ARGENTINE SOCIETY OF CARDIOLOGY

Consensus on Inotropes and Mechanical Circulatory Support

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Summary

INTRODUCTION

Sixteen years have elapsed since the Intrathoracic Organ Transplantation Council presented its Consensus on Circulatory Assistance at the XXXIII Argentine Congress of Cardiology, published one year later in the Argentine Journal of Cardiology. This has been a period that has witnessed a prodigious progress in circulatory assistance, with the development of devices that by adopting continuous flow have allowed their miniaturization and a reduction in the technical failures that plagued the use of the first designs. (1-3)
We now present an update of that Consensus, surpassed by time, associating a consideration on the use of inotropes.

The inotropic agents mentioned in this consensus represent therapeutic modalities implemented in a wide variety of critically ill patients seeking dissimilar objectives, which, in this case, range from extreme hemodynamic support for various forms of severe heart failure (HF) and shock, organ perfusion during situations of instability, optimization of patients at risk of instability for cardiac surgery, attempt to correct postoperative ventricular dysfunction or low cardiac output syndrome (LCOS), to support for the failing right ventricle (RV) due to massive pulmonary thromboembolism (PT), or in the period after heart transplantation or after implantation of a left ventricular assist device (LVAD). Regarding acute mechanical circulatory support (MCS), it seeks circulatory assistance to reverse acute cardiovascular failure secondary to cardiogenic shock (CS) following myocardial infarction, acute myocarditis or peripartum cardiomyopathy, to stabilize a patient with mechanical complication, as part of cardiac arrest resuscitation or to provide circulatory support for high-risk procedures.

Aside from the emergency, durable devices attempt to generate hemodynamic support to reach heart transplantation in a candidate who would probably be unable to do so without support (bridge to transplantation), to evaluate a patient with characteristics that rule out transplantation but that could, eventually, be modified (bridge to candidacy), or to become the definitive therapeutic option for those who are not, nor theoretically will be, candidates for transplantation (destination therapy).

Due to multiple circumstances, this Consensus implied an unusual challenge. First, unlike other consensuses it focuses on two therapeutic methods applicable to the various scenarios mentioned. Second, and in the particular case of inotropes, the challenge was due to the limited evidence perceived in favor of any recommendation, together with a general agreement on the associated increase in mortality, added to the notable differences among these drugs.

Another circumstance to consider is what happened with the intra-aortic balloon pump (IABP), that represented the most widely used form of assistance and historically had a class I recommendation in CS, and which after the SHOCK II Trial was downgraded to IIa and IIb in later guidelines, raising questions about its contemporary role. (4, 5)

Methodology

Two methods of agreement were used to build the present document: the Delphi technique and nominal groups. The document obtained was based on scientific evidence and on the judgment and clinical experience of the participating group of experts.

The Writing Committee included cardiologists, intensivists, surgeons, and interventional cardiologists who addressed approaches for each treatment, inotrope use and circulatory support. Regarding each question, the corresponding bibliographic information was analyzed grouped according to the degree of agreement, and recommendations were formulated. An initial recommendation document was then drafted. A group of independent experts constituted the Review Committee. They analyzed the document and the corrections, which were discussed again until a final consensus was reached.

As in other consensuses, the recommendations were classified first into classes, according to the level of agreement reached and, second, according to the level of evidence (Table I).

The purpose of this document is to provide physicians with a practical tool to guide their actions in the presence of critical patients. It is important to stress that these guidelines do not represent a substitute for the good judgment of the responsible physician in charge of an individual patient, but rather constitute general norms tending to recommend conducts in complex situations. It should be emphasized, especially in the case of circulatory support, that the implementation of the recommendations could be affected by the availability and experience of the healthcare setting.

Inotropic drugs

Inotropes are a heterogeneous group of drugs that share the ability of increasing cardiac contractility, differing in many other effects and, in addition, exerting their actions through various mechanisms. We will briefly describe inotropic agents considering their indications.

Digoxin: It is a membrane Na/K pump inhibitor, allowing intracellular Na increase, which can be exchanged for Ca elevating its cytoplasmic levels.

It suppresses neurohormonal activation in chronic systolic HF and can be used as long-term therapy. In patients with HF and atrial fibrillation, it provides a certain inotropic effect and control of the ventricular response. It was widely used until the Digitalis Investigation Group (DIG) observed a reduction in the number of re-hospitalizations albeit without effect and, on the contrary, with a tendency to increase mortality. (6, 7)

Table I. Scenarios and main indications for the use of inotropes

Recommendations

CLASS I: conditions for which there is evidence and/or general agreement that the procedure or treatment is beneficial, useful and efficient.

CLASS II: conditions for which there is conflictive evidence and/or divergent opinion about the usefulness/efficacy of the procedure or treatment.

CLASS IIa: the weight of the evidence/opinion is in favor of usefulness/efficacy.

CLASS IIb: the usefulness/efficacy is less well established by the evidence/opinion.

CLASS III: conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/efficient and in certain cases may be even harmful.

Levels of evidence (on which the agreed recommendation is based)

Level of evidence A: solid evidence, derived from randomized clinical studies or meta-analyses. Multiple groups of populations at risk evaluated.

General consistency in the direction and magnitude of the effect.

Level of evidence B: evidence derived from only one randomized clinical study or large non-randomized studies. Limited groups of populations at risk evaluated

Level of evidence C: expert consensus or opinion and/or small,studies, retrospective studies, registries.

Dopamine: It is an endogenous catecholamine, precursor of norepinephrine, which shows dose-dependent effects associated with its affinity to various receptors. At low doses, less than 3 μg/kg/min it acts on dopaminergic (D)1 and D2 receptors causing arterial vasodilation, including cerebral, coronary, splanchnic and renal arteries. At intermediate doses, between 3 and 10 μg/kg/min it generates inotropic and chronotropic effects interacting with beta receptors, while, at doses higher than 10 μg/kg/min, it presents alpha effects. Due to its ability to increase renal blood flow as a result of its action on dopaminergic receptors, as well as its independent natriuretic and diuretic effects, low-dose dopamine has been considered a "renoprotective" agent. In a meta-analysis comparing low-dose dopamine versus placebo, Friedrich et al. reported absence of differences in both mortality and need for renal replacement therapy. In agreement with this study, the Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE AHF) study did not detect any change in the diuretic rhythm or renal function, while the meta-analysis of Xing et al. reported an improvement in both the diuretic rhythm and renal function, but without modifying mortality. (8-10)

In the 2013 guidelines of the American College of Cardiology/American Heart Society (ACC/AHA), the use of a renal dose of dopamine has Class IIb recommendation, level of evidence B to preserve kidney function and increase urine output in patients with HF. (11)

In the Sepsis Occurrence in Acutely Ill Patients II (SOAP II) study, dopamine was compared with norepinephrine in patients with different types of shock, including CS, but no differences in mortality were observed at 28 days. However, arrhythmic events doubled among those who received dopamine. A subgroup analysis showed increased mortality in the dopamine group among patients with CS. (12)

Dobutamine: It is a synthetic sympathomimetic, catecholaminergic drug that increases the intracellular level of cyclic adenosine monophosphate (cAMP), and acts through beta-1 receptors generating a positive inotropic effect, and on beta-2 receptors inducing vasodilation. Beta-2 stimulation is modest, and there is also a weak alpha-1 effect. It produces a significant increase in cardiac output (CO) together with a reduction in systemic vascular resistance (SVR) and no significant change in blood pressure. At high doses, greater than 10-15 mg/kg/min, it generates tachycardia, presenting a proarrhythmic effect. At doses of 2.5 to 15 mg/kg/min, both contractility and CO increase in a dose-dependent manner. It can decrease coronary vascular resistance by improving myocardial flow, but it should be used with caution in coronary patients. (13)

