Decompensated heart failure (DHF) is one of the main causes of hospital admissions anywhere in the world and is responsible for a significant amount of public health expenditures. Epidemiological data indicate that heart failure (HF) incidence is increasing progressively, particularly in the elderly.

DHF is a clinical syndrome that more investments in human and physical resources must be done. Also, new treatment options should be directed to improving quality of life, decreasing the length of stay of hospitalized patients and increasing survival.

The clinical syndrome of DHF, until recently, has been poorly studied and not clearly characterized. One of the very first documents to focus on this entity was the Ist Latin American Guidelines on Decompensated Heart Failure. DHF is generally defined as a clinical syndrome in which a structural or functional heart abnormality leads to the incapacity of the heart to eject and/or accommodate blood within physiologic pressure values, thus causing functional limitation and requiring immediate therapeutic intervention. This broad definition encompasses three major points: a pathophysiological explanation, a clinical picture presentation and the need for urgent therapeutic intervention.

DHF can be divided in three categories:

1) Acute HF (without a previous diagnosis): Corresponds to the clinical situation in which the clinical syndrome of heart failure occurs HF in patients with no previous signs and symptoms of heart failure.

2) Chronic DHF (acute exacerbation of a chronic condition): corresponds to the clinical situation in which there is acute or gradual exacerbation of signs and symptoms of HF in patients at rest with a previous diagnosis of HF that require additional and immediate therapy.

3) Refractory chronic HF (chronic low output and/or various degrees of congestion): corresponds to the clinical situation in which patients with a previously diagnosed HF present low output and/or systemic congestion and/or persistent functional limitation refractory to the best possible drug treatment

Two major clinical presentations need also be defined, since they deserve special attention:

1) Pulmonary edema: corresponds to the clinical situation in which there is a rapid increase in the pulmonary capillary pressure leading to an increase of fluid in the interstitial and alveolar pulmonary spaces causing sudden and intense dyspnea at rest.

2) Cardiogenic shock: characterized by severe arterial hypotension (systolic pressure <90 mmHg or 30% below baseline levels) for a minimum period of 30 minutes, with signs of tissue hypoperfusion and organic dysfunction (tachycardia, pale skin, cold extremities, mental confusion, oliguria and metabolic acidosis), due to a cardiac cause.

Many international studies have tried to identify the factors associated with hospital admissions for DHF. In approximately 30% of the cases, however, it is not possible to identify the reasons for clinical decompensations. The most common reasons for dec compensation are listed in table 1.

The first step is to decide whether the patient needs to be admitted, or if he can be managed in the emergency room. The main reasons to admit a patient with ADHF can be divided into 3 categories:

1) Immediate hospitalization, representing situations in which there is immediate risk of death;

2) Urgent hospitalization: when there is no immediate risk of death, but the patient can evolve into that if urgent interventions are not taken.

3) Optional: the need for admission depends on the interaction of clinical and laboratory variables, together with the patient prognosis.

The criteria for hospitalization are listed in table 2.
2) Hemodynamic stabilization

The second goal is to improve hemodynamics and tissue perfusion. In many patients with severe episodes of DHF, peripheral hypoperfusion is not easily identified clinically. Unrecognized low cardiac output states can lead to end organ damage and further worsening of heart failure and impair prognosis. In particular, concomitant diuretic administration in a low cardiac output state can further decrease the effective output, leading to a spiral of progressive deterioration. Hemodynamic stabilization can be achieved by the administration of intravenous vasodilators, inotropic agents or a combination of both. Some patients will need hemodynamic support with circulatory assist devices.

3) Relief of congestion

The third goal is to decrease volume overload, which can be achieved with intravenous diuretics, and inotropic agents to increase renal perfusion.

GENERAL THERAPEUTIC MEASURES

There are several interventions that should be initiated in DHF patients (table 3):

Diet

Low-sodium diet should be instituted to all patients. For those patients with diuretic resistance, water intake should be restricted to the minimum tolerated (usually 800 - 1,000 ml per day).

Exercise

For the acute decompensated patient, exercise should be restricted to physiotherapy. After initial stabilization, physical activity can be progressively increased to going to the bathroom and walking around the room. After hospital discharge a rehabilitation program should be instituted.

