Favorable Effects of the Optimized Drug Treatment of Heart Failure on Ventricular Arrhythmias

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Summary

Background: Ventricular arrhythmic events have a strong impact on the mortality of patients with heart failure. The benefits of the optimized drug treatment of heart failure in reducing ventricular arrhythmia have not been well documented yet.

Objective: To analyze the effects of the optimized drug treatment of heart failure on ventricular arrhythmia.

***Methods:*This is a clinical study with a non-randomized design of 85 consecutive (open cohort) non-selected patients, with a mean age of 63.8±12.2 years; 42 were males and 43 were females. All patients had a diagnosis of heart failure (HF), NYHA Functional Class II to IV, EF ≤ 0.40 and, after treatment optimization, they were followed from January 2002 to May 2004, regarding the ventricular arrhythmia behavior, at admission and at the end of the study.**

Results: At the start of the study, 60% of patients presented more than 1,000 ventricular extrasystoles in 24 hours, 100% pairs and 100% nonsustained ventricular tachycardia (NSVT). During a follow-up period of 8 to 27 months (20.0 + 4.8 months) a significant decrease in the total number of ventricular extrasystoles/24 hrs, number of pairs and number of NSVT episodes was observed (p<0.05). The improvement in functional class and performance at the six-minute walk test was also observed. A decrease in hospital admissions was also observed in relation to the period prior to the study inclusion (4.8 hospital admissions/patient/year and at the end of the study, 2.7 hospital admissions/patient/year) (p<0.005).

Conclusion: The optimized treatment of HF decreased the incidence of ventricular arrhythmias. The improvement in the functional class, physical performance and the decreased number of hospitalizations can be attributed to the optimized treatment of HF. (Arq Bras Cardiol 2008;91(6):363-369)

Key words: heart failure/therapy; arrhythmias, cardiac

Introduction

The mortality due to heart failure (HF) has decreased in the last years, a fact attributed to the use of several drugs without a primary antiarrhythmic action: betablockers[1-5], angiotensin-converting enzyme inhibitors (ACEI)[6-9], angiotensin-receptor blockers (ARB)[10] and aldosterone antagonists[11,12].

Several studies have confirmed that the ventricular arrhythmias are independent risk markers, but they depend on the degree of the associated ventricular dysfunction[13]. It has been demonstrated that betablockers not only decrease mortality due to the disease progression, but also due to sudden death. This favorable effect seems to be related to the effect of the drugs on the neurohormonal dysfunction and ventricular remodeling[14,15].

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Manuscript received February 21, 2008; revised manuscript received April 15, 2008; accepted May 07, 2008..

The onset of the cardiac resynchronization therapy – with or without the concomitant implant of the implantable cardioverter-defibrillator (ICD) – resulted in the improvement of functional class, hemodynamic data and quality of life and in the decrease of ventricular arrhythmias[16-20]. These data, derived from the non-pharmacological treatment of the HF, once more have led to the discussion about the meaning of heart arrhythmias in the context of ventricular dysfunction.

The benefits of the drug treatment of ventricular arrhythmias in HF are still debatable, due to the inclusion of antiarrhythmic drugs[21].

The aim of the present study is to verify whether the optimized HF treatment is enough, on its own, to decrease the incidence of ventricular arrhythmic events.

Methods

This study protocol was previously approved by the Ethics Committee in Research of the Institution and all patients signed the free and informed consent form before study admission.

To calculate the sample size, it was admitted that 30 to

50% of the patients with HF die within 5 years after the diagnosis[6,7]. Around 50% of them die of sudden death, with a large percentage of them being attributed to ventricular arrhythmias[13,22]. The power of detection of the sample was calculated through the appropriate methodology for paired data (before and after)[23]. It was concluded that the sample used had a power of detection of 99.8%.

This was a clinical non-randomized study of 115 consecutive and non-selected patients (open cohort) with a diagnosis of HF due to systolic dysfunction of any etiology, of any ethnicity or gender, aged > 18 years, with functional class II to IV (NYHA), EF ≤ 0.40 (assessed by M-mode transthoracic echocardiography, Teicholz method).

