Current Insights into the Modern Treatment of Decompensated Heart Failure

Fábio Vilas-Boas, MD, PhD[1] and Ferenc Follath, MD, FESC[2]
Hospital Espanhol – Cardiology Division[1], University Hospital Zürich[2] - Steering Group Drug Therapy
Salvador, BA, Brazil – Zürich, Switzerland

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[1]. Epidemiological data indicate that heart failure (HF) incidence is increasing progressively, particularly in the elderly[2].

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[3]. 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 or/ and 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:

Key words

Heart failure, acute, decompensated, treatment.

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, paleness, 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[4]. The most common reasons for decompensation are listed in table 1.

Table 1 - Causes of decompensations of HF

Inappropriate reduction of therapy
Pulmonary embolism
Arrhythmias
Systemic infection
Sodium retention or cardiodepressant drugs
Physical, emotional or environmental excesses
Development of comorbidities
Acute myocardial infarction
Cardiac valve disruption/perforation (endocarditis)
Acute myocarditis

HF - heart failure

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 laboratorial variables, together with the patient prognosis.

The criteria for hospitalization are listed in table 2.

Mailing Address: **Fábio Vilas-Boas** • Hospital Espanhol – Serviço de Cardiologia - Av. Sete de Setembro, 2152/2002 - 40080-002 - Salvador – BA
Email: fabiovboas@cardiol.br
Received on 08/07/06 • Accepted on 08/30/06

Table 2 - Criteria for hospitalization of DHF

Criteria for immediate hospitalization
Pulmonary edema or respiratory discomfort in the sitting position
Arterial oxygen saturation < 90%
Heart rate >120 bpm in the absence of chronic atrial fibrillation
Systolic arterial pressure < 80 mmHg
Mental abnormality attributed to hypoperfusion
Decompensation in the presence of acute coronary syndromes
Acute DHF
Criteria for emergency hospitalization
Serious hepatic distension, large volume ascites or anasarca
Decompensation in the presence of acutely decompensated conditions, such as pulmonary disease or renal dysfunction
Rapid and progressive onset of HF symptoms
Consider hospitalization
Rapid decrease in serum sodium below 130 mEq/L
Rapid increase in creatinine, above 2.5 mg/dl
Persistent symptoms at rest, in spite of optimized oral treatment
Comorbidities with expected impairment of HF

Modified from reference 3; DHF - decompensated heart failure; HF - heart failure.

Treatment

Treatment of chronic HF is well established in national and international guidelines, based on evidence derived from multiple randomized clinical trials[5-7]. For DHF, data from clinical trials is scarce. Recently, international guidelines have been published and have brought some light in this area[3,8].

Treatment targets for decompensated heart failure should be mainly directed to rapid improvement of symptoms without worsening renal function. In the acutely decompensated patient, there is no reason to limit interventions to those that may have a positive effect on middle or long term mortality. In contrast, short term mortality and safety are the main issues in DHF. Thus, any intervention should improve symptoms and be at least neutral regarding prognosis compared with current treatment options[9].

Goals of therapies

Treatment of DHF should be targeted to three major goals:

1) Tissue oxygenation

The first goal is to improve tissue oxygenation. Oxygen should be given to all patients in order to achieve oxygen saturation higher than 95%. The role of continuous positive airway pressure and other forms of non-invasive ventilation is well established in the management of pulmonary edema[10]. They should be instituted in all patients that fail to respond to oxygen by mask. Endotracheal intubation and mechanical ventilation shouldn't be delayed until the patient becomes unresponsive, since some times it may be too late.

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[11].

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[12].