ACE inhibitors

ACEIs should be given to all patients with systolic dysfunction and the target dose should be those of clinical trials. During episodes of acute decompensation, ACEI should not be discontinued, but the doses initially adjusted according to blood pressure, renal function and potassium levels. After stabilization of these parameters, they should be re-up-titrated to the maximum tolerated doses. It’s important to recognize that some patients may not tolerate ACEIs (hypotension and renal dysfunction) if they were over-diuresed.

Angiotensin receptor blockers (ARBs)

ARBs are often reserved for those patients with ACEIs intolerance. However, in decompensated patients that
Aldosterone antagonists

Spironolactone or eplerenone should be part of the treatment of all patients with advanced HF, unless contraindicated\(^{15,20}\). During episodes of decompensation their use can help improve diuresis and diminish the risk of furosemide induced hypokalemia.

Betablockers

There is solid evidence for the use of betablockers (BB) in all stages of HF\(^{21-23}\). It has become increasingly common to see patients with severe HF under BB present to emergency rooms with DHF. Carvedilol, metoprolol succinate or bisoprolol are the BB approved for systolic HF. Other agents should not be used for HF\(^{24}\).

Whether or not we should discontinue BB during an episode of decomposition is a matter of intense debate. Retrospective analyses of randomized clinical trials suggest that the discontinuation or dose reduction of BB while the patient is decompensated may be associated with increased mortality\(^{25}\). Therefore, every effort should be made in order to keep the patient on his previous dose of BB, or reduce the dose if hypotension is present. In cardiogenic shock or in patients with severe hypotension, BB should be interrupted. One must also remember that many patients needing an inotrope are on chronic BB treatment, and they will not adequately respond to beta-agonists\(^{26,27}\).

Digoxin

The role of digoxin in the DHF patient is a matter of controversy. It probably has no place in the acute treatment, except for rapid atrial fibrillation. After clinical stabilization it can be re-started, provided that serum levels are normal and if patients remain symptomatic under ACEI, betablockers and diuretics\(^{28}\).

INTRAVENOUS TREATMENT

Most of the traditional drugs used in the intravenous treatment of DHF were approved based on hemodynamic effects. Until recently there was a lack of randomized clinical trials with hard endpoints (such as symptomatic improvement, mortality, length of hospital stay and hospital readmissions) to effectively guide therapy in this area.

Therapeutic options are similar in most parts of the world, except for some newer drugs. The calcium sensitizing agent levosimendan is available in many countries in Europe, Latin America and Asia. The use of milrinone in Latin America is not as common as in USA and other parts of the world. The synthetic natriuretic peptide nesiritide is available in the USA and selected countries in Latin America. Furthermore, the issue of pricing of newer drugs may be a major limitation in their application in the health system of developing countries.
Diuretics

Intravenous diuretics should be administered to all patients with evidence of fluid overload. The minimum effective dose should be looked for an individual patient. Since most patients with HF are on chronic oral diuretics, it's expected to find increasing levels of diuretic resistance. In such cases, the dose should be up-titrated in order to provide continuous and effective urinary output. An easy way to start IV diuretics is to give a bolus of half the daily dose that the patient was receiving in the preceding days before admission. The issue of whether to choose a continuous or intermittent infusion should be addressed in light of the severity of congestion and the availability of hospital resources. A patient with mild congestion can be adequately managed with intermittent I.V. injections, whereas an extremely fluid overloaded patient is better managed with continuous infusion. Association of diuretics with different mechanisms and sites of action should be managed with continuous infusion, guided treatment failed to show any benefit.

Sodium nitroprusside

Sodium nitroprusside is a more potent vasodilator than nitroglycerine. The data on its safety and efficacy in the management of DHF is based only on surrogate endpoints, and there are virtually no data on mortality and symptoms improvement. It's useful in patients with systemic or pulmonary hypertension, acute mitral or aortic insufficiency and in those with objective evidence of high systemic vascular resistance. It should be used with caution in patients with renal failure due to the risk of cyanide poisoning. The initial dose is 0.2 μg/Kg/min⁻¹ and should be titrated every five minutes.

