférica e grave congestão pulmonar. Já a nitroglicerina é preferível nos pacientes com cardiopatia isquêmica ou com insuficiência coronariana aguda associada à insuficiência cardíaca. Os agentes inotrópicos positivos estão indicados nos pacientes com IC aguda e evidências de baixo débito cardíaco (perfil hemodinâmico C), a fim de garantir a melhora da perfusão tissular mediante aumento do débito cardíaco, principalmente, nos pacientes hipotensos e com piora da função renal. A associação de inotrópicos com vasodilatadores deve ser considerada quando existe a combinação de baixo débito cardíaco e aumento significativo de resistência vascular pulmonar e ou sistêmica.

Descritores: *Insuficiência Cardíaca Aguda; Diuréticos; Inotrópicos; Vasodilatadores.*

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INTRODUCTION

Acute heart failure (AHF) can be defined as the new onset or recurrence of symptoms and signs of gradual or rapid development of heart failure (HF) that requires urgent intravenous therapy and subsequent hospitalization. In the United States, approximately one million hospitalizations are recorded annually, 80% of which are rehospitalizations.[1] According to the ADHERE (Acute Decompensated Heart Failure National Registry) and EHFS II (Euro Heart Failure Survey) registries II registries, AHF disproportionately affects elderly African American individuals aged approximately 75 years, with similarity in both sexes. Approximately 70% of patients have coronary artery disease, 70% have hypertension, 40% have diabetes, 30% have arterial fibrillation, 30% have chronic kidney disease, and 40% have preserved left ventricular ejection fraction.[2-4]

Several drugs have been used to control symptoms and correct hemodynamic disorders in patients with AHF, such as diuretics and vasodilator and inotropic agents.[5] The clinical decision on the use of these drugs is fundamentally based on the characterization of the predominant hemodynamic profile in each case.[6,7] The 2-min bedside noninvasive definition of clinical and hemodynamic profiles from aspects of physical examination is a safe and widely used strategy to guide the use of vasodilator drugs and/or inotropic agents in patients with acute HF.[6,7]

Therapy for AHF

Unlike the therapy for chronic HF, which relies on evidence-based medicine, the therapy for AHF is empirical and aims at reducing the immediate risk of death and providing clinical stabilization with subsequent optimization of oral therapy before hospital discharge. The evidence shows that this therapy is based on the intravenous administration of diuretics in more than 90% of patients, venous vasodilator drugs in 40% of patients, inotropic drugs in 50% of patients, and a combination of vasodilator drugs and inotropic agents in an even lower percentage of patients.[2,3] The decision on the therapeutic approach of AHF depends mainly on an adequate clinical evaluation of correct characterization and classification of the hemodynamic profile, which is based on the presence or absence of or association with congestion or hypervolemia and hypovolemia with or without signs of low cardiac output (hypoperfusion) (Figure 1).[6,7]

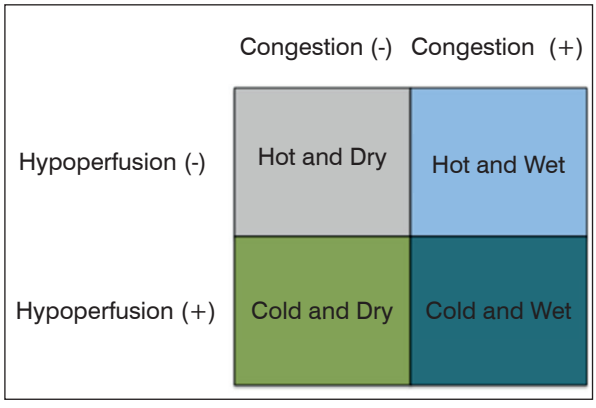

Figure 1. Hemodynamic profiles in acute heart failure.

Classification of the hemodynamic profile

The clinical presentations of HF can be categorized according to the adequacy of peripheral perfusion (hot and cold) and the presence of congestion (wet and dry). Less than 10% of patients have a hot and dry profile (Profile A) or cold and dry profile (Profile L). More than 70% of patients with HF have a hot and dry humid profile (Profile B). This group has a normal or high systolic blood pressure. Around 20% of patients have a cold and dry profile (Profile C). This group includes patients with cardiogenic shock and low cardiac output syndrome.

