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Carvedilol in Patients with Acutely Decompensated Systolic Heart Failure: Effects on Survival

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Abstract: Ninety-eight patients with acutely decompensated systolic heart failure were admitted to the Hospital Universitario de Los Andes between 2005 and 2011, in Mérida, Venezuela. Medical Treatment: Protocol 1: Furosemide 20 mg IV every 8 hours (28 patients). Protocol 2: Furosemide 20 IV every 24 hours plus cautious uptitration of carvedilol (70 patients). Heart rate decreased from 99.19±12.38 to 67.64±11.27 (bpm) ($p < 0.0001$) with protocol 2. Daily weight changes were similar both protocols. Mean maximum dose of carvedilol was 59.37 mg, furosemide 240 mg for protocol 1 and 80 mg for protocol 2. 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. Survival probability was significantly higher, in patients assigned to protocol 2 versus protocol 1 (72% vs 38%, $p< 0.046$). Cox multiple regression analysis indicated that, medical treatment with carvedilol, was significantly and independently associated to survival, only in those patients who were in sinus rhythm. Cautious uptitration of carvedilol, in still decompensated patients with sinus rhythm, increases long term survival.

Keywords: Furosemide, Carvedilol, Acute Decompensated Systolic Heart Failure, Heart Rate, Survival Probability

1. Introduction

The natural history of patients with chronic systolic heart failure is characterized by the recurrence of congestive signs and symptoms [1] These episodes, of acutely decompensated heart failure, appear within one hundred days to six months post-discharge and are associated to diminished survival [2, 3]. The onset of decompensation is usually gradual, fluid overload predominates over decreased tissue perfusion [4-8] and there is biochemical evidence of neurohormonal activation [9, 10] and myocytolisis [11]. The results of current therapeutic strategies, based on frequent and high doses of diuretics, increase morbidity and mortality [12-15]. Although, its use is still controversial, in hypervolemic uncompensated patients [16, 17], a cardioprotective strategy with beta-adrenergic blockers appears to improve survival [18, 19]. Beta blockers are contraindicated in patients with acutely decompensated heart failure. Current therapeutic strategies increase morbidity and mortality. We have compared the effects of frequent doses of diuretics vs a single dose of diuretics and cautious uptitration of carvedilol. 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, Consequently, selected patients with acutely decompensated heart failure can be compensated, during a 96 h period of observation, with a cautious uptitration of carvedilol and single daily dose of diuretics [20]. We previously reported the short term effects of these two opposite strategies and now

describe their long term effects on survival.

2. Methods

We retrospectively reviewed the medical records of patients admitted, with acutely decompensated heart failure, to the Hospital Universitario de Los Andes and to the Instituto Venezolano del Seguro Social in Mérida, Venezuela, between 2005 and 2011. All patients were congestive, normothermic and with adequate perfusion pressure (Systolic blood pressure > 90 mmHg (Profile B, Functional class III/IV) [7]. Medical treatment was based on two opposite therapeutic strategies [20]. 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. 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: 65-70 bpm) and preceded 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 patients. 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 [16, 17]. Protocols had been previously approved by the Commission for Clinical Research of the Instituto de Investigations Cardiovascular of the University of Los Andes. Informed consent was obtained from all participants in the study.

3. Statistical Analysis

Data are expressed as absolute numbers and percentages. The one sample Kolmogorov –Smirnov and the Shapiro-Wilk tests were used to analyze for normal or not normal distribution of the data. Continuous normally distributed variables are expressed as mean±standard deviation. Intra e intergroup comparisons for daily heart rate and dry weight changes were performed by means of repetitive analysis of variance. Survival probability was estimated by the Kaplan-Meier method and differences in survival between groups were assessed by the log-rank test. Cox regression analysis was used to determine a possible association between survival and potentially explanatory independent variables such as: Medical treatment, age, heart rhythm and the absolute changes in heart rate and daily weight. Statistical significance was considered for $p < 0.05$.