The patients excluded from the study were the ones that did not agree to participate at any phase of the follow-up; those likely to undergo surgical correction (myocardial revascularization surgery, valve replacement, awaiting heart transplant, defined candidates to ICD); patients who had AMI or angina with less than 30 days of evolution; those with concomitant disease that could impair the diagnosis; those with renal failure (creatinine ≥ 3.0 mg/dl), serum potassium > 5.5 mEq/l; liver failure, characterized by enzymes > 3-fold the reference values; incapacity of undergoing regular follow-up; contraindication or intolerance to ACEI, ARB, carvedilol and spironolactone; those with ventricular arrhythmia that justified the use of drug treatment – at the discretion of the investigator or that had already received it during a visit to the Emergency Department; patients using antiarrhythmic drugs, of which withdrawal could not be the responsibility of the investigator or was not admitted by the patient (based on previous instructions accepted by the patient or his/her tutor); patients using amiodarone (currently or in the last six months).

All patients received the optimized treatment for HF, according to the recommendations of the ACC/AHA (American College of Cardiology/American Heart Association), of the European Society of Cardiology and II Directives (Review) of the Brazilian Society of Cardiology (SBC)[24-27], including as standard therapy: ACEI or ARB and betablockers at the maximum tolerated doses, diuretics and spironolactone, with or without digoxin. Nitrates and hydralazine were not used. The minimum follow-up period was 8 months.

The patients were scheduled to be seen by the investigator for evaluation and drug dose adjustment every two weeks during the first three months, in order to reach the target-dose of ACEI (20 to 40 mg/day of Enalapril) or ARB (50 to 100 mg/day of Losartan), betablocker (Carvedilol, 25 to 50 mg/day), spironolactone (25 mg/day) and, subsequently, every two months. The treatment was considered optimized when the patient tolerated at least the lower limit of the recommended doses, according to the directives. All patients were instructed to seek the Emergency Department of the study base-hospital in case of clinical worsening, where they were also admitted, whenever necessary.

The following examinations were requested at the admission and throughout the follow-up period (every two months): 12-derivation electrocardiogram (ECG); chest teleradiography (x-ray); transthoracic Doppler echocardiogram; 24-hour Holter monitoring; six-minute walk test.

The data related to hospital admissions were recorded regarding the frequency and the cause, with the latter classified as caused by HF worsening, heart arrhythmia or other cause. The deaths were classified as sudden death, inside or outside the hospital, due to HF worsening or due to another cause (cardiovascular or not).

The comparative statistical analysis of the ventricular arrhythmias took into account the first assessment at the study admission and the last, at the end of the study or the last visit before death. To compare the ventricular arrhythmias at admission and after the optimized HF treatment, McNemar test was used for the binary categorical variables (bigeminism, trigeminism, pairs) and the Marginal Homogeneity test was used for the ordinal categorical variables: isolated extrasystoles and nonsustained ventricular tachycardia (NSVT). The three tests are adequate to compare paired data; in this case, the same patient being assessed at two different moments. The several combinations of ventricular arrhythmia types that the patients presented were also evaluated, as well as the general percentage of improvement or worsening of these patients. The level of significance was set at 5% and the statistical analysis was carried out with the software SPSS 12.0.

Results

Of the 115 patients admitted with a diagnosis of HF, 12 were excluded at the initial phase of the study. The main reasons were: lack of adherence to the instructions and follow-up difficulties due to address changes; 9 others were excluded at the optimization phase of the treatment and 9 more during the follow-up, as they did not tolerate the maintenance or progression of the drug dose or because they were considered for the use of antiarrhythmic drugs or heart resynchronization therapy, with or without the ICD implant. A total of 85 (eighty-five) patients completed the entire follow-up period. The demographic and clinical characteristics of the patients at admission are shown in Table 1. The data regarding the etiology of the HF, the clinical manifestations, the functional class, the Doppler echocardiogram, the 24-hour Holter, the six-minute walk test and drug use were recorded.