ACE inhibitors

ACEIs should be given to all patients with systolic dysfunction and the target dose should be those of clinical trials[13,14]. During episodes of acute decompensation, ACEI should not be discontinued, but the doses initially adjusted according to blood pressure, renal function and potassium levels[15]. After stabilization of these parameters, they should be re-up-titrated to the maximum tolerated doses[16]. 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

Table 3 - Initial pharmacological approach to the treatment of decompensated heart failure

1) Discontinue all myocardial depressant medications, potentially related to the episode of decompensation.
2) Adjust diuretics doses to eliminate volume overload. Start with I.V. furosemide, using as initial dose, half the previous oral daily dose. Adjust for the next 48-72h, or start a continuous furosemide drip. Objective: loose 1-2 Kg/day.
3) Adjust the dose of ACE inhibitor: try to target the enalapril equivalent dose of 20 mg/day. Start with 2.5 mg twice a day if SBP > 85 mmHg, in the absence of hypotensive symptoms and renal dysfunction.
4) For low-output syndromes (nausea, vomiting, tissue hypoperfusion) without significant hypotension (SAP > 90 mmHg), start with levosimendan.
5) For low-output syndromes with significant hypotension (SAP < 90 mmHg), start with dopamine (5-10 μg/kg.min^{-1}) or norepinephrine (0.01 μg/kg.min^{-1}) associated or not with dobutamine (5-10 μg/kg.min^{-1}). Optionally, after stabilization start levosimendan to wean dobutamine.
6) Withdraw digoxin until serum level is available.
7) Start/ maintain spironolactone, according to renal function, paying careful attention to development of hyperkalemia.
8) If ACEI is contraindicated due to cough, start candesartan 8 to 16 mg/day.
9) If ACEI/ARB is contra-indicated, start oral hydralazine 50 – 400 mg/day associated with oral nitrate (isosorbide dinitrate 20mg bid).
10) Consider anticoagulation with low-molecular weight heparin in all patients.
11) Correct all acid-base and hydroelectrolytic imbalances.

are refractory to standard therapy, and that still have an adequate blood pressure, a closely monitored association of an ARB on top of ACEIs can improve symptoms and decrease the number of re-hospitalizations[17,18].

Aldosterone antagonists

Spironolactone or eplerenone should be part of the treatment of all patients with advanced HF, unless contraindicated[19,20]. 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 decompensation 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[29]. 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 considered when the patient shows decreased response to a single diuretic agent (diuretic resistance)[30]. It must be recognized that, even though diuretics are effective in improving symptoms and treating congestion, their use can lead to worsening renal function, and life-threatening electrolyte disturbances[31,32]. Dose reduction is necessary as soon as the signs of hypervolemia disappear.

Intravenous vasodilators

Vasodilator based therapies have not been very common in everyday practice despite a clear physiological rational for their use[33,34]. 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[35]. 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[36].

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[37]. 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[38]. There are no data on its efficacy in hard endpoints.

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 0.2μg/Kg/min^{-1} and should be titrated every five minutes[39].

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[40,41,42]. 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[43]. Recently, questions regarding its safety have been raised. Retrospective data suggest potential adverse effects on renal function and mortality[44,45]. A randomized controlled mortality clinical trial was recently announced to be started in 2007[46]. Nesiritide remains a promising new agent, but its safety profile must be better demonstrated before widespread application.

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} [47]. 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[48]. 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[49].

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 inotropes[50]. 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 drugs[51]. Many patients with DHF may suffer from low cardiac output with unrecognized tissue hypoperfusion[52]. 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 pro-inflammatory activation due to mesenteric and peripheral hypoperfusion.

Most inotropic agents increase intracellular calcium levels[53]. For this reason, they are commonly associated with significant side effects, such as increased myocardial oxygen consumption, arrhythmias and increased long term mortality[54,55]. The availability of new inotropic agents demands a reconsideration of its role in the management of DHF[56].

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 guaranties 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 endpoints[58]; 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 term[59,60]. As already stated, in patients on BB being admitted to emergency rooms the use of dobutamine is the wrong choice[26, 27].

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 mortality[61,62]. Milrinone seems useful in DHF patients with pulmonary hypertension and in those previously treated with beta-blockers[63]. 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 C[64]. 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 costs[65,66]. 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 hospitalization[67].