Treatment of AHF

The pharmacological treatment of AHF aims at rapidly relieving congestion and improving hemodynamics to prevent or treat ischemic damage to target organs such as the kidneys, myocardium, and visceral organs. The implementation of intravenous therapy is based on hemodynamic profiles (Figure 2).

Diuretics are essential drugs for immediate relief and control of systemic and pulmonary congestion, promoting rapid excretion of sodium and water.[8,9] The diuretic agent that acts on the Henle's loop (furosemide) is the most potent, increasing renal excretion of sodium by 20% to 35%, being efficient even in patients with moderate renal dysfunction (creatinine clearance <30 mL/min). It has a rapid and short onset of action and should be used intravenously at short intervals for greater efficiency. Its dosage depends on the severity and the presence, persistence, or recurrence of congestion, ranging from 40 to 320 mg/day.[9] In severe congestion (anasarca) or urgent need to relieve congestion, the use of continuous intravenous infusion at a dose of 20–80 mg/h is more effective and favors a more predictable water loss.[8,9] Its most important adverse effects are dehydration, activation of the renin-angiotensin-aldosterone system, potassium depletion, hyperuricemia, and gout. In loop diuretic resistance, the combination with thiazide diuretics in a daily dose of 25–50 mg/day or even the infusion of hypertonic sodium chloride solution may be necessary. During diuretic therapy, it is essential to monitor the patient regarding evidence of congestion, oxygenation, daily weight, diuresis, low-sodium diet, and fluid restriction, if necessary. It is important to observe for side effects such as electrolyte disturbances, symptomatic hypotension, worsening renal function, and metabolic alkalosis.

Vasodilator agents (sodium nitroprusside or nitroglycerin) administered intravenously may be necessary and are highly effective in the management of AHF. They may be necessary to correct extremely high filling pressures and/or increase in left ventricular afterload in patients with AHF in hot and dry hemodynamic profile or in extreme afterload.[6]

Sodium nitroprusside is a powerful arterial and venous vasodilator agent that acts by rapidly and drastically reducing pre- and afterload and pulmonary and systemic vascular resistance, reducing filling pressures, and increasing cardiac output. Indications for vasodilator therapy using this drug in the context of HF include the following: fast and early vasodilator therapy with sodium nitroprusside is recommended for patients with urgent need for afterload reduction (e.g., severe hypertension or hypertensive emergency with acute pulmonary edema); vasodilator therapy is also a component of therapy for patients with refractory