Nesiritide

The synthetic form of endogenous B-type natriuretic peptide has been used in the USA in the last five years and, recently, has become available in selected countries in Latin America and Europe. Many small clinical trials with surrogate endpoints indicate that nesiritide is probably safe and effective in many important parameters of HF treatment. However, it has never been tested in a large randomized clinical trial, targeted to hard endpoints. In a small randomized trial, nesiritide was superior to placebo for symptomatic improvement at three hours, but similar to nitroglycerine; pulmonary wedge pressure decreased more significantly with nesiritide than with nitroglycerin, at the cost of more prolonged hypotension. Recently, questions regarding its safety have been raised. Retrospective data suggest potential adverse effects on renal function and mortality. A randomized controlled mortality clinical trial was recently announced to be started in 2007. Nesiritide remains a promising new agent, but its safety profile must be better demonstrated before widespread application.

Intravenous vasodilators

Vasodilator based therapies have not been very common in everyday practice despite a clear physiological rational for their use. However, there are some limitations to this kind of therapy:

- a) ICU admission is usually required to monitor blood pressure.
- b) Pulmonary artery catheter (PAC) is often needed to tailor therapy to hemodynamic parameters in severely ill patients.
- c) Hospital resource utilization, including ICU costs are higher with this approach.

Retrospective data suggests that PAC insertion is associated with increased mortality and a moratorium has been called for this procedure. Recently, the role of PAC in the management of DHF was clarified in a randomized clinical trial. When compared with usual treatment, based on physical exam, and a few non-invasive criteria, PAC guided treatment failed to show any benefit.

Nitroglycerine

Nitroglycerine is an arterial and venous vasodilator that acts through increasing cGMP. It’s useful in the management of DHF of ischemic etiology, such as post-MI patients. The initial dose is 0.5 μg/Kg/min⁻¹ and it can be titrated according to symptoms and blood pressure. It should not be used in hypotensive patients or in right ventricle infarction. There are no data on its efficacy in hard endpoints.

Vasopressors

Vasoactive drugs that are available in most places of the world are dopamine and norepinephrine. They’re indicated in DHF in patients with symptomatic hypotension with or without shock, refractory to volume correction. In this scenario, the initial treatment can be made with dopamine or norepinephrine, depending on the severity of hypotension.

a) Dopamine

Dopamine has been used in doses that vary between 2 – 20 μg/kg.min⁻¹, but its alpha-adrenergic actions are more pronounced after >10 μg/kg.min⁻¹. It also has beta-adrenergic effects that occur at the cost of an increased calcium influx to the cytoplasm. Dopamine is associated with increased heart rate, myocardial oxygen consumption, myocardial ischemia and ventricular arrhythmias. There is a controversy regarding its renal vasodilator effects that would justify the use of low dose dopamine in DHF with renal dysfunction. The available evidence indicates that this effect doesn’t exist and, consequently this practice should be abandoned.
b) Norepinephrine

Norepinephrine has high affinity for the alpha-adrenergic and moderate for the beta-adrenergic receptors, resulting in increased vasoconstriction, increased heart rate, increased inotropism and increased myocardial oxygen uptake. The vasoconstriction induced by norepinephrine can lead into decrease in tissue perfusion of the periphery, or even to microcirculatory deficits. There is evidence that cathecolamines can induce systemic inflammatory response. Due to these potentially negative effects, norepinephrine should be used only in the management of cardiogenic shock, refractory to other measures of circulatory support, including restoration of volemia, and the use of inotropes50. In DHF, it should usually be associated with other inotropic agents.

**Inotropic agents**

For those patients with low cardiac output syndromes, inotropic agents belong to the most commonly used drugs51. Many patients with DHF may suffer from low cardiac output with unrecognized tissue hypoperfusion52. This situation is more common in chronic DHF than in new acute DHF patients. This could be due to a state of chronic adaptation to low output with activation of compensatory mechanisms that make identification more difficult. The consequences of this state of “adapted” low output are often devastating to the organism, including worsening renal and liver function and more proinflammatory activation due to mesenteric and peripheral hypoperfusion.