4. Results

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]. However, during the last four years [20072011] most patients received protocol 2 [47 patients] and the remainder Protocol 1 [7 patients]. Baseline characteristics for all patients are shown in Table 1. 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] [21]. As can be seen in Table 2, 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 hours observation period was 59.37 mg, furosemide 240 mg for protocol 1 and 80 mg for protocol 2 and captopril 75 mg.

Table 1. *Baseline demographic, clinical and echocardiographic characteristics.*

Characteristics	**Median. (n=98)**
Demographic variables.	
Age (years)	64.87±13.04
Sex (M/F)	79/19
Clinical variables.	
Weight (kg)	70.46±12.45
Heart rate (beats per minute)	97.41±14.73
Systolic pressure (mmHg)	129.44±17.84
Diastolic pressure (mmHg)	83.97±11.67
NYHA Functional class (III/IV)	69/29
Heart rhythm (Sinus rhythm/Atrial Fibrillation)	69/29
Aetiology (%)	
Hypertensive	25.64
Ischemic	15.38
Mixed	38.47
Chagásic	2.56

Characteristics	Median. (n=98)
Idiopathic	17.95
Treatment (n / %)	
Furosemide	98/100
Digital	45/44.1
Captopril	29/28.42
Beta-blockers	60/58.8
Laboratory	
Creatine (mg/dl)	1.54±0.57
Potassium (mEq/lt)	4.13±0.51
Proteins (g/%)	6.55±0.48
Echocardiography.	
Ejection fraction (%)	25.18±8.82
Sphericity Index	0.73±0.07
Left ventricular diastolic diameter (mm)	61.15±5.62
Left ventricular diastolic volume (cc)	188.12±40.97
Relation E/e´	20.97±10.01
Wedge Pressure for (mmHg)	28.61±13.54

Table 2. *Demographic and Baseline Characteristics of the Study Patients for Group.*

Characteristics	Group n: 28	Group n: 70	P Value
Demographic variables.			
Age (yrs)	63.04±13.04	65.60±12.46	
Sex. (M/F)	21/7	58/12	
Clinical variables.			
Weight (kg)	66,32±11.6	72.35±12.87	
Heart rate (bpm) £	91.37±14,92	99.19±12.38	0.03
Systolic pressure (mmHg)	119±19,67	133.61±15.31	
Diastolic pressure (mmHg) £	79.11±13.16	85.91±10.50	0.04
(NYHA) Functional class (III/IV)	19/9	50/20	
Heart Rhythm (RS/AF)	19/9	50/20	
Etiology (%)			
Hypertensive	35.71	38.57	
ischemic	21.43	41.43	
Mixed	21.43	17.14	
Chagásica	3.57	0	
Idiopathic	17.86	2.86	
Treatment of revenue (nº/%)			
Furosemide	28/100	70/100	
Digital	15/53.57	30/42.85	
Captopril	20/71.43	9/12.86	
Beta-blocking	15/53.57	45/64.28	
Laboratory			
Creatine (mg/dl) £	1,45±0.31	1,65±0.76	0.08
Potassium (mEq/lt)	3.96±0.25	4.36±0.68	
Proteins (g/dl)	6.44±0.47	6.72±0.49	
Echocardiography.			
Ejection fraction FEVI (%) £	20.10±5.60	26,85±9.08	0.008
Esfericidad Of Index	0.74±0.07	0,74±0.7	
LVDD (mm)	60.59±5.16	59.57±6.47	
Relation E/e´	21.87±11,28	20,00±8,68	
Wedge of Pressure for Nagueh (mmHg)	30.55±16,.0	26,.5±9.00	

Effects on Clinical Variables and Mortality

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 [Figure 1]. Daily dry weight decreased significantly, in both groups of patients, during the four days observation period. Intergroup comparisons for the absolute daily changes in dry weight were similar [Figure 2].

