Review Article

CLINICAL INVESTIGATION

Review of therapeutic strategies, aimed at counteracting the alterations of the autonomous nervous system, in cardiovascular diseases. Survival study

Abstract

Current therapeutic strategies increase mortality and enhance neurohormonal activation. The results of current therapeutic strategies, based on high and frequent doses of diuretics, increase morbidity and mortality.

Keyword: Morbidity • Therapeutic strategies • Mortality • Neurohormonal activation

Received: 22-Feb-2023, Manuscript No. fmci-23-89904; **Editor assigned:** 23-Feb-2023, PreQC No. fmci-23-89904 (PQ); **Reviewed:** 25-Feb-2023, QC No. fmci-23-89904 (Q); **Revised:** 26-Feb-2023, Manuscript No. fmci-23-89904 (R); **Published:** 28-Feb-2023; DOI: 10.37532/2041-6792.2023.13 (2).360-364

Jose hipolito donis hernandez*, Francisco Jose Sanchez Rivas, Diego Fernando Davila, Carmen Mazzei de

*Department Medicine, Cardiovascular Investigation Institute, The Andes University Hospital, The Andes University, Mérida, Venezuela

Department Medicine, Cardiovascular Investigation Institute, The Andes University Hospital, The Andes University, Mérida, Venezuela

Department Medicine, Cardiovascular Investigation Institute, The Andes University Hospital, The Andes University, Mérida, Venezuela

Department Medicine, Cardiovascular Investigation Institute, The Andes University Hospital, The Andes University, Mérida, Venezuela

*Author for correspondence: E-mail: donis_jose@hotmail.com

Introduction

The natural history of patients with chronic systolic heart failure is characterized by the recurrence of congestive signs and symptoms [1]. Recurrent episodes of acutely decompensated heart failure are a public health problem [2]. These episodes, of acutely decompensated heart failure, appear within one hundred days to six months' post-discharge and are associated to diminished survival. Current therapeutic strategies increase mortality and enhance neurohormonal activation [2-4]. Although, beta blockers are contain dicated in acutely decompensated heart failure [5-8]. The first report on the beneficial effects of the non-selective beta blocker practolol, published in 1975, included patients who were still hypervolemic which documented the benefits of their use and recently published investigations clearly indicate that decompensated patients do tolerate beta blockers [9, 10]. The onset of decompensation is usually gradual, fluid overload predominates over decreased tissue perfusion and there is biochemical evidence of neurohormonal activation and myocytolisis [11-18]. The results of current therapeutic strategies, based on high and frequent doses of diuretics, increase morbidity and mortality [19-22]. Although, its use is still controversial, in hypervolemic uncompensated patients a cardioprotective strategy with beta-adrenergic blockers appears to improve survival [23-26]. Beta blockers are contraindicated in patients with acutely decompensated heart failure. The pathophysiology of acute decompensation, of chronic and stable heart failure patients, is still incompletely understood. Possible mechanisms are non-adherence to diet or pharmacological therapy, arrhythmias, impaired cardiac contractility, and renal insufficiency. We previously reported the short-term effects of these two opposite strategies, consequently, selected patients with acutely decompensated heart failure can be compensated, during a 96-h period of observation, with a cautious up titration of carvedilol and single daily dose of diuretics All of these abnormalities lead to or contribute with neurohormonal activation, progressive fluid retention, body weight gain and congestion [27, 28]. More recently, Fallick C et al., proposed that, a sympathetically mediated shift between extracellular fluid volume and effective circulating blood volume, would partially explain the development of congestion, even in the absence of weight gain [29]. Since alpha receptors predominate in the splanchnic blood reservoir those investigators went on to state that: "Although, β blockade is still contraindicated in the setting of acute decompensation, perhaps judicious use of combined α and β blockade could be considered in the future We have compared the effects of frequent doses of diuretics vs a single dose of diuretics and cautious up titration of carvedilol [30]. Our results indicate that, although clinical compensation is achieved with both strategies; the effects on neurohormonal activation and ventricular arrhythmias are opposite and we previously reported the short-term effects of these two opposite strategies [27]. All patients were congestive, normothermic and with adequate perfusion pressure (Systolic blood pressure >90 mmHg (Profile B, Functional class III/IV) [14]. Medical treatment was based on two opposite therapeutic strategies [27]. Protocol 1: Furosemide 20