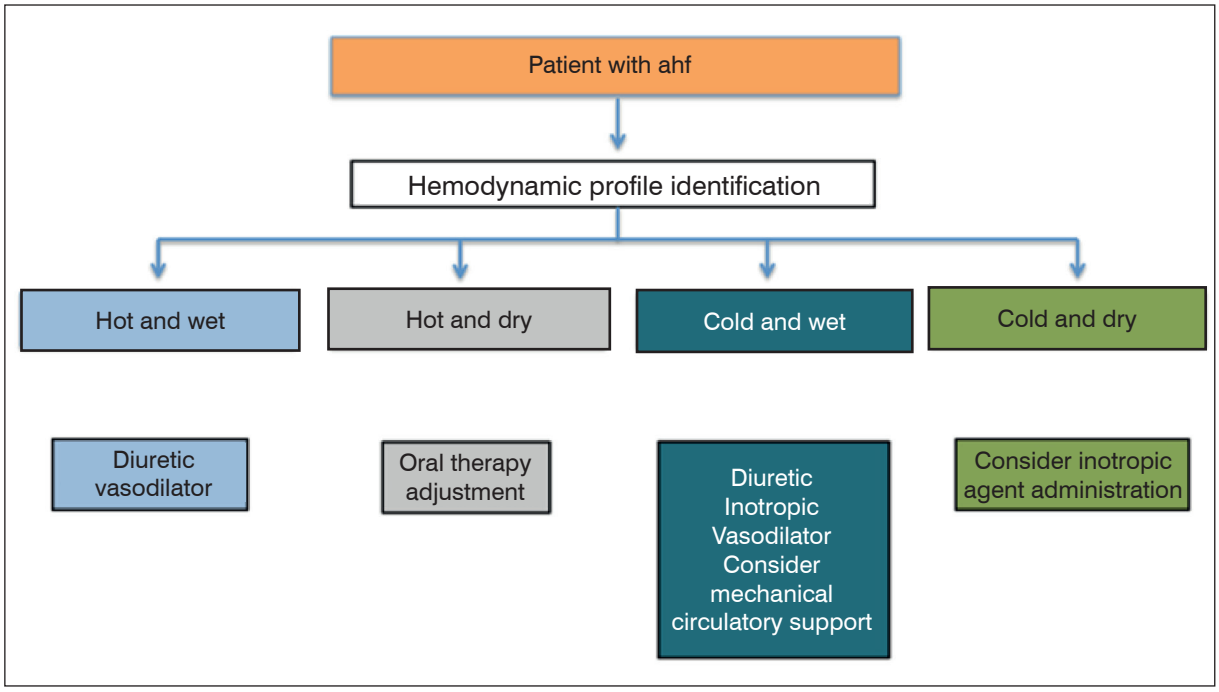

Figure 2. Management of patients with AHF based on hemodynamic profiles.

and low cardiac outputs that persist with high filling pressures or signs of hypoperfusion even with administration of inotropic agents. These patients should receive sodium nitroprusside in progressive doses of 0.5–15 mcg/kg/min.[6,7] We suggest early vasodilator therapy (usually nitroprusside) in patients with severe hypertension, acute mitral valve regurgitation or acute aortic regurgitation, and mechanical complications of infarction such as interventricular communication and acute mitral valve insufficiency. In AHF due to severe aortic valve stenosis, sodium nitroprusside should also be used in low doses to reduce pre- and afterload.[11] The use of these agents should be reduced or discontinued in the presence of symptomatic hypotension. The main limitation in the use of nitroprusside in AHF is the need for invasive pressure monitoring in the intensive care setting because its metabolism results in cyanide production. The accumulation of nitroprusside metabolites can lead to the development of cyanide, or rarely thiocyanate, being potentially fatal in high doses and prolonged use. Doses >10 mcg/min generally do not provide greater benefit and may increase the risk of toxicity to thiocyanate.

Nitroglycerin causes increased venous vasodilatation and reduced ventricular filling pressure by venous dilatation, reducing afterload by arterial vasodilatation. In higher doses, nitrates decrease systemic vascular resistance and afterload and may increase systolic volume and cardiac output. It is the treatment of choice in AHF due to ischemic heart disease or in acute coronary insufficiency complicated by HF. An initial dose of 5–10 mcg/min of intravenous nitroglycerin is recommended with increments of 5–10 mcg/min every 3–5 min, as required and tolerated (dose range of 10–200 mcg/min).[10] Tachyphylaxis can occur in a matter of hours with the administration of high doses of nitroglycerin. Potential adverse effects of nitroglycerin include hypotension and headache. Nitrate therapy should be avoided or used with caution in situations where hypotension is likely present or may result in severe decompensation, such as right ventricular infarction or aortic stenosis. Nitrate administration is contraindicated after use of phosphodiesterase-5 inhibitors, such as sildenafil.