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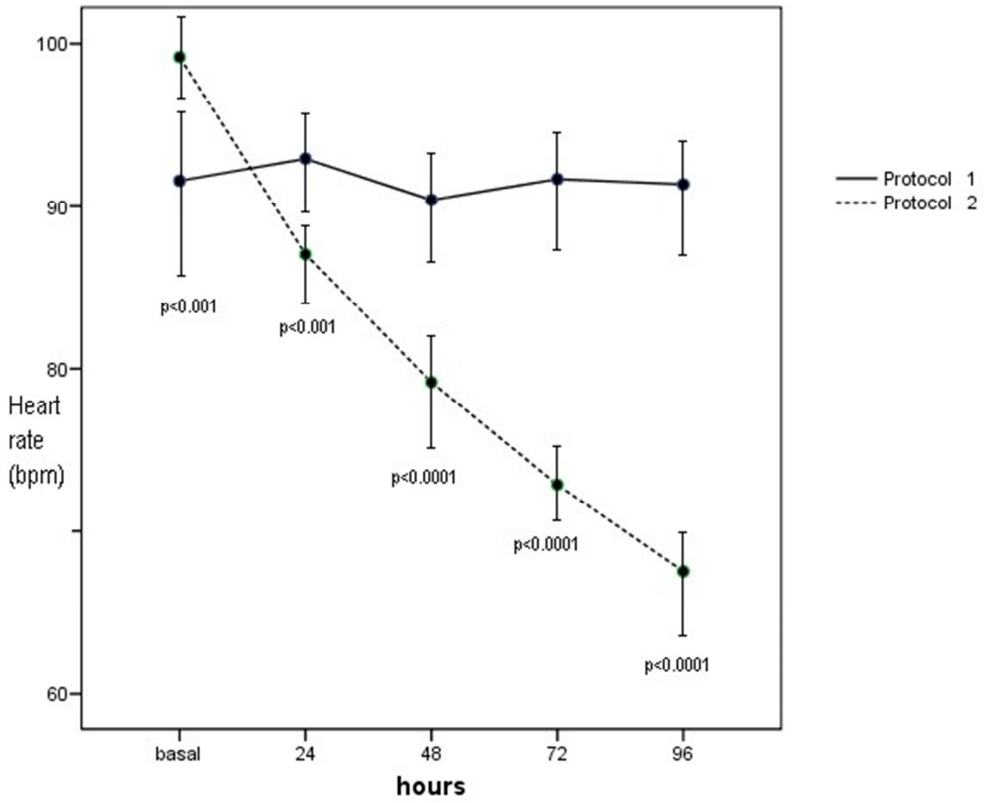

Figure 1. *Heart rate changes with furosemide (Protocol 1) versus carvedilol (Protocol 2). Heart rate decreased significantly with carvedilol, but it remained unchanged with furosemide.*