The Flolan International Randomized Survival Trial (FIRST), designed to assess the effect of the pulmonary vasodilator epoprostenol plus conventional therapy versus only conventional therapy in advanced HF, compared patients treated and not treated with dobutamine. It should be noted that those who received dobutamine (80 patients) represented a more severe population with 89% of cases in functional class IV (FC IV) with respect to those who did not receive it (391 patients), where 53% were in FC IV. The study endpoints were HF worsening, need for vasoactive drugs, cardiac resuscitation, myocardial infarction, and total mortality. (14)

The dobutamine "group" showed a higher incidence of first event (85.3% vs. 64.5%, P=0.0006) and mortality (70.5% vs. 37.1%, P=0.0001). An objectionable conclusion of the study was that dobutamine would represent an independent risk factor for mortality. (14)

Adrenaline (epinephrine): It is an endogenous catecholamine synthesized by the adrenal medulla with potent alpha-1, beta-1 and beta-2 agonist effects. Beta effects predominate at low doses, whereas alpha effects are evident at high doses. Epinephrine interaction with beta-1 receptors increases inotropism, mediated by beta-2 receptors it enhances chronotropism, and through alpha-1 receptors it generates arterial and venous vasoconstriction. Among its adverse effects are myocardial ischemia, tachyarrhythmias, splanchnic ischemia, hyperglycemia (secondary to hepatic glycogenolysis and decreased insulin sensitivity) and metabolic acidosis. (15)

Isoproterenol: It is a synthetic non-selective beta agonist with significant pulmonary and systemic inotropic, chronotropic and vasodilator effects, as well as a bronchodilator influence. Its main indications depend on its chronotropic effects, so it is used to increase heart rate in bradyarrhythmias, as a temporary measure until pacemaker implantation, and in the postoperative period of heart-transplantation, adding to its positive chronotropic and inotropic effects, the decrease in pulmonary resistances.

Milrinone: It is a bipyridine derivative that acts as a phosphodiesterase III (FDEIII) inhibitor preventing the degradation of cAMP, which by activating protein kinase A increases the entry of calcium into the cell with the consequent inotropic enhancement. These inotropic effects of milrinone are independent of the beta receptor, differentiating it from catecholamines and making it preferable in patients who are stabilized under beta-blockers. It presents systemic, coronary and pulmonary vasodilator effects, and can reduce right ventricular afterload and lower pulmonary pressures and resistances. It is usually administered intravenously, at a dose between 0.25 and 0.75 μg/kg/min and there are reports on its use by inhalation with exclusive effects on the lungs, avoiding its systemic action. It was initially used with a loading or bolus dose with significant vasodilator effects, which is why the 2013 ACC/AHA guidelines recommend avoiding it. (11, 16-18)

It has renal elimination and a half-life of several hours (3 to 6 hours), a period that must elapse before assessing the decrease or suspension of its dose. In case of infusion combined with catecholamines, milrinone should be previously suspended.

The Outcomes of Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study, randomly assessed milrinone, associated for 48 hours with conventional treatment for decompensated HF, versus placebo. All patients had some indication for inotrope use, but it was not an absolute requirement due to low CO. Among the 951 patients included, with an average ejection fraction (EF) of 23%, milrinone compared with placebo was associated with an increase in hypotension and atrial arrhythmias, and with no difference in mortality during hospitalization and at 60 days, or in the number of rehospitalizations. In a subsequent analysis, higher mortality was found in patients with ischemic-necrotic cardiomyopathies and benefit among those of different etiology. (19, 20)

Levosimendan: It is a calcium sensitizer that generates a conformational change in troponin C, prolonging systolic actin-myosin interaction. The increase in inotropism is not accompanied by an increase in cAMP or intracellular calcium and thus does not produce a significant increase in myocardial oxygen consumption. Its calcium sensitizing effects occur only in systole, having shown positive lusitropic effects. It causes opening of adenosine triphosphate (ATP)-sensitive potassium channels, which, at the vascular level, generates vasodilation and, at the mitochondrial level, ischemic preconditioning and cardioprotection. At high doses, it elicits phosphodiesterase III (PDE-III) inhibition. Levosimendan represents one of the most widely valued inotropic agents and is considered for HF, acute myocardial infarction (AMI), cardiac surgery, and in outpatients. (21)

Use of inotropic drugs

The appropriate role of inotropic therapy has been a difficult question to solve due to the limited evidence analyzed in large randomized controlled studies or from comparison among different drugs, certain methodological criticisms, and results which are mostly neutral or negative. Still, their use is common, based on pathophysiological considerations, but with great variability observed between institutions.

Any consideration on their rational employment should try to establish which use is supported by evidence, when it is utilized empirically and which use should be considered inappropriate, and assess these differences by trying to establish advantages of one inotropic drug over another in different scenarios. (16, 17)

The use of inotropic agents can be considered in two major scenarios (Table II):

1-During hospitalization, which is the most widely used indication for HF, cardiac surgery, post-transplantation, and after LVAD implantation or other conditions, and

2-Chronic use in ambulatory patients, administered at home or during short-term planned hospital admissions.

Use in hospitalized patients

The main indication for inotropic agents during hospitalization is evidence of tissue hypoperfusion, as a

result of primary or secondary abnormal contractility. Inotropes work by increasing contractility regardless of changes in heart rate (HR) and/or loading conditions. However, most of them cause an increase in HR, with a direct or indirect vasodilator effect. The increase in CO will be accompanied by increased myocardial oxygen demand, ischemia, and a proarrhythmic effect. (16, 17)

Critical support for hypotension with hypoperfusion Cardiogenic shock

Revascularization strategies and adjunctive therapy have led to a decrease of up to 3-4% in acute myocardial infarction (AMI) mortality. In this context, CS represents the main cause of AMI mortality as it occurs in 7-8% of cases, raising its mortality to 40-50%.

Cardiogenic shock is a primary cardiac disorder that generates inefficient CO with clinical, hemodynamic and biochemical manifestations of tissue hypoperfusion. In addition to an acute coronary event, other causes that can result in CS are acute myocarditis, various cardiomyopathies, tachyarrhythmias, massive pulmonary embolism (PE) and valve disease.

The 2017 European ST-segment elevation AMI (STEMI) guidelines consider dobutamine as the initial inotropic agent, although the recommendation is class IIb with level of evidence C. In case vasopressors are required, the recommendation is norepinephrine over dopamine, while levosimendan is considered an alternative for patients under beta-blocker treatment. Finally, they recommend avoiding the use of PDE-III inhibitors in coronary patients. (22)

The 2013 US STEMI guidelines coincide in associating dopamine with increased risk. (23)

In the 2013 ACCF/AHA HF guidelines, the temporary use of inotropes in CS was characterized as a class I recommendation until revascularization (in the case of a coronary event) or other definitive therapy

Table II. Scenarios and main indications for the use of inotropes

Scenario	Indication/Type of therapy	Clinical condition with potential application
1) Use during hospitalization		
	Critical support in hypotension with hypoperfusion	Cardiogenic shock
		Low cardiac output after cardiac surgery
	Support until resolution of another condition	Myocardial infarction
		Non-cardiac disease: sepsis, pneumonia, GI hemorrhage
		Recovery from non-cardiac surgery
	Resolution of congestion with hypoperfusion →	Acute Heart Failure with low cardiac output
	Resolution of congestion with target organ damage →	AHF with kidhey and/or hepatic failure
	Routine use during hospitalization for AHF →	AHF with congestion and without hypoperfusion
	Right ventricular failure	Pulmonary hypertension
		RV infarction
		Post cardiac transplant
		Post left ventricular assist device implantation
2) Chronic use not related to hospitalization		
	Ambulatory intermittent IV therapy in advanced HF	Bridge to transplantation
		Palliative care
	Continuous IV therapy in advanced HF	Bridge to transplantation
		Palliative care

such as circulatory support or transplantation, seeking to maintain tissue perfusion while preserving vital organs. The level of recommendation was C. (11)

The 2016 HF European guidelines coincide in granting a class IIb recommendation with level of evidence C to the use of inotropic agents in CS, also recommending dobutamine as initial treatment and proposing the alternatives of levosimendan and milrinone, the latter in non-coronary patients. (24)

In all recommendations, circulatory support should be considered early in refractory patients.