Randomized clinical trials have suggested that levosimendan is safe and effective in a variety of etiologies of DHF, particularly in patients already taking betablockers[68-70]. 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 trial[71] 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, SURVIVE[72], compared levosimendan against dobutamine in patients considered candidates for inotropic support. The primary endpoint 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 $\mu g/kg.min^{-1}$) and the high standardized maintenance dose of levosimendan (0.2 $\mu g/kg.min^{-1}$), 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 its maintenance doses should be reduced to 0.1 $\mu g/kg.min^{-1}$ and that it should be avoided in hypotensive patients. The loading dose should also be reduced to 6-12 $\mu g/kg$ infused over 10 minutes, restricted to those patients with systolic pressure higher than 110 mmHg and in whom an immediate response is needed. Further trials should be done to validate this practice.

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 of 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].

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 $\mu g/kg.min^{-1}$ 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.

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[74,75]

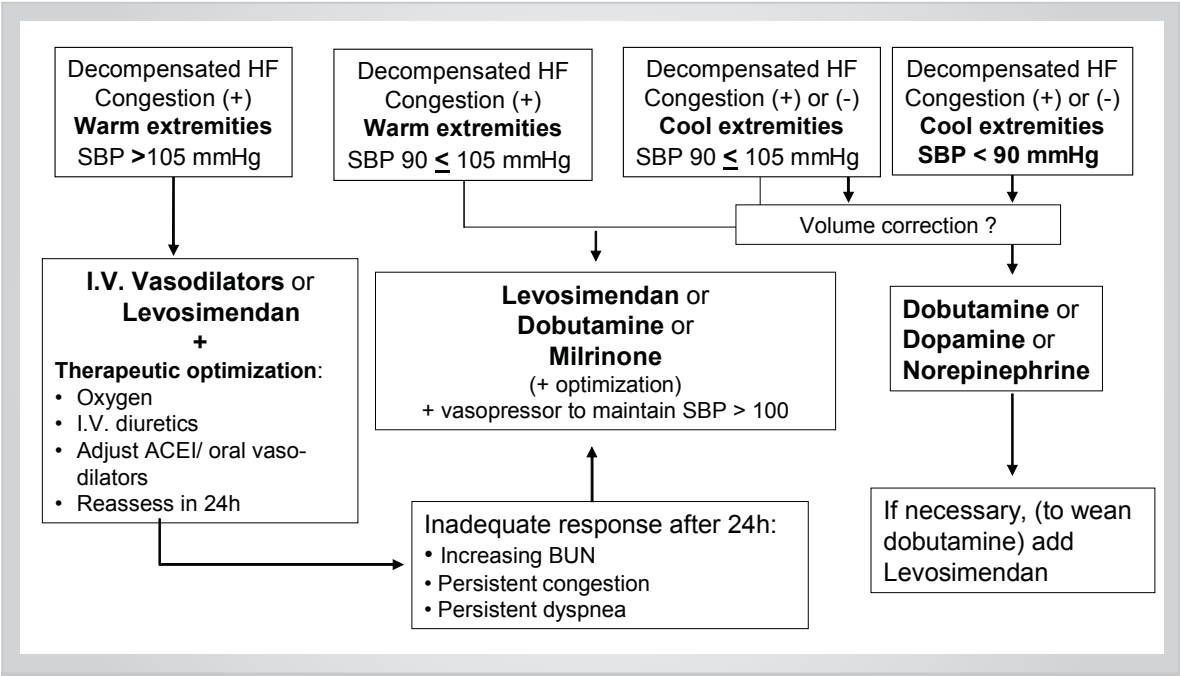

Fig. 1 *- Algorithm for current IV therapies in Decompensated HF.*

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.