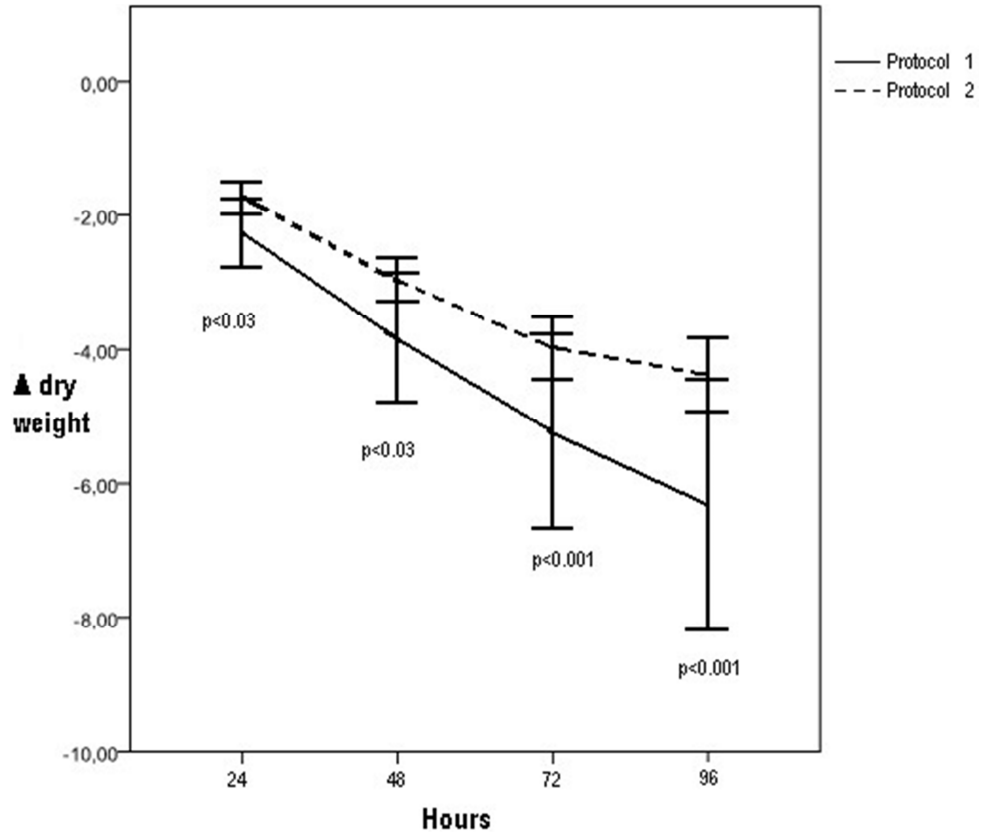

Figure 2. *Absolute daily changes in dry weight with furosemide (Protocol 1) versus Carvedilol (Protocol 2). Weight decreased significantly, during the 96 hours observation period, with both protocols. However, intergroup comparisons revealed no significant differences.* ▲*=Absolute changes in dry weight.*

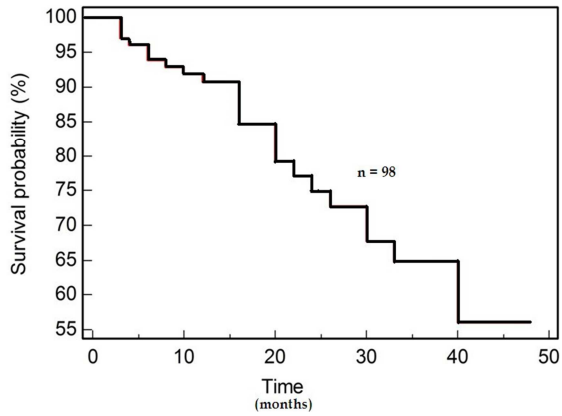

Figure 3. *Survival probability for the entire group of patients (n=98). For the whole group of patients, survival probability was close to 60%, at fifty months of follow up.*

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] [Figure 4]. Discrimination of patients in sinus rhythm versus atrial fibrillation showed a higher survival only in the former (Figures 5 and 6). The magnitude of the heart rate change, with carvedilol in patients in sinus rhythm or in atrial fibrillation, was not statistically different [Figure 7]. Cox multiple regression analysis indicated that, medical treatment with carvedilol, was significantly and independently associated to survival, only in those patients who were in sinus rhythm [Tables 3 and 4].

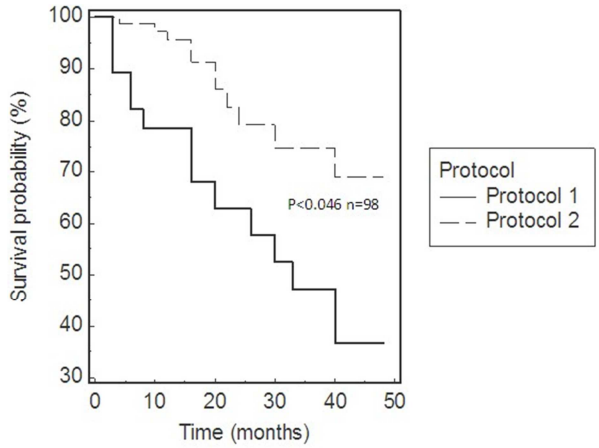

Figure 4. *Survival probability for decompensated patients in sinus rhythm and in atrial fibrillation. Survival was significantly lower with Protocol 1 (Furosemide) versus Protocol 2 (Carvedilol).*