mg IV every 8 hours and Protocol 2: Furosemide 20 mg IV every 24 hours plus cautious up titration of carvedilol. Up titration of carvedilol was carried out by increasing the initial dose of 3.125 mg, by 3.125 mg every 12 hours. Up titration was heart rate oriented (Target: 65-70 bpm) and proceeded by a thorough clinical evaluation. Betablockers on admission were switched to carvedilol [Protocol 2]. Patients in both protocols received digitalis and prophylaxis for deep venous thrombo-embolism. Captopril 6.25 mg every 8 hours was also administrated to protocol 1 patient. Two-dimensional transthoracic echocardiogram was performed upon admission and daily dry weight was determined every 24 hours, during the observation period of 96 hours. Upon termination of the in-hospital observation period, patients were discharged and followed in the outpatient clinic. Standard treatment for chronic congestive heart failure was now administered to patients in both protocols [27]. In this review now describe their long-term effects on survival Baseline demographic, clinical and echocardiographic characteristics. The medical records of ninety-eight patients were identified. Initially, patients were consecutively assigned to each protocol [Protocol 1: 21 patients and Protocol 2: 23patients. However, during the last four years [2007-2011] most patients received protocol 2 (47 patients) and the remainder Protocol 17 patients. Baseline characteristics for all patients are shown as Mean age was 64. 87 ± 13. 04 years and males predominated. Baseline heart rate was 97. 41 ± 14. 73 beats per minute and systolic blood pressure 129.44 ± 17. 84 mmHg. Most patients were in functional class III (NYHA 58%). Sinus rhythm was present in more than half (52.24%) and atrial fibrillation in the remaining patients (47.76%). Renal function was borderline and the most frequently prescribed drug was furosemide. All patients had severely depressed left ventricular function (Ejection fraction: (28.61 ± 13.54), and increased pulmonary wedge pressure [28.61 ± 13.54 mm Hg] [28]. As can be seen in, patients assigned to protocol 2 had higher baseline heart rate, diastolic blood pressure, serum creatinine and left ventricular ejection fraction. Mean maximum dose of carvedilol for the 96 hour observation period was 59.37 mg, furosemide 240 mg for protocol 1 and 80 mg for protocol 2 and captopril 75 mg. Heart rate decreased from 99.19 ± 12.38 bpm to 67.64 ± 11.27 ($p< 0.0001$), in protocol 2 patients but, it remained unchanged in protocol 1 patients. Intergroup comparisons for the absolute daily changes in dry weight were similar. Daily dry weight decreased significantly, in both groups of patients, during the four-day observation period. For the whole group of patients, survival probability was close to 60% at fifty months of follow up. There were fourteen deaths with protocol 1 and eleven with protocol 2. According to use or not use of carvedilol, survival probability was significantly higher, in patients assigned to protocol 2 versus protocol 1 (72% vs 38%, $p< 0.046$). Discrimination of patients in sinus rhythm versus atrial fibrillation showed a higher survival only in the former. The magnitude of the heart rate change, with carvedilol in patients in sinus rhythm or in atrial fibrillation, was not statistically different. The Kaplan-Mier analysis of our database showed that, for the whole group of patients, survival probability was close to 60% at fifty months of follow up. However, patients receiving carvedilol, had a better survival than those assigned to frequent doses of furosemide. Patients in sinus rhythm, compared to those with atrial fibrillation as the predominate heart rhythm, were the only ones to have an increased survival. Cox regression analysis confirmed that, carvedilol and sinus rhythm, were the only variables independently associated with survival recent prospective and retrospective studies, in decompensated patients, have paid particular attention to the relationship of continuation, withdrawal or newly starting of beta blockers [31-34]. All of these studies consistently demonstrated that, short term cardiac mortality and morbidity, were significantly lower in those patients newly started or continued on beta blockers. Our findings indicate that long term survival is also positively influenced by the administration of carvedilol, to acutely decompensated patients. Why is the non-selective beta blocker carvedilol tolerated by decompensated patients and at the same time associated with increased survival?

First of all, we should emphasize that, our patients were B category of the classification proposed by Nohria A et al in this investigation [14]. They were predominantly congestive, with adequate perfusion pressure and their baseline heart rate gradually over 96 hour observation period thus, cardiac sympathetic drive and its well-known deleterious consequences on the myocardium were attenuated [35-37].

Secondly, carvedilol, a non-selective beta blocker is known to also block α1 receptors and augment renal blood Flow increases renal blood flow Since, an enhanced renal sympathetic nerve activity is part of the final common pathway leading to increase renal sodium reabsorption and decreases cardiac sympathetic drive to a greater extent than selective beta-adrenergic blockers Since, an enhanced renal sympathetic nerve activity is part of the final common pathway leading to increase renal sodium reabsorption [11] and the control of renal tubular sodium reabsorption and renal blood flow are mediated by α1B and α1A adrenoceptors; it is plausible that the non-selective beta-blocker carvedilol is enhancing diuresis. [38, 39]. Moreover, it appears to suppress aldosterone production [40-42]. All together, these mechanisms could diminish myocardial injury during compensation and contribute to prevent further damage and future cardiovascular events.

