



Review of Therapeutic Strategies, Aimed at Counteracting the Alterations of the Autonomous Nervous System, in Cardiovascular Diseases, Survival study

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ABSTRACT

The autonomic nervous system, through its sympathetic and parasympathetic divisions, has a fundamental role in the pathogenesis of cardiac diseases. Acute and chronic left ventricular systolic dysfunction is present in diseases such as Acute decompensation of chronic congestive heart failure and Systolic heart failure of etiology. All two diseases have sympathetic hyperactive, as, a common denominator. We, at the Instituto of Investigations Cardiovascular of la Universidad de Los Andes, have conceived therapeutic strategies aimed at counteracting this autonomic abnormality. We can conclude with this analysis that indicated, the medical treatment with Carvedilol was significantly associated with 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 to its unique pharmacological characteristic α of and β blocker.

Keywords: Decompensated heart failure, Furosemide, Carvedilol Neurohormonal Activation (CNA), Beta-blockers, Norepinephrine, Survival

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 with diminished survival [2-4]. Current therapeutic strategies increase mortality and enhance neurohormonal activation [5-7]. Although beta blockers are contraindicated in acutely decompensated heart failure [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 indicate that decompensated patients do tolerate beta blockers [9]. The onset of decompensation is usually gradual, fluid overload predominates over decreased tissue perfusion and there is biochemical evidence of neurohormonal activation and myocytolysis [10-18]. 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 [8]. 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 hour period of observation, with a cautious up-titration of carvedilol and a single daily dose of diuretics [27]. All of these abnormalities lead to or contribute to neurohormonal activation, progressive fluid retention, body weight gain, and congestion [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 [27,30]. 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 [31]. 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.

Protocol 2: Furosemide 20 mg IV every 24 hours plus cautious up-titration of carvedilol.

Uptitration of carvedilol was carried out by increasing the initial dose of 3.125 mg, by 3.125 mg every 12 hours. Uptitration was heart rate oriented (Target: 65 bpm-70 bpm) and preceded by a thorough clinical evaluation. Beta-blockers on admission were switched to carvedilol (Protocol 2). Patients in both protocols received digitalis and prophylaxis for deep venous thromboembolism. Captopril 6.25 mg every 8 hours was also administered to protocol 1 patients. A 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 [32]. This review now describes 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 2:23 patients). However, during the last four years (2007-2011) most patients received protocol 2 (47 patients) and the remainder Protocol 1 (7 patients). Baseline characteristics for all patients are shown as a Mean age was 64.87 years \pm 13.04 years and males predominated. The baseline heart rate was 97.41 \pm 14.73 beats per minute and systolic blood pressure was 129.44 mmHg \pm 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 \pm 13.54) and increased pulmonary wedge pressure (28.61 mmHg \pm 13.54 mm Hg) [28]. As can be seen in, patients assigned to protocol 2 had higher baseline heart rates, diastolic blood pressure, serum creatinine, and left ventricular ejection fraction. The mean maximum dose of carvedilol for the 96 hours 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 bpm \pm 12.38 bpm to 67.64 \pm 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 days observation period. For the whole group of patients, the 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 the 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 with sinus rhythm or 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 better survival than those assigned to frequent doses of furosemide. Patients in sinus rhythm, compared to those with atrial fibrillation as the predominant heart rhythm, were the only ones to have 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 new starting of beta-blockers [10,26,33,34]. 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 hours 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 α_1 receptors and augment renal blood flow increasing renal blood flow [38]. 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 and the control of renal tubular sodium reabsorption and renal blood flow are mediated by α^1_B and α^1_A adrenoceptors; it is plausible that the non-selective beta-blocker carvedilol is enhancing diuresis. [11,39]. Moreover, it appears to suppress aldosterone production [40]. Altogether, these mechanisms could diminish myocardial injury during compensation and contribute to preventing further damage and future cardiovascular events [41].

Thirdly, the novel mechanism hypothesized by Fallick C et al, could by restoring systemic venous capacitance, contribute to preventing 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 with 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 to its unique pharmacological characteristic of α and β blockers.

DECLARATIONS

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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