Most inotropic agents increase intracellular calcium levels53. For this reason, they are commonly associated with significant side effects, such as increased myocardial oxygen consumption, arrhythmias and increased long term mortality54,55. The availability of new inotropic agents demands a reconsideration of its role in the management of DHF56.

Dobutamine

Even though many data point to potential adverse effects on mortality, dobutamine continues to be the most common inotropic agent used. Possible reasons for the widespread use of an agent with a questionable safety profile may be: 1) hemodynamic efficacy with dose dependent increases of cardiac output, even though there are no data correlating hemodynamic improvements and hard endpoints (mortality, hospital readmissions)57; 2) physicians are tempted to adopt a strategy that guarantees a rapid achievement of “optimal hemodynamic parameters”, without considering the fact that this strategy is not associated with improvement in any type of solid clinical endpoints58; 3) comfortable posology with an easily adjustable dosage that doesn’t cause hypotension, gives a sense of safety to the medical and nursing staff. All these aspects don’t seem enough to justify the widespread use of a strategy that brings benefits only in the very short term, but with potential adverse effects in the long term59,60. As already stated, in patients on BB being admitted to emergency rooms the use of dobutamine is the wrong choice56,57.

For these reasons, we believe that dobutamine should be reserved for the treatment of DHF with hypotension, or those in cardiogenic shock. It frequently needs to be associated with a vasoactive agent (dopamine or norepinephrine). As soon as the patient is stabilized, dobutamine should be slowly down-titrated. The initial dose is 5 μg/kg.min⁻¹ and it can be up-titrated to 20 μg/kg.min⁻¹. The main side effect is tachycardia, ventricular and atrial arrhythmias and myocardial ischemia.

**Milrinone**

Milrinone is a phosphodiesterase inhibitor that has both inotropic and vasodilator properties (inodilator). It has never been very popular in Latin-America. A possible reason for this is the cost and recent data indicating potential adverse effects on mortality51,62. Milrinone seems useful in DHF patients with pulmonary hypertension and in those previously treated with beta-blockers63. Due to its vasodilating effects, should not be used in hypotensive patients. The usual doses are 12.5 – 25 μg/kg.min⁻¹, with or without bolus doses.

**Levosimendan**

Levosimendan is a new agent that exerts an inotropic effect through calcium sensitization acting on troponin C64. It also has vasodilating properties due to activation of ATP dependent potassium channels in the arterial wall. Its mechanisms of action have a potential for improving clinical and hemodynamic conditions at modest metabolic and cellular costs55,66. Levosimendan improves myocardial contractility in a comparable level to other beta-agonists and phosphodiesterase inhibitors and its long lasting effects may bring some advantage in the initial management of hospitalization67.

Randomized clinical trials have suggested that levensimendan is safe and effective in a variety of etiologies of DHF, particularly in patients already taking beta-blockers68,69. The main side effects are related to its vasodilating effects, particularly hypotension. It’s interesting to note, however, that in many published
studies, the incidence of hypotension was comparable
to that under dobutamine.68

However, two recent large randomized clinical trials
of levosimendan in DHF have been recently presented
and deserve special considerations. The REVIVE trial71
compared levosimendan against placebo in patients
considered refractory to the initial treatment with
I.V. diuretics. The primary endpoint of symptomatic
improvement over the course of hospitalization was
achieved in 33% more levosimendan patients than with
placebo. In a similar way, 29% fewer patients worsened
over the same time frame. B-type natriuretic peptide levels
decreased significantly more with levosimendan and the
length of hospital stay was almost two days shorter. In
contrast, hypotension episodes were more frequent with
levosimendan, and also there was an excess of ventricular
and atrial arrhythmias. A trend towards higher number
of deaths was observed, which didn't reach statistical
significance. These data should be considered in the
light of the initial bolus and high uniform maintenance
doses employed in this particular study, which doesn't
resemble what is done in clinical practice. Also,
levosimendan was used together with other vasodilators
and phosphodiesterase inhibitors after intense diuresis,
which may have led to unrecognized hypovolemia and
massive vasodilatation. The other trial, SURVIVE72,
compared levosimendan against dobutamine in patients
considered candidates for inotropic support. The primary
day of 180 days mortality wasn't reached, but there
was a trend to lower hospital mortality. Again, one has to
consider the low dose of dobutamine employed in this trial
(6 µg/kg.min⁻¹) and the high standardized maintenance
dose of levosimendan (0.2 µg/kg.min⁻¹), which is different
from the use of levosimendan in countries with everyday
experience with this drug. In both trials hemodynamic
monitoring was not carried out despite the inclusion of
severely ill patients, what doesn't reflect clinical practice
in real world, where the compound is approved and has
been clinically used.