Thirdly, the novel mechanism hypothesized by Fallick C et al, could by restoring systemic venous capacitance, contribute to prevent additional episodes of decompensation and myocardial injury [29].

Conclusion

In summary, we can conclude with this analysis that indicated, the medical treatment with Carvedilol was significantly associated to survival, only in those patients who were in sinus rhyme and cautious up titration of carvedilol, is still decompensated with sinus rhythm, increases long term survival. the observed beneficial effects of cautious up titration of carvedilol, in decompensated patients in sinus rhythm, are very likely due its unique pharmacological characteristic of α and β blocker.

References

1. Tsutsui M, Tsuchihashi M and Takeshita A. Mortality and Readmission of hospitalized Patients with Congestive Heart Failure and Preserved Versus Depressed Systolic Function. *Am J Cardiol*. 2001; 88:530-33.

2. Redfield MM. Heart failure-an epidemic of uncertain proportions. *New Eng J Med*. 2002;347:1397-402.

3. Feinglass J, Lee PI, Mehta S, et al. Systolic function, readmission rates, and survival among consecutively hospitalized patients with congestive heart failure. *Am Heart J*. 1997;134:728-36.

4. Solomon SD, Dobson J, Pocock S, et al. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circ*. 2007;116:1482-87.

5. Elkayam U, Tasissa G, Binanay C, et al. Use and impact of inotropes and vasodilator therapy in hospitalized patients with severe heart failure. *Am Heart J*. 2007;153:98-104.
6. FrancisGS, SiegelRM, Goldsmith SR, et al. Acute vasoconstrictor response to intravenous furosemide in patient switch chronic congestive heart failure. *Ann Intern Med*. 1985;103:1-6.
7. Constanzo MR, Johannes RS, Pine M, et al. The safety of intravenous diuretics alone versus diuretics plus parenteral vasoactive therapies in hospitalized patients with acutely decompensated heart failure: a. *Am Heart J*.

8. Konishi M, Maejima Y, Inagaki H. Clinical characteristics of acute decompensated heart failure with rapid onset symptoms. *J Card Fail*. 2009;15:300-04.

9. Nieminen MS, Bohm M, Cowie MR, et al. 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 Cardiology. *Eur Heart* J. 2005;26:384-416.

10. Waagstein F, Hjalmarson A, Varnauskas E. Effect of chronic beta-adrenergic receptor blockade congestive cardiomyopathy. *Br Heart J*. 1975;37:1022-36.
11. Fonarow GC, Abraham WT, Albert NM, et al. Influence of betablocker continuation or withdrawal on outcomes in patients hospitalized with heart failure. *Am Coll Cardiol*. 2008;52:190-9.

12. Konishi M, Maejima Y, Inagaki H. Clinical characteristics of acute decompensated heart failure with rapid onset symptoms. *J Card Fail*. 2009;15:300-04.

13. Schiff GD, Fung S, Speroff T, et al. Decompensated heart failure: Symptoms, patterns of onset and contributing factors. *Am J Med*. 2003;114:625-30.

14. Drazner MH, Hellkamp AS, Leier CV, et al. Value of clinician assessment of hemodynamics in advanced heart failure. *Circ Heart Fail*. 2008;1:170-77.

15. Nohria A, Tsang SW, Fang JC, et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. *J Am Coll Cardiol*. 2003;41:1797-84.

16. Tuy T, Peacock WF. Fluid overload assessment and management in heart failure patients. *Semin Nephrol*. 2012;32:112-20.

17. Khoury AM, Davila DF, Bellabarba G, et al. Acute effects of digitalis and enalapril on the neurohormonal profile of chagasic patients with severe congestive heart failure. *Int J Cardiol*. 1996;57:21-9.

18. Gheorghiade M, Pang PS, Ambrosy AP, et al. A comprehensive, longitudinal description of the in-hospital and post-discharge clinical, laboratory, and neurohormonal course of patients with heart failure who die or are re-hospitalized within 90 days: analysis from the EVEREST trial. *Heart Fail Rev*. 2012;17:485-509.

19. Felker GM, Hasselblad V, Wilson WH et al. Troponin I in acute decompensated heart failure: insights from the ASCEND-HF study. *EurJ Heart Fail*. 2012;14:1257-64.