Inotropic intravenous agents, such as dobutamine, milrinone, and levosimendan, have different mechanisms of action (Figure 3), being indispensable and formally indicated as a saving measure in patients with severe left and/or right ventricular systolic dysfunction in low cardiac output syndrome or cardiogenic shock (cold and wet (C) or cold and dry hemodynamic profiles) or after volume replacement. [12-15] Temporary intravenous inotropic support is recommended in patients with AHF with signs of low cardiac output or cardiogenic shock to maintain systemic tissue perfusion and preserve organ function until compensation or initiation of definitive therapy (e.g., coronary revascularization, mechanical circulatory support, and heart transplantation). Inotropic agents may increase heart rate and myocardial oxygen consumption and cause ischemia in patients with ischemic heart disease. Moreover, inotropic agents can aggravate atrial and ventricular arrhythmias.[12-14] Given these concerns, careful patient selection is necessary in the correct choice and use of the inotropic agent. [15]

Dobutamine is an inodilator, acting primarily on adrenergic beta-1 receptors, with minimal effects on beta-2 and alpha-1 receptors. The hemodynamic effects of dobutamine include increase in systolic volume and cardiac output and decrease in systemic vascular resistance and pulmonary capillary pressure.[12-15] It should be initially administered at a dose of 5 mcg/kg/min and, if tolerated and necessary, can be gradually increased to 20 mcg/kg/min. The most frequent adverse effects are dose-dependent, such as tachycardia and ventricular and supraventricular arrhythmias. It is important to emphasize that it does not cause hypotension, since its vasodilator effect is compensated by increased systolic volume and cardiac output. Dobutamine is the inotropic agent of choice in most cases, especially in the presence of cardiogenic shock, severe hypotension, severe hypoperfusion

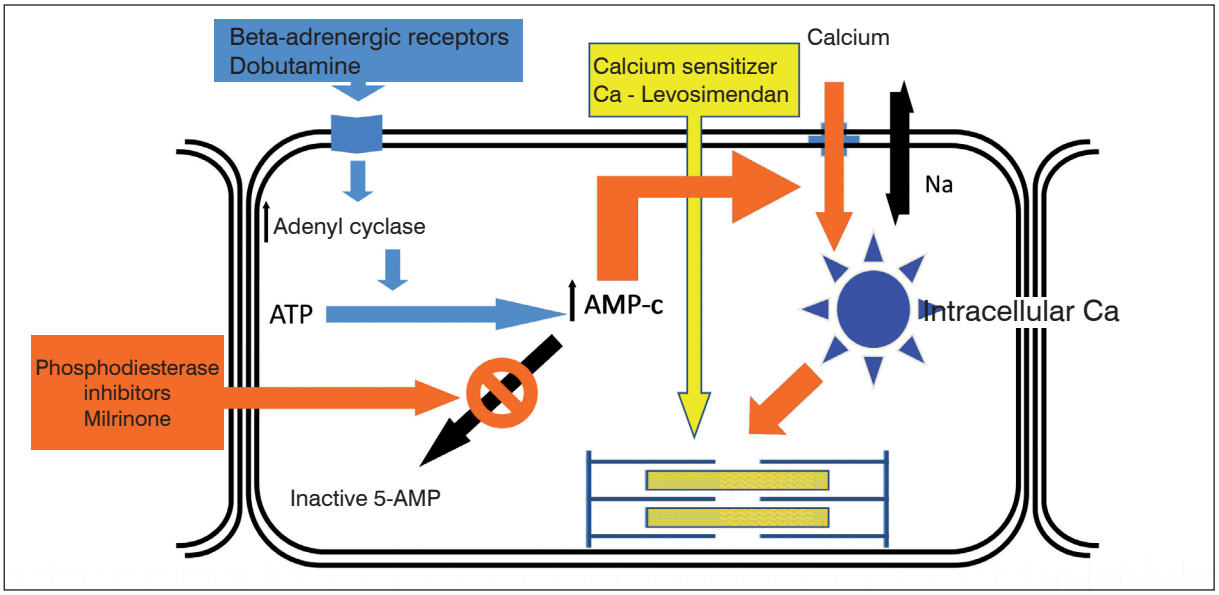

Figure 3. Inotropic agent: mechanisms of action.

with renal failure, or pulmonary congestion.[15,-18] Even patients using beta-blockers can greatly benefit from the hemodynamic effects of dobutamine, besides having a lower risk of arrhythmias. Thus, beta-blockers should not be suspended in acute decompensation of HF. Rarely, dobutamine might cause hypersensitivity syndrome associated with eosinophilia, skin rash, fever, and eosinophilic myocarditis in prolonged use as a bridge to transplantation. In view of this clinical picture, it is recommended to replace dobutamine with milrinone. In the presence of eosinophilic myocarditis confirmed by biopsy, treatment with corticosteroids is recommended.