Use as support until the resolution of another condition

a) Myocardial infarction
   In AMI, the only indication for inotropic agents is the development of CS. A Cochrane review poses the benefit of levosimendan vs. dobutamine with respect to short-term mortality, although defining the evidence as low quality. (25)
b) Non-cardiac conditions (pneumonia, sepsis, gastrointestinal bleeding or non-cardiac surgery)
   In different situations, patients are treated with inotropic agents for non-cardiac conditions that lead to impaired myocardial function. (16, 17)

Resolution of congestion with hypoperfusion (but without shock)

Some patients with chronic HF are usually hospitalized for congestion requiring a negative balance based on intravenous diuretics. Following Stevenson and Nohria, these patients should be characterized as humid and hot, the vast majority, or humid and cold, approximately 10% of the total. In the latter, the use of inotropes can be considered. (16, 17, 24)

Resolution of congestion with target organ damage

Acute heart failure (AHF) with kidney (cardiorenal syndrome) and/or hepatic failure

Congestion with target organ damage, such as cardiorenal syndrome and liver impairment evidences the presence of low CO. Cardiorenal syndrome treatment targets are the evaluation of precipitating causes, hemodynamic and perfusion organ improvement, symptom relief and protection of renal function and myocardial perfusion. Current therapy focuses on the use of diuretics, inotropic and vasoactive agents, and neurohormonal antagonists.

The role of inotropic agents in cardiorenal syndrome is unknown, so their use cannot be routinely recommended.

Routine use of inotropic agents during hospitalization for AHF

Acute heart failure with congestion and no hypoperfusion

The routine use of inotropic agents in AHF without hypoperfusion has not shown benefits and has been associated with an increased risk of arrhythmias, particularly with the use of milrinone in ischemic heart disease. (16, 17, 24)

Right ventricular failure

a) Pulmonary hypertension
   In this scenario, vasopressor and inotropic therapy should be started seeking to increase right ventricular contractility and stroke volume by reducing its end-diastole volume and pressure. Norepinephrine is a first-choice vasopressor to support blood pressure and improve perfusion without generating changes in pulmonary vascular resistance. Dobutamine, levosimendan and milrinone improve contractility and increase CO. Levosimendan favorably modifies right ventricular-pulmonary artery coupling by combining its positive inotropic effects on the RV with pulmonary vasodilation. Both levosimendan and milrinone may be preferable over dobutamine in pulmonary hypertension secondary to left ventricular failure (14-16)
b) Right ventricular infarction
   Initial management of right ventricular infarction includes optimization of right ventricular preload, and in cases without response, the procedure should be similar to that for CS and right ventricular failure in pulmonary hypertension.
c) High-risk pulmonary embolism
   Right ventricular failure represents the main cause of early mortality in PE. The first objective is to maintain blood pressure, which needs vasopressor administration. Increased right ventricular contractility with reduced right afterload requires inotropic agents, such as dobutamine, milrinone or levosimendan. The use of inhaled milrinone has been proposed due to the absence of systemic vasodilation. All these are temporary measures until pulmonary reperfusion is obtained by pharmacological or mechanical means. (16-18)
d) Post-transplant right ventricular failure
   Primary graft dysfunction affects 5-10% of transplants constituting the main cause of early mortality.
e) Post-implant left ventricular assist device failure
   In this situation, 25% of patients develop RV failure, which is a main cause of early morbidity and mortality.

Inotropes in cardiac surgery

Another scenario with not adequately justified high use of inotropic agents, is cardiac surgery, in its preoperative, intraoperative and postoperative stages. In a recent meta-analysis, Belleti et al. describe that between 20% and 90% of operated patients receive inotropic agents, a circumstance that is influenced by factors such as the preoperative situation, complexity of the procedure, patient's response to the intervention,

and doctors' performance. (26)

The need for intraoperative and postoperative use of inotropes should be considered after (and never before) adjusting loading, internal milieu, heart rate and atrioventricular synchrony conditions.

Preoperative use of inotropic agents: It comprises two different situations; one, the therapeutic use, in a patient referred to surgery for refractory HF or CS of previous onset or representing the indication of the procedure (mechanical complications of AMI). The indication of inotropes resembles their use in CS outside cardiac surgery.

Another possibility is preoperative use as a preventive strategy in stable patients but at risk of developing HF or CS in the postoperative period, especially those with severe ventricular function impairment. Although inodilators generate a rapid increase in CO (and cardiac index) associated with decreased ventricular filling pressures and peripheral and pulmonary resistances which, in theory, could minimize or protect from the damage that ischemic injury induced by cardiopulmonary bypass (CPB) generates both on the heart and other organs (mainly the kidney), in practice the preoperative use of both milrinone and dobutamine has not been associated with clinical benefit and, on the contrary, has suggested an increase in mortality. (26)

However, in the case of levosimendan, some randomized studies, meta-analyses and consensuses advocate its role in the preoperative period of cardiac surgery. In most cases, the drug was infused for 24 hours before surgery and, after completing the indication, the patients underwent surgery. (27, 28)

Other studies, which have been reported as preoperative use of levosimendan, do not reflect it, as in the case of the Levosimendan in Cardio-Thoracic Surgery (LEVO CTS) and Levosimendan in Coronary Artery Revascularization (LICORN) studies. LEVO CTS is a phase 3 study led by Mehta et al., comparing levosimendan with placebo in patients with EF <35% who underwent coronary artery bypass graft surgery (CABG) with CPB or mitral valve procedures. The drug was started once in the operating room 20 minutes before induction of anesthesia, with reduction in LCOS and postoperative inotropic drug administration among those treated, but with no differences regarding mortality, renal failure, perioperative infarction, or circulatory assistance requirement. (29).

In another randomized, controlled study, Chooley et al. compared patients undergoing CABG with or without valve surgery in 13 institutions in France. The onset of levosimendan administration occurred after anesthesia induction, resulting in intraoperative use of the drug. No differences in mortality, need for renal replacement or circulatory assistance were observed. The study did not use a bolus dose and was criticized for the use of a low infusion dose, having made an incorrect calculation to detect effects on postoperative LCOS. (30)

Conversely, Landoni et al., performed a meta-analysis of randomized controlled trials of levosimendan in cardiac surgery. It included 440 patients undergoing CABG with or without CPB, valve replacement, or combined surgery who received the drug at different times of the perioperative period, with or without a bolus dose. Use of levosimendan was associated with a significant reduction in mortality (11/235 vs. 26/205, P=0.003). Different subanalyses showed that the benefit occurred in those undergoing CABG with CPB and in whom a bolus followed by prolonged infusion was used. (31)

Harrison et al. analyzed 1,155 patients from 14 randomized studies and found decreased mortality in those with reduced preoperative EF regardless of the administration time. (28)

Postoperative levosimendan

The CHEETAH study compared levosimendan with placebo in patients who developed postoperative LCOS. The study was carried out in 14 centers in Italy, Russia and Brazil, with the inclusion of 1,000 patients to assess 30-day mortality, but was stopped for futility after enrolling 506 patients. Mean EF was 50% in both groups and no differences in mortality were observed. Various details compromise the study results. First, the drug was prepared in an unusual way, and the dose used was extremely conservative, without bolus, so it could not be ruled out that a higher dose could have been effective.