Table 3. *Multivariate analysis by Cox regression model for patients in sinus rthmths.*

Variable Basal	β Coefficient	Hazard Ratio (95% CI)	P Value
Medical treatment	-1.171	0.310 (0.101 to 0.954)	0.041
Age	0.025	2.070 (0.991 to 1.061)	0.150
Δ Weigth	0.083	1.086 (0.900 to 1.311)	0.389
Δ Heart rate	0.027	1.027 (0.9623 to 1.095)	0.415

Δ Absolute changes

Table 4. *Multivariate analysis by Cox regression model for patients in atrial fibrillation.*

Variable Basal	β Coefficient	Hazard Ratio (95% CI)	P Value
Medical treatment	-0.948	0.388 (0.084 to 1.780)	0.223
Age	0.025	1.025 (0.959 to 1.096)	0.469
Δ Weight	0.066	0.936 (0.832 to 1.053)	0.271
Δ Heart rate	0.074	1.077 (0.987 to 1.176)	0.096

Δ Absolute Chages

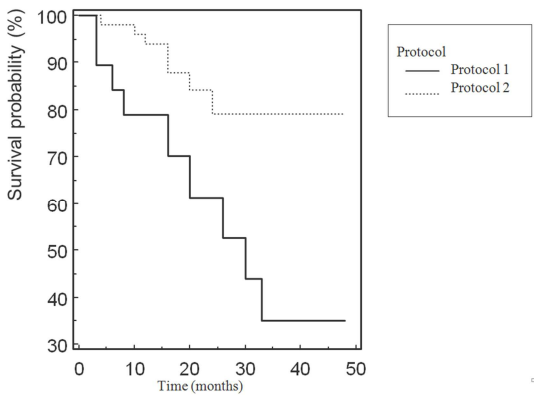

Figure 5. *Survival probability for decompensated patients in sinus rhythm. Survival was significantly lower with Protocol 1 (Furosemide) versus Protocol 2 (Carvedilol).*

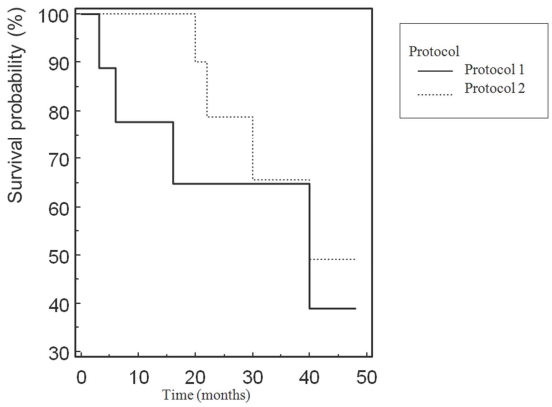

Figure 6. *Survival probability for decompensated patients in atrial fibrilation. Survival was not significantly different with Protocol 1 (Furosemide) versus Protocol 2 (Carvedilol).*