20. Peacock WF, Costanzo MR, De Marco T, et al. ADHERE Scientific Advisory Committee and Investigators. Impact of intravenous loop diuretics on outcomes of patients hospitalized with acute decompensated heart failure: insights from the ADHERE registry. *Cardiology*. 2009;113:12-19.

21. Vaz PA, Otawa K, Zimmermann AV, et al. The impact of impaired renal function on mortality in patients with acutely decompensated chronic heart failure. *Eur J Heart Fail*. 2010;12:122-28.

22. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011;364:797-805.

23. Konish M, Haraguchi G, Ohigashi H et al. Progression of Hyponatremia is Associated with Increased Cardiac Mortality in Patients Hospitalized for Acute Decompensated Heart Failure. *J Cardiac Fail*. 2012;18:620-25.

24. Mc JJ. Systolic Heart Failure. *N Eng J Med*. 2010;362:228-38.

25. Mc JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2012;14:802-69.

26. Fonarow GC, Abraham WT, Albert NM, et al.

Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure: findings from the OPTIMIZEHF program. *J Am Coll Cardiol*. 2008;52:190-99.

27. Orso F, Baldasseroni S, Fabbri G, et al. Italian Survey on Acute Heart Failure Investigators. Role of Beta Blockers in patients admitted for worsening heart failure in a real world: data from the Italian Survey on Acute Heart Failure. *Eur J Heart Fail*. 2009;11:77-84.

28. Lobo VL, Comenares MH, Donis JH, et al. Acutely decompensated heart failure: Effects of carvedilol on clinical status, neurohormonal activation and ventricular arrhythmias. *Int J Cardiol*. 2010;144:302-03.

29. OH JK, Park SJ, Nagueh SF. Stablished and novel clinical applications of diastolic function assessment by echocardiography. *Circ Cardiovasc Imaging*. 2011;4:444-55.

30. Fallick C, Sobotka PA, Dunlap ME. Sympathetically mediated changes in capacitance: redistribution of the venous reservoir as a cause of decompensation. *Circ Heart Fail*. 2011;4:669-75.

31. Gelman S, Mushlin PS. Catecholamine-induced changes in the splanchnic circulation affecting systemic hemodynamics. *Anesthesiology*. 2004;100:434-39.

32. Francis GS, Siegel RM, Goldsmith SR, et al. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. *Ann Intern Med*. 1985; 103:1-6.

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

34. Metra M, Torp PC, Cleland JG, et al. COMET investigators. Should beta-blocker therapy be reduced or withdrawn after an episode of decompensated heart failure? Results from COMET. *Eur J Heart Fail*. 2007;9:901-09.

35. Jondeau G, Neuder Y, Eicher JC, et al. B-CONVINCED Investigators. B-CONVINCED: Beta-blocker CONtinuation Vs. INterruption in patients with Congestive heart failure hospitalizED for a decompensation episode. *Eur Heart J*. 2009; 30:2186-92.

36. Kaye DM, Lefkovits J, Jennings GL, et al. Adverse consequences of high sympathetic nervous activity in the failing human heart. *J Am Coll Cardiol*. 1995;26:1257-63.

37. Davila DF, Nunez TJ, Odreman R, et al. Mechanisms of neurohormonal activation in chronic congestive heart failure: pathophysiology and therapeutic implications. *Int J Cardiol*. 2005;101:343-46.

38. Davila DF, Donis JH, Bellabarba G, et al. Cardiac afferents and neurohormonal activation in congestive heart failure. *Med Hypotheses*. 2000; 54:242-53.

39. Nikolaidis LA, Poornima I, Parikh P, et al. The effects of combined versus selective adrenergic blockade on left ventricular and systemic hemodynamics, myocardial substrate preference, and regional perfusion in conscious dogs with dilated cardiomyopathy. *J Am Coll Cardiol*. 2006;47:1871-81.

40. Azevedo ER, Kubo T, Mak S, et al. Nonselective versus selective beta-adrenergic receptor blockade in congestive heart failure: differential effects on sympathetic activity. *Circulation*. 2001;104:2194-99.

41. Aggarwal A, Wong J, Campbell DJ. Carvedilol reduces aldosterone release in systolic heart failure. *Heart Lung Circ*. 2006;15:306-09.

42. Hawkins NM, Petrie MC, Macdonald MR, et al. Heart failure and chronic obstructive pulmonary disease the quandary of Beta-blockers and Beta-agonists. *J Am Coll Cardiol*. 2011;57:2127-38.