Less than 50% of cases were CABG with only 2.2% (!!!) under CPB, when classically the greatest benefit was reported among these patients. Another point is given by the absence of CO assessments, which could imply the inclusion of patients with less possibility of benefit from the use of inotropes. (32)

Use of inotropic agents in outpatients

Ambulatory use of inotropic agents can occur in two different contexts: as bridge to transplantation or LVAD implantation, or as palliative treatment, and can be used continuously, intermittently or in pulses. (16, 17, 33)

In a systematic review, Nizamic et al. identified 66 inotropic therapy studies in outpatients, including 13 randomized controlled, 4 non-randomized, and 49 observational studies, mostly with a small number of patients [median of 34.5 cases (range 2 to 471)]. The most widely used drug was dobutamine (74.2% of the studies) and in 50% of them administration was intermittent. (33)

Among the total number of studies, the indication of use was unspecified in 51.5%, it was a combination of bridge and palliative use in 19.7%, bridge therapy in 16.7% and palliative use in 12.1%. Mortality was 4.2% per month with no difference between palliative use and bridge therapy. There were also no differences between continuous and intermittent use. All-cause

hospitalization was 22.2% per month, while that for HF was 10.1% per month. Before inotropic use, all patients were on FC III or IV, while after use, a 1.2-point reduction was observed. (33)

In the 2013 HF US guidelines, the use of inotropic agents as bridge to transplantation or circulatory support is considered as a IIa indication with level of evidence B, continuous use as palliative therapy is recommended as IIb with level of evidence B, while routine continuous use is contraindicated (III, B). (11)

On the other hand, the 2016 European guidelines make no reference to the chronic use of inotropic agents. (24)

Recommendations on the use of inotropes

Class I

If their use is necessary, the starting drug should be dobutamine (Level of evidence B).

The use of inotropes as temporary hemodynamic support should be considered after correction of loading conditions and acid-base disorders and optimization of heart rate and atrioventricular synchrony (Level of evidence B).

Class IIa

In patients developing CS under beta-blockers, a non-adrenergic inotropic agent (milrinone or levosimendan) should be used (Level of evidence B).

In patients who are not under beta-blocker treatment at the time of decompensation, the starting drug should be dobutamine (Level of evidence B).

In case of preoperative use of levosimendan (in coronary surgery) in selected high-risk patients with low EF, the infusion should be started 24 hours prior to the intervention (Level of evidence B).

Postoperative use (cardiac surgery) in LCOS after optimization of loading conditions, heart rate and atrioventricular synchrony (Level of evidence B).

As right ventricular support in post-transplantation or in right ventricular failure after LVAD implantation (Level of evidence B).

Use of inhaled milrinone to reduce pulmonary resistance in patients with arterial hypotension who would hardly tolerate the systemic effects of the drug (Level of evidence B).

In patients with difficult CPB weaning refractory to volume (Level of evidence C).

In patients with advanced HF awaiting transplantation or circulatory assistance (Level of evidence C).

Use of non-adrenergic inotropic agents in patients with stress cardiomyopathies (TakoTsubo) (Level of evidence C).

Class IIb

Patients admitted with advanced HF, systolic dysfunction with evidence of hypotension or hypoperfusion (but without CS) (Level of evidence C).

Palliative treatment in patients with advanced HF who are not candidates for transplantation (Tx) or circulatory assist devices (Level of evidence C).

Class III

Routine use in cardiac surgery.

Use prior to optimization of loading conditions, heart rate and atrio-ventricular (AV) synchrony.

Chronic use in the absence of a different specific indication for palliative care.

Routine use in patients hospitalized for HF with systolic dysfunction without hypotension or hypoperfusion.

As intermittent or continuous therapy in the absence of specific indications.

Preoperative use in stable patients without high risk characteristics (Level of evidence B).

Use of loading doses of milrinone (Level of evidence B).

Use of milrinone in coronary patients (Level of evidence B).

Mechanical circulatory support

Mechanical circulatory support is the partial or total cardiocirculatory function replacement by devices. It can be classified in various ways, the most important being its consideration as short-term or acute support and long-term or durable assistance.

Acute support

It uses temporary, mostly percutaneous implant devices (intra-aortic balloon pump, Impella®), although there are surgical implant devices (Levitronix Centrimag®). The purpose of their use is to obtain hemodynamic stability in a patient with refractory CS, but they can also be used prophylactically in stable patients who will undergo procedures such as cardiac surgery, arrhythmia ablation, high-risk angioplasty, percutaneous aortic valve implantation, etc.

Conceptually, in the unstable patient with failed pharmacological treatment, the improved circulatory contribution generated by the device will go from avoiding immediate death to achieving some hemodynamic stability, preventing the progression to multiorgan failure and reducing the need for inotropic and/or vasopressor agents, precluding their negative effects (Figure 1).

The underlying disease will define the objective of acute circulatory support, delineated as:

Bridge to decision: Care delivered in an extremely critical context (e.g., cardiac arrest or deep and refractory CS-INTERMACS 1®) in patients who would otherwise die in the short term, with the aim of saving time to decide whether he/she will eventually be a candidate for another form of therapy.

Bridge to bridge: Short-term support to stabilize systemic perfusion. If the patient is stabilized, but does not present myocardial recovery in days or weeks, the passage to another longer support device

will be required.

Bridge to recovery: Support initiated in the belief that there is a chance that the heart muscle will recover after a short time of assistance.

Bridge to transplantation: It is started in patients on the waiting list or candidates for transplantation who will not survive with pharmacological treatment without circulatory support. In this context, although short-term circulatory support devices may be the first line of treatment in patients in shock, and even transplantation may eventually be undertaken under this support, in general, these patients require the implantation of a durable device that will allow their clinical optimization since the waiting time can be long.

Acute support devices are:

Intra-aortic balloon pump

The intra-aortic balloon pump (IABP) represents the most widely used device, having had 52 years of uninterrupted use. From a physiological point of view, the mechanism of action produces counterpulsation, consisting of blood volume displacement secondary to its diastolic inflation and presystolic deflation. This elevates aortic diastolic pressure enhancing coronary flow (by increasing coronary perfusion pressure) and reducing ventricular ejection impedance, which decreases cardiac work and myocardial oxygen consumption, especially during the period of isovolumic contraction. The device generates limited circulatory support capable of increasing CO between 0.5 and 1 liter/minute.

Indications for the use of intra-aortic balloon pump (Table III)

1) Intra-aortic balloon pump in ischemic heart disease

- **Unstable and refractory angina:** Based on its mechanism of action, IABP is particularly suitable for patients with coronary heart disease. Historically, the device has been successful in different forms of unstable angina and in the era prior to coronary angiography and percutaneous coronary intervention (PCI) its use was effective in stabilizing a significant percentage (greater than 90%) of unstable conditions. Currently, rare refractory cases with early access to hemodynamic procedures would be stabilized with IABP, if available. (33)
- **IABP in acute myocardial infarction:** The device has been used in different AMI scenarios, both with and without CS, and in cases of mechanical complications. Historically, a number of retrospective observational studies and case series have suggested its usefulness in the treatment of AMI with CS, mainly in the era of thrombolytic therapy, leading to its widespread use and Class I recommendation in treatment guidelines. In 2012, the publication of the Shock II Trial strongly questioned its utility in this scenario. The study observed the lack of counterpulsation benefit in 600 patients with ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI) and CS, randomized to IABP, or its non-use in the context of early revascularization, analyzing 30-day mortality as primary endpoint. Mortality was 39.7% in the IABP group compared with 41.3% in the control group (p=0.69). Neither were significant differences observed in the multiple secondary endpoints, including markers (lactate, creatinine, C-reactive protein) or safety issues (bleeding, vascular ischemia, sepsis or stroke). Follow-up at one year continued to show lack of benefit. (4, 5, 33)

Beyond important study criticisms, one of the consequences was the modification in the level of recommendation for IABP in the main scientific societies, which was downgraded from IB to IIa with level of evidence B for North-American guidelines and from IC to IIb with level of evidence B for the European Society of Cardiology. (5)