References

1. Cleland JG, Gemmell I, Khand A, Boddy A. Is the prognosis of heart failure improving? Eur J Heart Fail 1999; 1: 229–41.
2. Barker WH, Mullooly JP, Getchell W. Changing incidence and survival for heart failure in a well-defined older population, 1970-1974 and 1990-1994. Circulation. 2006;113(6):799-805.
3. Bocchi EA, Vilas-Boas F, Perrone S, et al. I Latin American Guidelines for the Assessment and Management of Decompensated Heart Failure. Arq Bras Cardiol. 2005;85 Suppl 3:49-94; 1-48.
4. Sarmento PM, Fonseca C, Marques F, Ceia F, Aleixo A. Acutely decompensated heart failure: characteristics of hospitalized patients and opportunities to improve their care. Rev Port Cardiol. 2006;25(1):13-27.
5. Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J. 2005;26(11):1115-40.
6. Revisão das II Diretrizes da Sociedade Brasileira de Cardiologia para o Diagnóstico e Tratamento da Insuficiência Cardíaca. Arq Bras Cardiol. 2002;79 (supl. IV): 1-30.
7. Hunt AS, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol. 2005;46(6):e1-82.
8. Nieminen MS, Bohm M, Cowie MR, et al. ESC Committee for Practice Guideline (CPG). Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. Eur Heart J. 2005;26(4):384-416.
9. Jaagosild P, Dawson NV, Thomas C, et al. Outcomes of acute exacerbation of severe congestive heart failure: quality of life, resource use, and survival. Arch Intern Med 1998; 158: 1081–89.
10. Pang D, Keenan SP, Cook DJ, et al. The effect of positive pressure airway support on mortality and the need for intubation in cardiogenic pulmonary edema: a systematic review. Chest 1998;114:1185–1192.
11. Stevenson LW, Colucci WS. Management of patients hospitalized with heart failure. In: Smith TW, ed. Cardiovascular Therapeutics. Philadelphia, Penna: Saunders; 1996:199 –209.

12. Piepoli MF, Davos C, Francis DP, Coats AJ. ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH).. BMJ. 2004;328(7433):189.

13. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429-35.

14. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.

15. Pflugfelder PW, Baird MG, Tonkon MJ, DiBianco R, Pitt B, for the Quinapril Heart Failure Trial Investigators. Clinical consequences of angiotensin-converting enzyme inhibitor withdrawal in chronic heart failure: a double-blind, placebo-controlled study of quinapril. J Am Coll Cardiol 1993;22:1557-63.

16. Massie BM, Armstrong PW, Cleland JG, et al. Toleration of high doses of angiotensin-converting enzyme inhibitors in patients with chronic heart failure: results from the ATLAS trial: the Assessment of Treatment with Lisinopril and Survival. Arch Intern Med 2001;161:165-71.

17. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345:1667-75.

18. McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left ventricular systolic function taking angiotensin-converting enzyme inhibitors: the CHARM-Added trial. Lancet 2003; 362:767-71.

19. Pitt B, Zannad F, Remme WJ, et al, for the Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709-17.

20. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309-1321

21. Packer M, Bristow MR, Cohn JN, et al, for the U.S. Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996;334:1349-55.

22. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet 2001;357:1385-90.

23. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651-8.

24. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomized controlled trial. Lancet 2003;362:7-13.

25. Gattis WA, O'Connor CM, Leimberger JD, Felker GM, Adams KF, Gheorghiade M. Clinical outcomes in patients on beta-blocker therapy admitted with worsening chronic heart failure. Am J Cardiol. 2003;91(2):169-74.

26. Bristow MR, Shakar SF, Linseman JV, Lowes BD. Inotropes and beta-blockers: is there a need for new guidelines? J Card Fail 2001;7(2 Suppl 1):8-12.

27. Metra M, Nodari S, D'Aloia A, et al. Beta-blocker therapy influences the hemodynamic response to inotropic agents in patients with heart failure: a randomized comparison of dobutamine and enoximone before and after chronic treatment with metoprolol or carvedilol. J Am Coll Cardiol 2002;40:1248–1258.

28. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336:525-534.

29. Dormans TP, van Meyel JJ, Gerlag PG, Tan Y, Russel FG, Smits P. Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. J Am Coll Cardiol 1996;28:376-82.

30. Ellison DH. The physiologic basis of diuretic synergism: its role in treating diuretic resistance. Ann Intern Med 1991;114:886-94.

31. Kishore J, Harjai MBBS, Homeyar K, et al. The prognostic implications of outpatient diuretic dose in heart failure . Int J Cardiol 1999;71:219-25.

32. Cooper HA, Dries DL, Davis CE, Shen YL, Domanski MJ. Diuretics and risk of arrhythmic death in patients with left ventricular dysfunction. Circulation. 1999;100(12):1311-5.