Taken together, the accumulated evidence on
levosimendan suggests that with other vasodilators
and phosphodiesterase inhibitors after intense diuresis,
the infusion rate can be reduced or, as we prefer, to add
the weaning process of dobutamine so that, after 24h, it can be discontinued. If hypotension occurs,
the infusion rate can be reduced or, as we prefer, to add
or increase the dose of dopamine or norepinephrine.

For patients who are on chronic oral treatment with
a betablocker, and there is a need for inotropic therapy,
levosimendan or milrinone should be the preferred choice
(since the mechanisms of action are post-receptor, and
then are not attenuated by betablockers). Hospital costs
of levosimendan are similar to dobutamine, despite higher
costs of the medication, indicating that the acquisition
costs alone should not influence which agent should be
utilized.23,76

HOW TO SELECT AN INTRAVENOUS TREATMENT
BASED ON CLINICAL AND HEMODYNAMIC
PARAMETERS

The flow diagram in figure 1 allows a rationalization of
the treatment of DHF, based on clinical and hemodynamic
parameters.

Those patients who present with warm extremities and
pulmonary or systemic congestion, without hypotension
are treated initially with intravenous diuretics and
optimization of oral therapy. The use of intravenous
vasodilators or levosimendan is optional. If the response
to initial treatment is considered inadequate after 24-48h
(worsening of renal function, persistent congestion and
dyspnea), levosimendan, if available and not used yet,
should be the next option.

Patients with cool extremities, with or without
hypotension should have their volume status checked
first. If the presence of congestion is not obvious, one
should check for hypovolemia and the need for volume
administration. For patients with systemic or pulmonary
congestion, without hypotension, levosimendan or an
intravenous vasodilator seem to be the best choice.
However, if hypotension is present, the initial choice
should rely on dobutamine associated with dopamine or
norepinephrine. After initial stabilization, levosimendan
can be added to wean dobutamine. In patients already
taking dobutamine, it's our practice to start levosimendan
at 0.05 - 0.1 µg/kg.min⁻¹ and, after 6h of simultaneous
infusion, start the weaning process of dobutamine so that,
after 24h, it can be discontinued. If hypotension occurs,
the infusion rate can be reduced or, as we prefer, to add
or increase the dose of dopamine or norepinephrine.

Combination of agents

The efficacy and safety of all available agents are dose
dependent, i.e., higher doses bring more pronounced
improvement in cardiac output, but potentially cause
more arrhythmias and other side effects. The combination
different inotropic agents can potentiate the beneficial
hemodynamic effects, but also cause synergistic toxicity.
This is particularly true for the association of dobutamine-
milrinone, agents that increase intracellular calcium. The
association of dobutamine with levosimendan, however,
seems more attractive, since it allows reducing the doses
of dobutamine.73

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SUMMARY

Treatment of DHF is a challenge even for the experienced physician. Advances in research have brought new treatment options that are helping change paradigms. The available evidence suggests that new drugs like levosimendan and nesiritide will assume relevant positions as alternatives or complements to treatment with traditional inotropic drugs like dobutamine. The physician responsible for treating these patients should learn how to use the best available evidence, in order to tailor treatment with safety and efficacy.

Potential Conflict of Interest
- F. Vilas-Boas has been part of Scientific Advisory Boards and received honoraria for lectures for Abbott Laboratories; he has also been member of Scientific Advisory Boards for Janssen-Cilag Latin America.
- F. Follath has been a member of Scientific Advisory Boards and received honoraria for lectures from Abbott.

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