Mechanical complications: They are infrequent

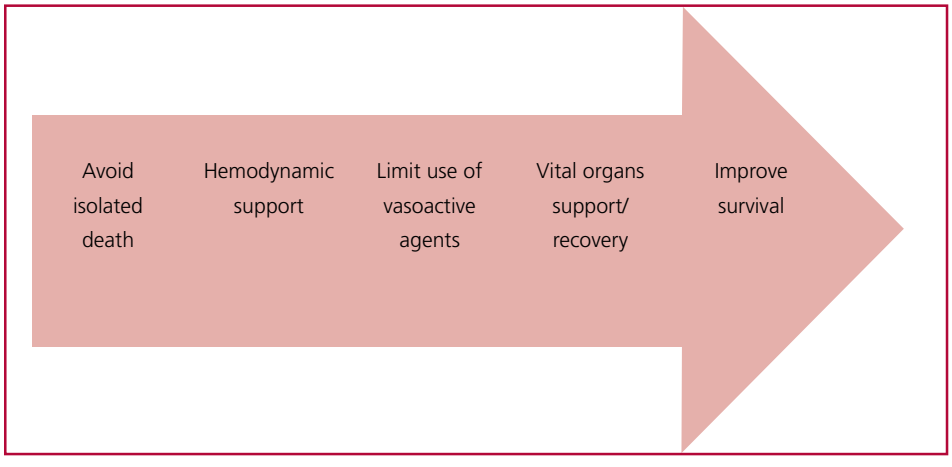


Fig. 1. Objectives of acute support

but very serious and are usually accompanied by hemodynamic instability, which can lead to the development of CS. Without surgical resolution, virtually all patients die in the short term; hence the need of how to handle the situation until the appropriate surgical moment. There is agreement to implant IABP in patients in shock, but the conduct in those who are unstable but without shock is not so clearly defined. (33, 34)

Kettner et al. analyzed the effect of IABP on mortality in a retrospective study of 81 patients followed up for 16 years, dividing the population into two categories: those with CS and those unstable but without CS. (34)

Intra-aortic balloon pump reduced 30-day mortality among patients with CS (61% vs. 100%, p=0.04) but not in unstable patients without CS (20% vs. 27%, p=0.7%), suggesting that patients with mechanical complications and CS should receive IABP as bridge to surgery. (34)

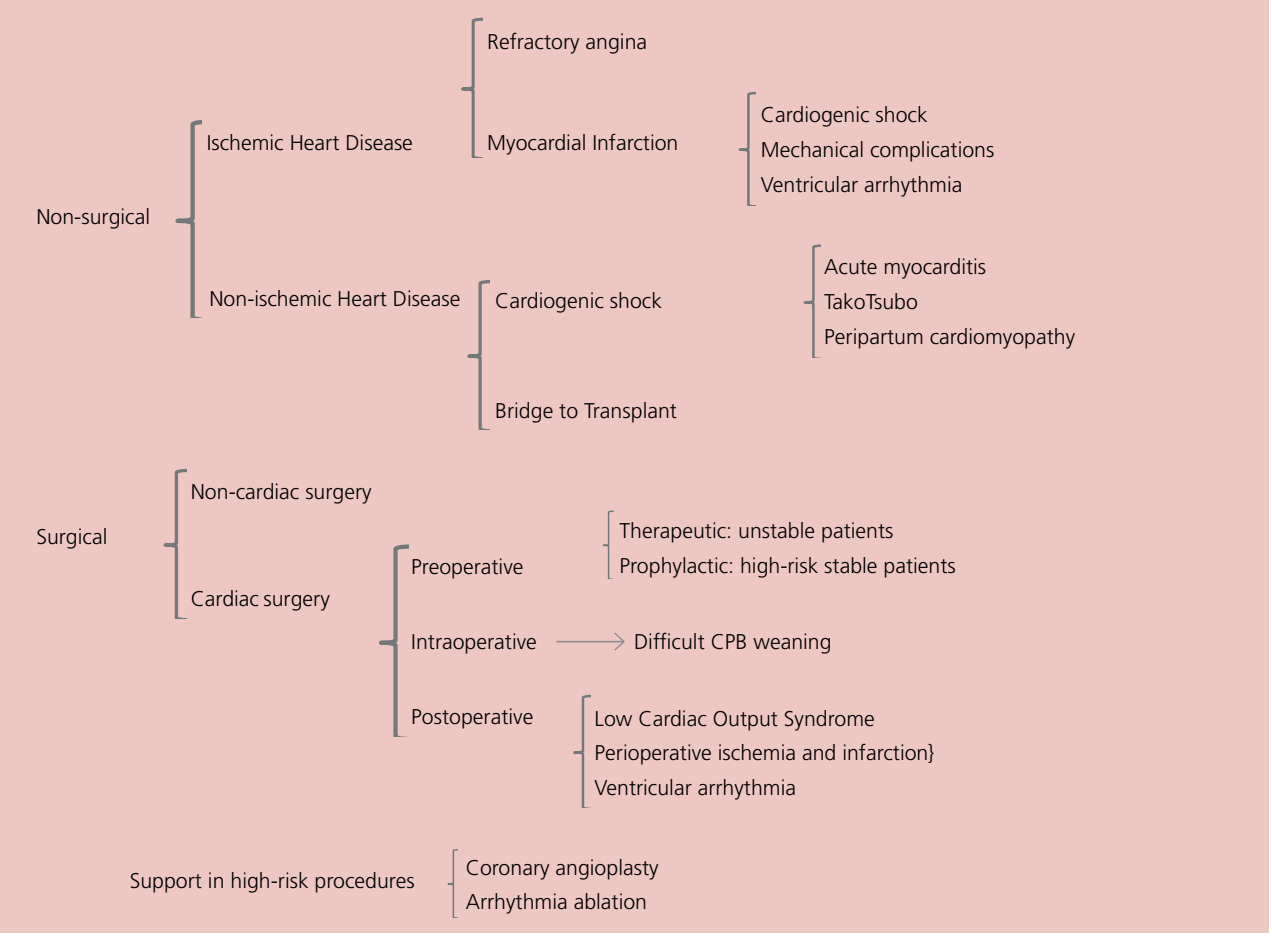
- **IABP in electrical storm:** When the etiology of arrhythmia is ischemic, the benefit is evident when the myocardial oxygen supply-demand imbalance is corrected, but even in patients without this substrate, a favorable effect of IABP has been postulated based on electro-mechanical coupling or excitation-contraction feedback, due to the fact that increased afterload induces enhanced ventricular ectopic beats and tachycardia. In addition, greater heart muscle stretching will shorten action potential duration, affecting refractoriness, while IABP, by reducing stretching and distension, will favorably modify myocardial irritability. (35)

2) IABP in cardiac surgery

Intra-aortic balloon pump is frequently used in cardiac surgery, especially to prevent or treat LCOS, in both preoperative and intraoperative or postoperative instances.

In a registry of 22,663 patients, its use for CPB weaning represented the third indication of service. Intraoperative use is limited to difficult CPB weaning, a scenario in which there is no, nor will there be, randomized evidence versus a true control group. In an approximation to this comparison, Downing et al. analyzed a group of 319 patients with difficult CPB weaning, comparing the 280 patients in whom the device was implanted versus the 39 in whom the proce-

Table III. Indications for use of Intra-aortic Balloon Pump



dure was tried, but failed.