The mean follow-up period of these 85 patients was 20.0±4.8 months (range: 8-27 months). As shown in Table 2, 100% of the patients at admission had ventricular arrhythmia of varied complexity. Table 3 shows that there was a statistically significant difference between the number of isolated ventricular extrasystoles (VES)/hour at admission and after the optimized treatment ($p<0.05$). There was a more significant decrease among the patients that presented extrasystoles > 1000 VES/h at admission.

The results show that there was a statistically significant difference between the patients that presented pairs of ventricular extrasystoles at the admission and after the optimized treatment ($p<0.05$). Among the patients that presented pairs at the admission, 30% ceased to present them at the end of the study (Table 4).

According to the Table 5, there was a statistically significant difference between the number of NSVT/24 h at the admission and after the optimized treatment ($p<0.05$). Among the patients that presented between 4 and 10 NSVT/24 h at the admission, 41% started to present up to 3/24 h at the end of

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Table 1 – Demographic and clinical characteristics of the 85 patients at study admission

Characteristics	Frequency	Percentage
Sex		
Male	43	50.6
Female	42	49.4
Ethnicity		
Caucasian	83	97.6
Non-Caucasian	2	2.4
Age in years (Mean ± SD)	**63.8 ± 12.2**	
Etiology of cardiopathy:		
Ischemic	27	31.8
Chagasic	23	27.1
Dilated	33	38.8
Rheumatic	02	2.3
Functional Class (NYHA)		
FC II	8	9.4
FC III	53	62.4
FC IV	24	28.2
Six-minute walk test (meters)		
< 250	43	50.6
251 to 300	31	36.5
301 to 350	8	9.4
Cardiothoracic index		
0.50 to 0.55	5	5.9
0.56 to 0.65	44	51.8
> 0.66	36	42.4
Ejection Fraction at Transthoracic Echo		
0.40 to 0.30	1	1.2
0.29 to 0.20	56	65.9
< 0.20	28	32.9
Digitalis Use		
Yes	56	65.9
No	29	34.1
ACEI		
Yes	80	94.1
No	5	5.9
Betablocker		
Yes	22	25.9
No	63	74.1

NYHA - New York Heart Association; ACEI - angiotensin converting enzyme inhibitor

Table 2 – Ventricular Arrhythmias at 24 h-Holter at study admission

Type of Arrhythmia	Frequency	Percentage
VES at Holter (in number/ h)		
1. VES 0 to 10	3	3.5
2. VES 11 to 50	24	28.2
3. VES 51 to 100	21	24.7
4. VES 101 to 500	18	21.2
5. VES 501 to 1,000	9	10.6
6. VES > 1,000	10	11.8
Pairs of VES		
Present	85	100.0
NSVT/24h		
1.Up to 3	29	34.1
2. From 4 to 10	34	40.0
3. From 11 to 50	16	18.8
4. > 50	6	7.1

VES - Ventricular Extrasystoles; NSVT - Nonsustained Ventricular Tachycardia

Table 3 – Comparison of isolated extrasystoles at admission and after optimized treatment

Number of extrasystoles/h	Number of Patients	
	At Admission	At the end of the study
0 to 10	3 (3.5%)	12 (14.1%)
11 to 50	24 (28.2%)	23 (27.0%)
51 to 100	21 (24.7%)	28 (33.0%)
101 to 500	18 (21.2%)	12 (14.1%)
501 to 1000	9 (10.6%)	7 (8.2%)
> 1000	10 (11.8%)	3 (3.6%)
Total	85	85

p value - Marginal Homogeneity Test < 0.001

Table 4 - Comparison of the presence of extrasystole pairs at admission and after the optimized treatment

Pairs at admission			Pairs at the end of the study		
			Yes	No	Total
	Yes	100%	60 (70%)	25 (30%)	85

p value - McNemar's Test = 0.001

the study. Of those patients with 11 to 50 NSVT/24 h at the admission, 81% started to present lower values at the end of the study. Additionally, there was an improvement of 83% among the patients that presented NSVT values > 50/24 h at the admission.