Milrinone is a phosphodiesterase inhibitor that increases myocardial inotropism by inhibiting degradation of adenosine monophosphate. Other direct effects of milrinone include reduction of systemic and pulmonary vascular resistance (via inhibition of peripheral phosphodiesterase) and improvement of left ventricular diastolic compliance.[12,13,16-18] These changes lead to an increase in cardiac index and decrease in afterload pressures and left ventricular filling. Patients should receive an attack dose of 50 mcg/kg within 10 min, followed by a maintenance dose of 0.375 mcg/kg/min to a maximum of 0.750 mcg/kg/min. Dose adjustment is necessary in the presence of renal failure, hypotension, or arrhythmias. The attack dose should be avoided in patients with hypotension, starting with low doses and progressively increasing the maintenance dose. The effects of milrinone are similar to those of dobutamine, except that it promotes greater pulmonary and systemic vasodilatation, which may increase hypotension.[13] Milrinone is preferred over dobutamine in cases of pulmonary hypertension with right ventricular dysfunction. Since it is an inotropic agent that acts independent of the adrenergic receptor, it may be preferred in patients with AHF using adrenergic beta-blockers.[6,7,17,18] In extreme low cardiac output, dobutamine can be combined with milrinone; however, this combination increases the risk for adverse effects.

Levosimendan is a calcium-sensitizing agent that exerts its hemodynamic effects by sensitizing the contractile proteins to the action of intracellular calcium binding to protein C without increasing intracellular calcium, which theoretically would reduce the risk of cardiac arrhythmias.[19] It also has a vasodilator effect by opening sensitive adenosine triphosphate channels in the vessel wall, promoting relaxation and vasodilatation. Levosimendan has not been shown to be superior or safer in the treatment of decompensated HF than dobutamine. The main limitation of its use is the significant hypotensive effect at the initial doses. Therefore, it should be avoided in patients with cardiogenic shock or severe hypotension. Levosimendan should be diluted in 5% glucose aqueous solution before administration. Treatment should start with an attack dose of 12–24 mcg/kg, infused within 10 min (peripheral or central intravenous route), followed by a continuous infusion of 0.1 mcg/kg/min for 24 h. There has been no report on repeated administration of levosimendan. If the hemodynamic response is excessive (hypotension, tachycardia), the infusion rate can be reduced to 0.05 mcg/kg/min. If the initial dose is tolerated and an increase in hemodynamic effect is required, the infusion rate can be increased to 0.2 mcg/kg/min.[19]

The therapeutic decision should be based on a careful individual clinical evaluation that takes the following into consideration: etiology of the heart disease, hemodynamic profile, heart rate, systemic arterial pressure, degree of pulmonary congestion, pulmonary arterial pressure, signs and severity of low cardiac output, severity of pulmonary congestion, and use of beta-blockers (Figures 4 and 5). The combination of diuretic, inotropic, and vasodilator agents should be used in patients with a combination of low cardiac output and high-volume overload because it follows classical pathophysiological principles applied to AHF.[15-17] It should be emphasized that a careful and continuous evaluation of the desirable therapeutic effects is mandatory, as well as the careful titration of doses and monitoring of adverse effects.