33. Steimle AE, Stevenson LW, Chelinsky-Fallick C, et al. Sustained hemodynamic efficacy of therapy tailored to reduce filling pressures in survivors with advanced heart failure. Circulation 1997; 96:1165-72.

34. Rohde LE, Furian T, Campos C, Biolo A, Rabelo E, Foppa M, et al. Implications of the hemodynamic optimization approach guided by right heart catheterization in patients with severe heart failure. Arq Bras Cardiol. 2002;78(3):261-6.

35. Chernow B. Pulmonary artery flotation catheters: A statement by the American College of Chest Physicians and the American Thoracic Society. Chest 1997;111:261.

36. Binanay C, Califf RM, Hasselblad V, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. JAMA. 2005;294(13):1625-33.

37. Jugdutt BI. Intravenous nitroglycerin unloading in acute myocardial infarction. Am J Cardiol. 1991;68(14):52D-63D.

38. Abrams J. How to use nitrates. Cardiovasc Drugs Ther. 2002;16(6):511-4.

39. Mills RM. The failing heart and the hemodynamic response to vasodilator therapy.Clin Cardiol. 2003;26(6):257-8.

40. Marcus LS, Hart D, Packer M, et al. Hemodynamic and renal excretory effects of human brain natriuretic peptide infusion in patients with congestive heart failure. A double-blind, placebo-controlled, randomized crossover trial. Circulation 1996;94:3184–9.

41. Colucci WS, Elkayam U, Horton DP, et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. Nesiritide Study Group. N Engl J Med 2000;343:246–53.

42. Silver MA, Horton DP, Ghali JK, Elkayam U. Effect of Nesiritide Versus Dobutamine on Short-Term Outcomes in the Treatment of Patients With Acutely Decompensated Heart Failure . J Am Coll Cardiol 2002;39:798–803.

43. The VMAC investigators. Intravenous nesiritide vs nitroglycerin for the treatment of decompensated congestive heart failure. JAMA 2002;287:1531-1540.

44. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. Circulation. 2005;111:1487–1491.

45. Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term Risk of Death After Treatment With Nesiritide for Decompensated Heart Failure. A Pooled Analysis of Randomized Controlled Trials. JAMA. 2005;293:1900-1905.

46. Scios. Scios announces international outcomes trial of NATRECOR® (nesiritide) [press release]. June 1, 2006. Available at: http://www.sciosinc.com/scios/pr_1149131419

47. Francis GS, Sharma B, Hodges M. Comparative hemodynamic effects of dopamine and dobutamine in patients with acute cardiogenic circulatory collapse. Am Heart J. 1982;103(6):995-1000.

48. Van De Borne P, Somers VK. Dopamine and congestive heart failure: pharmacology, clinical use, and precautions. Congest Heart Fail. 1999;5(5):216-221.

49. Kellum JA, M Decker J. Use of dopamine in acute renal failure: a meta-analysis. Crit Care Med. 2001;29(8):1526-31.

50. Schreiber W, Herkner H, Koreny M, et al. Predictors of survival in unselected patients with acute myocardial infarction requiring continuous catecholamine support. Resuscitation. 2002;55(3):269-76.

51. Leier CV, Binkley PF. Parenteral inotropic support for advanced congestive heart failure. Prog Cardiovasc Dis. 1998;41:207–224.

52. Ander DS, Jaggi M, Rivers E, et al. Undetected cardiogenic shock in patients with congestive heart failure presenting to the emergency department. Am J Cardiol. 1998;82(7):888-91.

53. Holubarsch C. New inotropic concepts: rationale for and differences between calcium sensitizers and phosphodiesterase inhibitors. Cardiology 1997;88 (suppl 2):12–20.

54. Dies F, Krell MJ, Whitlow P, et al. Intermittent dobutamine in ambulatory outpatients with chronic cardiac failure. Circulation 1986;74: II–38.

55. Hampton JR, van Veldhuisen DJ, Kleber FX, et al. Randomised study of effect of ibopamine on survival in patients with advanced severe failure: Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II). Lancet 1997; 349: 971–77.