In short, the presence of NSVT at the start of the study was compared to that at the end, as shown in Table 6. The results showed that there was a statistically significant difference between the percentage of the patients that presented NSVT at the admission and after the optimized treatment ($p<0.05$). It can be observed that, of the patients that presented NSVT at the admission, 31% ceased to present it at the end of the study. Although with no statistical significance, 24% of the patients increased the number of NSVT/24 h when compared to the admission data.

When analyzing all the combinations of ventricular arrhythmia types found in the 85 patients evaluated at admission (Table 2) and the end of the study (Tables 3 to 6), we observe that most patients (55%) presented all types of arrhythmia (VES, bigeminism, trigeminism, pairs and NSVT). In general, 53% of the patients presented improvement in the arrhythmias, with 33% of the patients persisting with the same characteristic seen at the admission and only 14% presenting worsening. It is noteworthy the fact that this worsening rate did not have statistical significance. According to the statistical test, it can be stated that the patients' improvement after the optimized treatment was significant.

There was a significant improvement of the heart failure FC and in the 6-minute walk test (Table 7) when comparing the admission data with those at the end of the study ($p< 0.001$).

No significant difference was observed regarding the echocardiographic parameters at the end of the study (Table 7).

A significant decrease in the number of hospitalizations was observed, when the admission data (4.8 hospitalizations/patient/year) were compared to those at the end of the study (2.7 hospitalizations/patient/year) ($p<0005$). A total of 27 deaths (31.8%) occurred throughout follow-up. There was no significant correlation between mortality and the occurrence of ventricular arrhythmia and most of the deaths were due to HF progression. Thus, 23 of the 27 patients who died due to HF worsening did not present concomitant worsening of ventricular arrhythmias.

Table 5 – Comparison of the number of NSVT at admission and after the optimized treatment

Number of NSVT/24h	Number of patients	
	At admission	At the end of the study
0	0	27 (31.8%)
Up to 3	29 (34.1%)	45 (52.9%)
4 to 10	34 (40.0%)	10 (11.7%)
11 to 50	16 (18.8%)	2 (2.4%)
> 50	6 (7.1%)	1(1.2%)
Total	85	85

** p value- Marginal Homogeneity Test = 0.029; NSVT - Nonsustained Ventricular Tachycardia*

Table 6 – Comparison* of the presence of NSVT at admission and after optimized treatment

			NSVT at end of the study		Total
			Yes	No	
NSVT at admission	Yes	100%	58 (68.2)	27 (31.8%)	56

** p value – McNemar's Test = 0.005; NSVT - Nonsustained Ventricular Tachycardia*

Table 7 – Characteristics of the groups regarding functional class (NYHA), six-minute walk test and echocardiographic findings at the end of the study (in %)

	Frequency	Percentage
HF Functional Class		
1. FC I	6	7.1
2. FC II	39	45.9
3. FC III	15	17.6
4. FC IV	25	29.4
Six-minute walk test (meters)		
1. < 250 m	33	38.8
2. From 251 to 300 m	5	5.9
3. From 301 to 350 m	24	28.2
4. From 351 to 450 m	17	20.0
5. From 451 to 600 m	5	5.9
6. > 600 m	1	1.2
LV ejection fraction (EF) at echocardiogram		
1. EF 0.40 to 0.30	6	7.1
2. EF 0.29 to 0.20	45	52.9
3. EF < 0.20	34	40.0

LV - Left Ventricle; HF - heart failure

Discussion

The results of the present study showed that, in patients undergoing optimized HF treatment, there was a significant decrease in ventricular arrhythmias. This finding has clinical and practical relevance.