FUTURE PERSPECTIVES

Despite therapeutic advances, AHF continues to have extremely high rates of hospitalizations, rehospitalizations, and hospital mortality, thus strongly demanding new drugs for its treatment. In this context, experiments with serelaxin and

nesiritide peptides failed. Despite showing interesting hemodynamic and natriuretic effects, they could not reduce mortality.[20] More recently, omecamtiv mecarbil, an inotropic agent that increases myocardial contractility by activating cardiac myosin and bonding and conformation with actin, was found to increase cardiac contractility without increasing intracellular calcium. In phase II studies, the intravenous and oral formulation of this molecule was proved to be safe and promoted significant hemodynamic effects compared to those of a placebo.[20] Regarding the vasodilator agents, riociguat molecule acts by activating the soluble guanylate cyclase molecule in the renal, pulmonary, and systemic vascular endothelium, increasing cyclic GMP (Cyclic Guanosine Monophosphate) and promoting vasodilatation. This drug has already been approved in the United States for treatment of pulmonary hypertension and has been tested in HF with reduced and preserved ejection fraction and pulmonary hypertension in phase II studies. These studies have reported that it has significant positive hemodynamic effects and good tolerance compared to a placebo.[20] Therefore, phase III studies, already underway, are expected to assess the reduction in morbidity and mortality in AHF.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

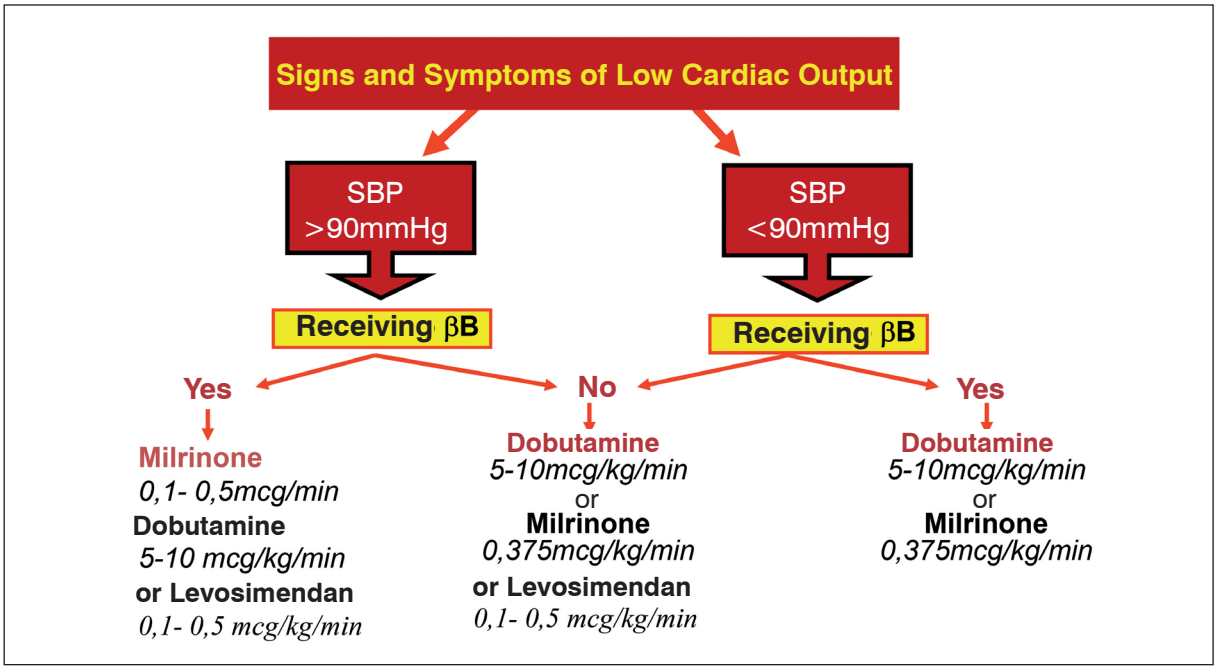

Figure 4. Choice of inotropic agent in decompensated heart failure.

Clinical picture	Preferential drug
• Cardiogenic shock or in the presence of hypotension	**Dobutamine**
• Chronic decompensated HF in patients using beta-blockers	**Milrinone/Dobutamine**
• Uncompensated HF with pulmonary hypertension	**Milrinone/Nipride**
• HF and myocardial ischemia	**Nitroglycerin**
• Arterial hypertension (APE)	**Sodium Nitroprusside**

Figure 5. Individualization of vasoactive drugs in AHF.

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