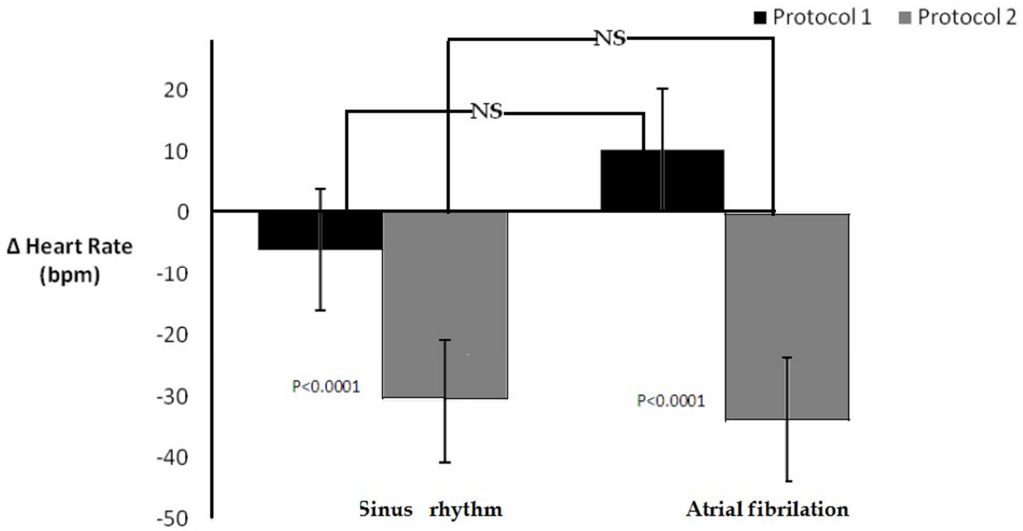

Figure 7. *Magnitude of the heart rate changes in patients in sinus rhythm or in atrial fibrillation. Heart rate decreased markedly and significantly in both groups of patients with Protocol 2 (Carvedilol), vs Protocol 1 (Furosemide). The magnitude of these negative heart rate changes were similar in patients with sinus rhythm compared to patients with atrial fibrillation.*

5. Discussion

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. All of these abnormalities lead to or contribute with neurohormonal activation, progressive fluid retention, body weight gain and congestion [22]. More recently, Fallick C et al., proposed that, a sympathetically mediated shift between extracellular fluid volumen and effective circulating blood volumen, would partially explain the development of congestion, even in the absence of weight gain [23]. Since alpha receptors predominate in the splanchnic blood reservoir [24], those investigators went on to state that: "Although, β blockade is still contraindicated in the setting of acute decompensation, perhaps judicious use of combined A and β blockade could be considered in the future".

For the past seven years, we at the Instituto de Investigations Cardiovascular of the University of Los Andes in Mérida, Venezuela have been compensating our systolic heart failure patients with carvedilol [20]. The rationality, for comparing this therapeutic strategy versus the conventional use of high and frequent doses of furosemide, was as follows: 1. Acute decompensation is characterized by congestion, neurohormonal activation and myocytolisis [4-11]. 2. Furosemide enhances neurohormonal activation [25] and increases morbidity and mortality [12-15]. 3. The first report on the beneficial effects of the non-selective beta blocker practolol, published in 1975, included patients who were still hypervolemic [26]. The U.S. Carvedilol Heart Failure Study Group also included hypervolemic patients as a high risk group. These still uncompensated patients had a long-term survival similar to that of euvolemic patients [27].

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 high and frequent dosis 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 [Tables 3 and 4]. Recent prospective and retrospective studies, in decompensated patients, have paid particular attention to the relationship of continuation, withdrawal or newly starting of beta blockers [18, 19, 28, 29]. 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 [7]. They were predominantly congestive, with adequate perfusion pressure and their baseline heart rate decreased gradually over the 96 hours observation period. Thus, cardiac sympathetic drive and its well-known deleterious consequences on the myocardium were attenuated [30-32]. Secondly, carvedilol increases renal blood flow [33] and decreases cardiac sympathetic drive to a greater extent than selective beta-adrenergic blockers [34]. Moreover, it appears to suppress aldosterone production [35]. 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 [23]. In summary, the observed beneficial effects of cautious uptitration of carvedilol, in decompensated patients in sinus rhythm, are very likely due its unique pharmacological characteristic of α and β blocker [36].

6. Limitations

Our study is a retrospective, opened label, nonrandomized clinical investigation with a small sample. Initially, we compared two opposite therapeutic strategies. However, in view of the very favourable changes, induced by carvedilol on heart rate, neurohormonal activation and non-sustained ventricular arrhythmias (20); the responsible investigators decided to assign most patients to this particular protocol. Although, the survival results may have been influenced by their decision, our findings are congruent with those reported in the literature. Furthermore, the already mentioned differences of carvedilol, with other beta-adrenergic blockers, could explain our findings.

7. Conclusions

In Summary, in this investigation 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 rthyms and cautious uptitration of carvedilol, is still decompensated with sinus rhythm, increases long term survival

Disclosure Section

All the authors do not have any possible conflicts of interest.

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