They observed that mortality in the latter group doubled that of the former (64% vs. 33%; p=0.03). In an extensive review of cardiac surgery, Baskett et al. defined this use as a class I recommendation with level of evidence C, in line with what was proposed by the 2012 SAC Cardiovascular Recovery Consensus. (33, 36-38)

In the postoperative period, the main indication for use is LCOS refractory to inotropic therapy, although it has also been employed, to a lesser extent, in postoperative ischemic events and in the presence of complex refractory ventricular arrhythmia. Postoperative use is usually associated with higher mortality compared with intraoperative or preoperative application. (33, 36, 38)

Postoperative use was graded as a class IIa recommendation, level of evidence C, by Baskett et al. for coronary patients, whereas, for the SAC Cardiovascular Recovery Consensus, postoperative use for both LCOS and ischemia was opportunely considered as class I, level of evidence C. (33, 38)

The most controversial indication in cardiac surgery is preoperative use in stable patients, but with characteristics that present them as potentially high-risk cases. Several studies, including patient series, case-control studies, small randomized controlled studies and some meta-analyses, have sustained the usefulness of preoperative use of IABP with reduced mortality or postoperative LCOS, or both, while others have failed to demonstrate benefits. Probably a good part of the explanation for such differences lies in correctly defining patients at high potential risk, including patients with low EF, previous surgery, refractory unstable angina, recent AMI, failed PCI and/or severe main coronary artery injury, alone or combined. (33, 38, 39)

Dyub et al., in a meta-analysis on 2,363 patients undergoing CABG, concluded that there is a beneficial effect of preoperative IABP on mortality, establishing that the necessary number of patients to treat was 17 in order to prevent one hospital death, which is reduced to 7 if only randomized studies are considered. (39)

In a systematic review and meta-analysis that included 46,067 patients, Poirier et al. analyzed recent evidence comparing randomized controlled studies vs. observational studies. In the former, a reduction in perioperative mortality was found, as well as a shorter stay in critical and hospital areas, an effect not observed in observational studies. An explanation could be related to the fact that many randomized studies (5 out of 8) corresponded to the same group and a single institution, in addition to a small number of patients, while observational studies included a high number of cases. (40)

Other indications for the use of IABP

IABP as support of percutaneous procedures: The Benchmark Registry detected percutaneous procedures as the most frequent indication for use of support. It is reasonable to consider that a patient with impaired ventricular function will poorly tolerate the ischemic insult added by the procedure, as well as those with an intervention on an artery that supplies an extensive territory (left main coronary artery injury). (33, 36)

IABP as bridge to transplantation: In an era where more than 50% of patients who arrive to transplantation are under MCS, IABP has a relevant role, especially in those with presumed long waiting time, and when a subclavian or axillary implant should be considered, which will allow these patients to move out of bed, avoiding the undesirable consequences of prolonged immobilization.

IABP in non-cardiac surgery: There are more than 100 reported cases of IABP use in non-cardiac surgery, most of them in abdominal procedures.

Usefulness in patients with extracorporeal membrane oxygenation (ECMO): The use of venoarterial ECMO is associated with increased ventricular afterload, which can be harmful in a patient with circulatory failure. Management of the situation involves various strategies, such as use of inotropic agents, vasodilators (if tolerated), placement of a left ventricular drainage, a septotomy procedure or IABP implantation.

Contraindications for the use of IABP: The main contraindication is determined by moderate or severe aortic regurgitation. Others are persistent ductus, dynamic obstruction of the left ventricular outflow tract, and aortic pathology (dissection-aneurysm, etc.). (41, 42)

IABP complications: The main complications are ischemic followed by hemorrhagic and infectious situations.

The following recommendations are established for the use of IABP:

Class I

Difficult CPB weaning in patients under refractory inotropic support (Level of evidence C).

As strategy to reduce afterload in patients under veno-arterial ECMO (Level of evidence C)

Class IIa

Mechanical complications of AMI (ventricular septal defect [VSD], acute mitral regurgitation [MR]) in patients with CS (Level of evidence B).

Preoperative use in cardiac surgery in unstable patients (Level of evidence B)

Preoperative use in cardiac surgery in stable high-risk patients (Level of evidence B)

Cardiogenic shock due to AMI, in patients who are refractory to inotropic agents (Level of evidence C)

Subclavian use as bridge to transplantation in experienced centers. (Level of evidence C)

Class III B

Use in all AMI patients with CS.

Preoperative use in stable low-risk patients.

Extracorporeal membrane oxygenation

The ECMO device, which consists of a centrifugal pump, a membrane oxygenator, a cannula system and a management console, represents an evolution of extracorporeal circulation.

There are two different ECMO configurations: veno-venous (V-V) and the veno-arterial (V-A). In V-V ECMO, blood is drained from the right circuit, and after it is oxygenated and CO2 is removed, it returns to the same venous circuit, providing only respiratory support. This form is used in refractory respiratory failure and in intensive care, so its analysis exceeds this Consensus. The V-A form of ECMO provides both respiratory and hemodynamic support, differentiating itself from the previous configuration in that blood returns to the arterial system, and is used for assistance in different scenarios of CS and cardiac arrest. (41, 42)

Hemodynamic effects of V-A ECMO: It allows restoring systemic blood flow, providing adequate tissue perfusion and rapidly decreasing the requirements for inotropic and vasopressor drugs. There are two competing hemodynamic effects on the left ventricle (LV) that result, on the one hand, from blood drainage from the venous system decreasing preload, while, on the other hand, the return of blood to the arterial system increases left ventricular afterload and cardiac work.

Complications: ECMO support is effective and safe when performed by experienced groups, but many of the complications are related to the critical clinical condition of the patients. Complications described include bleeding, thrombotic events, infections, neurological events, left ventricular distension, renal or hepatic dysfunction, and limb ischemia during peripheral cannulation.

Regarding left ventricular distension, it should be noted that ECMO does not return blood to the LV. When its function is severely impaired, the LV may be unable to pump the blood volume it receives through the pulmonary circulation, an effect magnified by the increased afterload generated. The use of inotropic agents during V-A ECMO support may facilitate ventricular ejection, while IABP represents another option. (41, 42)

Contraindications: They include the impossibility of performing anticoagulation, the presence of irreversible symptoms, multi-organ failure, prolonged resuscitation, aortic dissection and severe aortic regurgitation. In the case of peripheral cannulation, peripheral vascular disease can prevent its implementation.

ECMO in guidelines and consensuses

Although V-A ECMO is considered in conjunction with other forms of acute support, in some documents it is specifically analyzed.

The European guidelines for acute and chronic HF mention ECMO among the devices for acute support, intended for use in CS patients (INTERMACS 1) to provide hemodynamic stabilization, as bridge to decision or bridge to bridge, without establishing a specific recommendation.

The guidelines of the Brazilian Society of Cardiology establish the following recommendations for ECMO (41):

As bridge to decision (Class I recommendation, level of evidence C).

As bridge to recovery (Class I recommendation, level of evidence C).

As bridge to transplantation (Class IIa recommendation, level of evidence C).

Based on the above, the following recommendations for the use of V-A ECMO are considered:

Class IIa

If immediately available, use as bridge to decision after cardiac arrest with a short time of adequate resuscitation in selected patients (young people without evidence of previous disease) (Level of evidence C).

If immediately available, use as bridge to recovery in selected patients (Level of evidence C).

If available, use as bridge to transplantation in selected patients with progressive deterioration, refractory to inotropic agents and IABP, in a time-dependent strategy prior to irreversible multiorgan dysfunction (Level of evidence C).

If available, use is recommended as acute hemodynamic support in potentially recoverable patients with isolated severe left ventricular failure (CS-INTERMACS I), isolated right ventricular failure, or combined biventricular failure, refractory to pharmacological treatment, with or without added refractory respiratory failure (Level of evidence C).

Class IIb

Postoperative use in cardiac surgery in the event of difficult CPB weaning (Level of evidence C).

Class III

Use in all patients after cardiac arrest.

Use in patients with irreversible multiorgan failure.

Use in patients with evidence of neurological damage.

TandemHeart® (left atrial-aortic bypass)

The TandemHeart® (CardiacAssist, Pittsburgh, PA) is a radial, continuous flow device that represents a dependent, paracorporeal assistance, initially for exclusive left heart support, although its use exclusively for right heart assistance has recently been developed. In its left configuration, the system consists of a 21 Fr infusion cannula, positioned in the left atrium and requiring interatrial transseptal puncture, a 15 or 17

Fr return cannula, a centrifugal pump capable of generating a flow of 4 to 5 L/min and a control console. (41, 42)

The TandemHeart works in parallel (or in tandem) with the LV, redirecting blood from the left atrium into the peripheral arterial system, unloading the LV while reducing its wall tension, cardiac work, and oxygen consumption. The peripheral circulation is perfused by both pumps acting in parallel. For right support, the input cannula is placed in the right atrium and the output cannula in the pulmonary artery.