56. Packer M. The search for the ideal positive inotropic agent. N Engl J Med. 1993;329:201–202.

57. Connors AFJ, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. JAMA 1996; 276:889-97.

58. Hayes MA, Timmins AC, Yau EHS, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 1994;330:1717-22.

59. Capomolla S, Febo O, Opasich C, et al. Chronic infusion of dobutamine and nitroprusside in patients with end-stage heart failure awaiting heart transplantation: safety and clinical outcome. Eur J Heart Fail 2001;3(5):601-10.

60. Thackray S, Eastaugh J, Freemantle N, Cleland JGF. The effectiveness and relative effectiveness of intravenous inotropic drugs acting through the adrenergic pathway in patients with heart failure: a meta-regression analysis. Eur J Heart Fail 2002;4(4):515-29.

61. Cuffe MS, Califf RM, Adams KF, et al. Short term intravenous milrinone for acute exacerbation of chronic heart failure. A randomized controlled trial. JAMA 2002;287:1541-47.

62. Felker GM, Benza RL, Chandler AB, et al. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study.J Am Coll Cardiol. 2003;41:997-1003.

63. Lowes BD, Tsvetkova T, Eichhorn EJ, Gilbert EM, Bristow MR. Milrinone versus dobutamine in heart failure subjects treated chronically with carvedilol. Int J Cardiol. 2001;81(2-3):141-9.

64. Figgit D, Gillies PS, Goa KL. Levosimendan. Drugs 2001;61(5):613-627.

65. Hasenfuss G, Pieske B, Kretschmann B, Holubarsch C, Alpert NR, Just H. Effects of calcium sensitizers on intracellular calcium handling and myocardial energetics. J Cardiovasc Pharmacol 1995; 26 (suppl 1): S45–51.

66. Michaels AD, McKeown B, Kostal M, et al Effects of Intravenous Levosimendan on Human Coronary Vasomotor Regulation, Left Ventricular Wall Stress, and Myocardial Oxygen Uptake. Circulation. 2005;111:1504-1509.

67. Slawsky MT, Colucci WS, Gottlieb SS, et al. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Circulation 2000;102:2222–27.

68. Follath F, Cleland JGF, Just H, et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. Lancet 2002;360:196–202.

69. Nieminen MS, Moiseyev VS, Andrejevs N, et al. Randomized study on safety and effectiveness of levosimendan in patients with left ventricular failure after an acute myocardial infarction (RUSSLAN). European Heart Journal 2002;23:1422-32.

70. Lehmann A, Lang J, Boldt J, Isgro F, Kiessling AH. Levosimendan in patients with cardiogenic shock undergoing surgical revascularization: a case series. Med Sci Monit. 2004;10(8:MT89-93).

71. Packer M. REVIVE II: Multicenter placebo-controlled trial of levosimendan on clinical status in acutely decompensated heart failure. Program and abstracts from the American Heart Association Scientific Sessions 2005; November 13-16, 2005; Dallas, Texas. Late Breaking Clinical Trials II.

72. Mebazaa A. The SURVIVE Trial: Comparison of dobutamine and levosimendan on survival in acute decompensated heart failure. Program and abstracts from the American Heart Association Scientific Sessions 2005; November 13-16, 2005; Dallas, Texas. Late Breaking Clinical Trials IV.

73. Nanas JN, Papazoglou PP, Terrovitis JV, et al. Hemodynamic effects of levosimendan added to dobutamine in patients with decompensated advanced heart failure refractory to dobutamine alone. Am J Cardiol. 2004;94(10):1329-32.

74. Cleland JGF, Takala A, Apajasalo M, Zethraeus N, Kobelt G. Intravenous levosimendan treatment is cost-effective compared with dobutamine in severe low-output heart failure: an analysis based on the international LIDO trial. Eur J Heart Fail 2003;5;101-108.

75. Oliveira MT Jr, Follador W, Martins ML, et al. Cost analysis of the treatment of acute decompensated heart failure : Levosimendan versus Dobutamine. Arq Bras Cardiol. 2005;85(1):9-14.