Considering that the Brazilian literature has scarce data on the subject, the present study prospectively analyzed a population of symptomatic patients with HF, with documented ventricular arrhythmia and general characteristics that were very similar to those usually seen in outpatient clinics and medical offices. The studied sample consisted of patients with dilated cardiomyopathy, ischemic and Chagasic etiologies at similar proportions (around 1/3 of patients for each etiology).

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The recognition of HF as a neurohormonal dysfunction made betablockers and ACEI start to constitute the basis of what is called the "optimized treatment"[24-26]. Ever since the first studies with the ACEI and, later, with betablockers, there was evidence of an improvement in quality of life, decrease in hospitalizations, and increased survival of patients that used this therapeutic strategy[1-10]. In parallel, there was evidence of a decrease in the incidence of sudden death without the use of drugs with primary antiarrhythmic effect[5,11-12].

The optimized HF therapy has been frequently underused, and not only in Brazil, under the justification that the patients, notably those with FC III and IV of the NYHA, would not tolerate the recommended doses of the medications with effect on the decrease of mortality[28-30]. The more severe patients are precisely the ones that do not receive the medications at the doses recommended by the directives for the treatment of HF.

In the present study, in order to ascertain that the treatment would be in accordance with the study protocol, all of the patients in this population were regularly followed, by the same observer, as in a severe situation such as HF, in which ventricular arrhythmia is present in most cases, many of them could have altered or even discontinued therapeutic measures. This attitude has an essential aspect (even though it is acknowledged that it might be a bias) in a study that seeks to analyze the behavior of ventricular arrhythmia in patients with HF.

Based on observations of patients monitored by Holter, it has been demonstrated that the sudden betablocker withdrawal exposes the patient to an additional risk situation. The sudden withdrawal of the beta-adrenergic blockade and the increase in vagal tonus[31] influence the heart rate variability and predispose to the increase in ventricular arrhythmias[32]. This study used carvedilol as the betablocker, as the pertinent literature shows a more adequate profile of this substance, even in patients with marked ventricular dysfunction[33].

The RALES study[11] – which used spironolactone, an antagonist of aldosterone – demonstrated a decrease in the hospitalizations and mortality (total and sudden death) in HF, although with no definite evidence for its use in patients with FC II[11]. The EPHESUS study[12] used a selective antagonist of aldosterone (eplerenone)[12] and showed a decrease in hospitalizations and mortality (total and sudden death) in post-infarction patients with an ejection fraction < 0.40. Considering that there is no evidence of an unfavorable effect, we chose to prescribe spironolactone, at a dose of 25 mg/day, to all patients.

The clinical trials involving the cardiac resynchronization therapy have shown that, together with the improvement in the hemodynamic parameters that evaluate ventricular function, an important decrease in all forms of ventricular arrhythmia has been observed[16-20]. This finding demonstrates a well-documented fact, although not completely elucidated, that the ventricular arrhythmia represents the expression of HF severity and that of the subjacent ventricular dysfunction and that its improvement leads to the arrhythmia improvement[21,22]. Considering that the patients submitted to the cardiac resynchronization therapy could have the ventricular arrhythmia behavior modified by the therapeutic modality, we chose not to include patients carrying this device in this sample.

A series of publications in our country, such as that by Mady[34], had already documented that patients (in this case, Chagasic ones) with NYHA FC III and IV and EF < 30% have a very low survival rate. The studies by Rassi Jr. et al[22] , Laranja et al[35], De Paola et al[36] assessing populations of Chagasic patients, pointed out to a bad prognosis related to the presence of ventricular arrhythmia, atrioventricular blockade and atrial fibrillation in these patients, although they did not specifically analyze patients with HF and, in particular, those undergoing optimized treatment.

Rassi Jr. et al[22] demonstrated that the association between NSVT and ventricular dysfunction is related to a reserved prognosis, when compared to the patients with only one finding. This same author also demonstrated that the presence of NSVT at the Holter monitoring in a population of 424 Chagasic patients, followed on an outpatient basis for a long period of time, showed to be an independent variable associated with a higher death risk[22]. This same finding was documented, in Brazil as well as in the international literature, in patients with other forms of cardiomyopathies (dilated and ischemic)[13,21].