TandemHeart clinical data and guidelines

Thiele et al. described in 2001 the use of the TandemHeart in 18 patients with infarction and CS with significant cardiac index and mean arterial pressure improvement, decrease in filling pressures and 44% 30-day mortality. (43)

The 2015 Society for Cardiovascular Angiography and Interventions/American College of Cardiology/Heart Failure Society of America/Society of Thoracic Surgeons (SCAI/ACC/HFSA/STS) Clinical Expert Consensus suggests that the TandemHeart should be used in patients with severe left ventricular dysfunction (EF <35%) or recently decompensated HF associated wih complex angioplasty and continuous deterioration of CS despite IABP. (42)

The TandemHeart device is not available in Argentina.

Impella® devices

Impella® (Abiomed, Inc., Danvers, MA, United States) is a platform of percutaneous devices consisting of an axial flow micropump mounted at the end of an intravascular catheter that, based on the Archimedean screw principle, continuously pumps blood from the LV to the ascending aorta, constituting a dependent and paracorporeal assistance in series with the heart.

There are 4 different forms of Impella, three of them for left ventricular support: Impella 2.5 (2.5 L/m, with 12 Fr diameter), Impella CP (3.5 L/m with 14 Fr diameter) and Impella 5.0 (5 L/m with 21 Fr diameter), and Impella RP which has been developed for right heart support. In this case, it is implanted through the femoral vein in the inferior vena cava or right atrium with its distal end in the pulmonary artery, and is capable of generating up to 4 L/min with a diameter of 22 Fr. (41, 42)

From a hemodynamic point of view, by ejecting blood into the ascending aorta it unloads the LV and increases antegrade flow, reducing myocardial oxygen consumption and improving blood pressure with a reduction in pulmonary capillary pressure. Its effective performance requires a preserved right ventricular function or the use of some kind of right heart support. In contrast to ECMO, Impella does not offer the possibility of blood oxygenation. Left heart support devices have been approved by the United States Federal Drug and Device Administration (FDA) as circulatory support for up to 6 hours. Recently, as a result of the PROTECT I and PROTECT II studies, both Impella 2.5 and Impella CP have been authorized for use in stable patients undergoing high-risk PCI. (42)

Impella contraindications: They include the presence of a mechanical prosthesis in aortic position, left intraventricular thrombus, severe aortic stenosis, moderate to severe aortic regurgitation, interatrial or interventricular septal defect, significant aortic disease, significant peripheral vascular disease, severe right ventricular dysfunction, and impossibility of anticoagulation. (42)

The family of Impella devices is not available in Argentina.

Levitronix Centrimag®

The Centrimag® Acute Support System (Thoratec Corporation, Pleasanton, CA, United States) consists of a surgically implanted centrifugal pump capable of generating up to 10 L/min, a control console, and a cannula system that connects them to the patient. It is a radial, continuous flow device, whose magnetically levitated and hydrodynamically suspended rotor minimizes friction generating less hemolysis and inflammatory response, and is widely used in the United States and Europe to provide short and mid-term circulatory support in various scenarios. It is available for use in Argentina since 2007.

Centrimag is a versatile assistance tool that can be used for left, right and biventricular support, in which case two devices will be required, or be part of an ECMO circuit. (43)

As right support, Centrimag has been used for up to 30 days, while as left support it is only accepted for up to 6 hours, although in practice there are references of prolonged use, even longer than 90 days. (41-43)

The implantation requires a median sternotomy and CPB to allow the necessary cannulation maneuvers without generating greater hemodynamic compromise in CS patients.

Some recent experiences with Centrimag as bridge to next decision report between 44% and 73% 30-day survival. (41-43)

Recommendations for acute support

Class IIa

Recommendations are the same as those previously established for ECMO.

If available, use Levitronix Centrimag for patients with left, right, or biventricular failure, as bridge to decision, recovery, or transplantation in whom a need for support greater than 5-7 days is presumed (Recommendation level C).

Use as bridge to bridge in patients with a previous form of assistance (IABP or ECMO), without evidence of cardiac recovery after a period of initial support with these devices (Recommendation level C).

Class III

Use in patients with irreversible multiorgan dysfunction.

Use when there is evidence of neurological damage.

"Durable" devices

During the 1960s, and mainly since the start of the Artificial Heart Program of the National Heart, Lung, and Blood Institute in 1964, the main intention of circulatory support was to obtain the definitive replacement of the heart by means of a totally artificial heart. In the 1990s, LVAD became a bridge to transplantation, and it is still frequently used today. The observation of patients assisted for prolonged periods with modification of conditions that rendered them ineligible for transplantation, such as severe pulmonary hypertension or kidney or liver dysfunction, led to the concept of bridge to candidacy or to optimize a candidacy (to transplantation), which currently represents the second indication for the use of durable devices, after destination therapy. (41, 42)

In 2002, and after the publication of the REMATCH study, the durable HeartMate XVE® device (HeartMate I®) became the first approved definitive management strategy for patients not eligible for transplantation. In this study, 129 patients with advanced AHF in functional class IV, with EF <25%, were randomized to durable pulsatile device implantation or optimal medical treatment. The primary objective of the study was to compare survival in the two groups at one and two years, and a significant difference was observed in favor of LVAD. (44)

A second study (INTREPID) compared the Novacor® pulsatile device versus optimal medical treatment in another population of FC IV patients, not candidates for transplantation, confirming the benefit in favor of LVAD. (45)

Numerous technological advances and fundamentally the adoption of continuous flow significantly simplified the mechanics of LVAD by maintaining a single mobile part. This resulted in a decrease in the number of failures, which added to its miniaturization, allowed the application of LAVD to initially excluded population groups, such as women, young patients and even children.

In 2009, Slaughter et al. randomly compared the second-generation HeartMate II® device versus the HeartMate XVE®, and observed a notable increase in survival in those treated with the former device. Moreover, the primary composite endpoint of stroke-free time and need for LVAD repair or replacement at 2 years, added to the incidence of various complications, demonstrated the greater safety of the new technology. (46)

In 2008, HeartMate II was approved as bridge to transplantation, followed two years later by its approval as destination therapy.

INTERMACS: The INTERMACS Registry, representing a joint initiative of the Heart, Lung, and Blood Institute, the FDA and the Medicare and Medicaid Centers based at the University of Birmingham, Alabama, collects information on the implantation of durable devices in the United States and Canada. (41, 42)

A fundamental aspect of the registry was the development of INTERMACS profiles that allowed the proper characterization of patients with AHF, in FC IV. The seven profiles of increasing severity ranging from INTERMACS 7 (Heart Failure FC III) to INTERMACS 1 or refractory CS represent stages of growing severity suggesting the implantation of LVAD. Experience has shown that if one considered the early use of a durable LVAD in INTERMACS 5 to 7, the associated risks would outweigh the benefit, whereas, on the contrary, if one waited until INTERMACS 1, the possibility of patient recovery would be low and his survival minimal. The observation of the Registry suggests that implantation in INTERMACS profiles 3 and 4 seems to be the ideal balance between risks and benefits. (41, 42, 47)

Modern durable devices

The first generation of durable devices were large pulsatile pumps that, although superior in terms of survival versus medical treatment, presented a significant number of complications. In their second generation, the devices were smaller and more reliable and adopted continuous blood flow. The HeartMate II presents an internal rotor with fixedends and a magnetic field that continuously spins the rotor to pump blood. In the currently used third-generation of continuous flow devices, the rotor is suspended in the blood flow using a noncontact design through magnetic levitation, thus minimizing friction and material wear. These devices are smaller in size and weight, allowing them to be implanted in the pericardium.