When the ventricular arrhythmia was assessed in the present study, it was observed that, at a variable degree, all the patients presented it at the admission. This fact led us to consider whether our patients were actually more severe cases at the admission, which could have influenced the clinical outcomes. When the ventricular arrhythmia was evaluated at the end of the study, we observed that there was a significant difference in its occurrence. Additionally, we observed a significant decrease in the number of NSVT episodes at the end of the study and it is known in the literature that the NSVT behavior is the independent marker related to an unfavorable clinical outcome (occurrence of sustained ventricular tachycardia and sudden death)[22].

Based on our data and considering the behavior of the number of episodes of NSVT/24 h, it can be postulated that the optimized HF treatment is likely to have a favorable effect on the decrease of the ventricular arrhythmia.

As for the behavior of the heart failure FC, this study showed a significant improvement at the end of the study and this finding can be attributed to the effect of the optimized HF treatment. Along with the decrease in the arrhythmias, we observed a decrease in the number of hospitalizations, indicating clinical improvement with the treatment optimization. The same improvement, regarding the physical performance evaluated through the six-minute walk test, was observed at the end of the study.

Concerning the echocardiographic follow-up, at the admission and at the end of the study, there was no significant difference regarding the EF and the LV end-diastolic diameter. These results are in agreement with the literature data, which have shown that seriate EF evaluations can be employed in patients' follow-up, but the association of these measures with survival estimate is limited[37].

In the present series, there were 27 deaths (31.78% of the sample) among the 85 patients that underwent complete follow-up, which confirms the fact that the HF, regardless of the subjacent cardiopathy and despite the advancements attained with the optimized treatment, remains a very severe disease, with high mortality.

The main cause of death was the disease progression and not sudden death. Additionally, 23 of the 27 patients that died due to

the HF worsening did not present concomitant worsening of the ventricular arrhythmias. This fact is noteworthy, as the literature reports that around 40% of the patients with HF die suddenly and a large percentage of the deaths are due to ventricular arrhythmia.

In our series, the deaths were predominantly due to disease progression and fewer were due to sudden death. The present study did not aim at evaluating mortality outcomes, due to the sample size. However, it could be speculated whether the fact that these patients were undergoing optimized treatment, including the use of betablockers and spironolactone (drugs that have an effect in reducing total mortality and sudden death), would have reduced the sudden death incidence by decreasing ventricular arrhythmias.

The nine patients that were excluded from the comparative analysis – after the treatment optimization phase, due to some type of drug intolerance and who were also followed – died within an average 12-month period. These patients presented the highest number of hospitalizations, with longer average duration of hospital stay, when compared to the patients that completed the follow-up. Seven of them died to HF worsening and two due to sudden death, one in the hospital and one at home. The poor evolution of these nine patients was an expected clinical fact, as the condition of optimized treatment intolerance, of which beneficial effects have been previously demonstrated, put them in a worse prognosis subgroup[28-30,33].

The results of the present study emphasize and demonstrate the importance of the optimized clinical treatment in the improvement of ventricular arrhythmias, with an impact on the morbidity of patients with HF. Additionally, in agreement with the current literature, it demonstrates that ventricular arrhythmias are probably the consequence of the subjacent ventricular dysfunction, and that, although the rhythm disorder can be more or less significant in an individual patient, we do not have, to date, enough data to recommend the routine inclusion of antiarrhythmic drugs in the optimized treatment.

Conclusions

The optimized clinical treatment of HF had a favorable effect on the occurrence of ventricular arrhythmias and most of the deaths occurred due to the HF progression, which was not related to the behavior of the ventricular arrhythmias. The FC and physical performance improvement and the decrease in the hospitalizations must be attributed to the optimized HF treatment.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of doctoral submitted by Epotamenides Maria Good God, from USP-SP.

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