Their characteristics, added to improved results, have led durable devices to be considered as a therapeutic reality, so far only available for developed societies.

These devices are used for three different purposes: as bridge to transplantation, bridge to candidacy or destination therapy. (41, 42)

HeartMate II (Thoratec Corporation, Pleasanton, CA, United States): From INTERMACS data, it is the most widely used durable device in the United States and other countries. It is an axial continuous flow device with a rotating impeller that uses a principle similar to the Archimedes screw. It has a maximum displacement of 10 liters per minute and represents an exclusively dependent and intracorporeal left ventricular support, parallel to the circulation. (41,42)

Currently, more than 25,000 HeartMate II devices have been implanted with a reported maximum dura-

bility of 11 years.

HeartWare HVAD® (HeartWare, Framingham, MA, United States): It is a small, continuous radial flow device that allows intrapericardial placement. It represents an intracorporeal support, magnetically levitated and hydrodynamically suspended. Although it provides left ventricular support, its right use has been reported for biventricular assistance. It has a displacement volume of 50 mL and can generate a flow of 10 L/min. (41, 42)

It was approved in Europe in 2009, in Australia in 2011 and by the FDA as bridge to transplantation in 2012, after the results of the ADVANCE study. In 2017, the FDA approved its use as destination therapy based on the results of the ENDURANCE study. (41, 42, 48, 49)

HeartMate III®: It is a magnetically levitated and powered continuous flow device with intrapericardial implantation. Considered by some to be the first representative of a fourth-generation device, due to its supradiaphragmatic position, it would represent, in reality, another component of the third-generation device due to the lack of impeller supported by two bearers. It is capable of generating up to 10 L/min. (42)

The results of the MOMENTUM 3 study comparing HeartMate II and HeartMate III presented in 2019, showed significant benefits of HeartMate III for the primary combined endpoint of freedom from stroke, reoperation for LVAD replacement or removal, and more than 2 years durability. This LVAD presents a system of alternating rotor speed, generating a blood pulse. Although this pulse is not clinically evident, it would lead to better rotor clearing, avoiding blood stasis and preventing the formation of microthrombi. (50).

The main studies where these devices were evaluated are found in Table IV.

Guidelines and Consensuses on durable devices: Several guidelines and consensuses have established recommendations on the use of durable devices: the 2013 ACCF/AHA Guideline for the Management of Heart Failure published a recommendation for the implantation of a durable support, the International Society of Heart and Lung Transplantation, also in 2013, released an extensive document focused on the topic of circulatory support, the European Society of Cardiology reported recommendations for durable assistance in acute and chronic HF guidelines and the Brazilian Society of Cardiology issued very specific directions in this respect. (11, 24, 41, 42, 51)

The American Society HF guideline classifies this document as Class IIa, level of evidence B, considering the use of durable assistance reasonable to prolong life in selected patients with stage D HF and systolic dysfunction. (11)

The MCS guideline of the International Transplantation Society (2013) establishes, among others, the following recommendations:

Class I

All patients who are candidates for circulatory support must have previously undergone a transplantation evaluation (Level of evidence A).

All patients evaluated for support must have his/her INTERMACS profile established (Level of evidence C).

Pulmonary vascular resistances should be evaluated invasively in all candidates for support (Level of evidence C).

Patients with a history of treated cancer with long-term remission or who are considered disease-free may be candidates for MCS (bridge to transplantation), but require an oncological evaluation (Level of evidence C).

A psychiatric evaluation should be performed on all candidates for MCS (Level of evidence C).

Class IIa

Inotropic-dependent patients should be evaluated for MCS, due to their high mortality under medical treatment (Level of evidence B).

Patients with high mortality at one year according to prognostic scores should be evaluated for advanced therapies, including MCS (Level of evidence C).

Patients with history of treated malignancies and good life expectancy (> 2 years) may be candidates for MCS as destination therapy and require an oncological evaluation (Level of evidence C).

Class III

Patients with irreversible multiorgan dysfunction should not be considered for MCS (Level of evidence C).

Circulatory support is not recommended in patients with active cancer or with life expectancy <2 years (Level of evidence C).

Permanent dialysis should be considered a contraindication for MCS (Level of evidence C).

The European guidelines for acute and chronic HF establish two recommendations for durable support: Recommendation IIa with level of evidence C as bridge to transplantation and recommendation IIa with level of evidence B for non-transplantation candidates (destination therapy).

The Brazilian guidelines for circulatory support establish recommendations for durable devices in patients with systolic HF based on the INTERMACS level, coinciding in their use as bridge to transplantation, destination therapy, or bridge to candidacy:

Recommendation IIa (Level of evidence C) in patients with systolic HF and INTERMACS profiles 2 to 3.

Recommendation IIb (Level of evidence C) in patients with INTERMACS profile 4, and

Recommendation III (Level of evidence C) in cases with profiles 1, 5, 6 and 7.

Based on all of the above, the following recommendations for durable devices are established:

Table IV. Modern studies on durable devices

Parameters	HeartMate II Bridge to transplant	HeartMate II Destination therapy	ADVANCE	ENDURANCE	MOMENTUM 3 short-term	MOMENTUM 3 long-term
Comparison	HM II vs BMT	HM II vs HM XVE	HVAD vs other LVAD	HVAD vs HM II	HM II vs HM III	HM II vs HM III
Design	Non-randomized	Randomized 2:1	Non-randomized	Randomized 2:1	Randomized 1:1	Randomized 1:1
Number of patients	133	200	140	446	294	366
Patient profile	NYHA IV in waiting list for Tx	NYHA III y IV ineligible for Tx (Destination therapy)	NYHA IV in waiting list for Tx	INTERMACS 1-4 ineligible for Tx (Destination therapy)	INTERMACS 1-4 both in w. list as ineligible for Tx	INTERMACS 1-4 both in w. list as ineligible for Tx
Patient objective	improved survival at 6 months	improved free-of-event survival at 2 years	survival < 1 year	Non-inferiority event-free survival at 2 years	Improved free-of-event survival 6 months HMIII vs HMII (86.2% vs 76.8%)	Improved free-of-event survival 2 years
Functional capacity	Improved	Improved (both groups)	Improved (both groups)	Improved (both groups)	Improved (both groups)	Improved (both groups)
Quality of life	Improved	Improved (both groups)	Improved (both groups)	Improved (both groups)	Improved (both groups)	Improved (both groups)
Major adverse events	Bleeding, stroke, infections, device failure (in HM II)	Except stroke and reoperation for device failure (in HMII)	Similar stroke infection, bleeding device failure	Higher stroke rate in HVAD (9.7% vs 12.1%)	No thrombotic event in HMIII at 6 months Major dysfunction in HMII (13.4% vs 7.8%)	Minor stroke in HMIII

BMT: Best medical treatment. **HMII:** Heart Mate II. **HMIII:** Heart Mate III. **HVAD:** HeartWare. **Tx:** Transplantation.

Class I

All patients considered for durable support must undergo a transplant evaluation (Level of evidence A) and have a defined INTERMACS profile (Level of evidence C).

All patient candidates for durable support must have right ventricular function assessment and established risk of postoperative right failure.

Class IIa

Patients with severe systolic dysfunction and INTERMACS profiles 2 and 3 can be candidates for durable devices, both as bridge to transplantation, candidacy or destination therapy (Level of evidence C).

Class IIb

Patients with severe systolic dysfunction and INTERMACS profile 4 can be candidates for durable devices, both as bridge to transplantation, candidacy or target therapy (level of evidence C).

Class III

Patients with INTERMACS profiles 1, 5, 6 and 7 are not candidates for implantation of durable devices (Level of evidence C)

Patients with active malignancies or life expectancy <2 years are not considered candidates for durable devices.

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