# Effects of the Association of Dual-Site Dynamic Atrial Overdrive and Atenolol in Preventing Recurrent Atrial Fibrillation

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**Objective:** Evaluate the effects of optimized atrial stimulation - OAS (dual-site atrial pacing, heart rate above the intrinsic rate, and specific functional algorithm), and the use of atenolol in preventing recurrent atrial fibrillation (AF). Primary endpoint: to quantify the rate of AF episodes. Secondary endpoints: assessment of quality of life, specific cardiovascular symptoms, rate of hospital admissions, rate of electrical and pharmacological cardioversions, and adverse cardiac events.

**Methods:** Twenty-five patients with recurrent episodes of paroxysmal AF and sinus node disease had dual-site atrial and ventricular pacemakers implanted, and were started on atenolol, 100 mg/day. Next, they were randomized to two groups: GROUP I: first three months with OAS and the specific pacing algorithm (DAO) turned on, and three more months with the algorithm off. GROUP II: the inverse sequence to GROUP I. The pacing mode chosen was DDDR, and after three months patients underwent clinical and electronic evaluations of the stimulation system by: automatic mode switch (AMS), 24-hour Holter monitoring, Doppler echocardiogram, and SF-36 questionnaire. Following, a crossover comparison took place, and a new assessment was performed six months later.

**Results:** When compared to the group with the algorithm turned off, OAS patients had lower rates of: AF/week ($p < 0.001$); AMS activations ($p < 0.01$); hospitalizations ($p < 0.001$); cardioversions ($p < 0.001$), and higher scores on the physical and mental components of quality of life.

**Conclusion:** The hybrid therapy adopted, OAS associated with the use of atenolol, reduced the rate of recurrent AF and improved the clinical-functional status of patients with symptomatic bradyarrhythmias.

**Key words:** Dynamic atrial overdrive, recurrent atrial fibrillation, prevention of atrial fibrillation, dual-site atrial pacemaker.

AF is currently the biggest challenge for researchers in the area of cardiac arrhythmias, as it entails considerable morbimortality and with an incidence estimated to be 0.4% in the general population, and up to 5.9% in those above 65 years of age. It is the most common sustained cardiac arrhythmia, and its morbidity correlates with thromboembolic phenomena, with the loss of atrioventricular synchronism and with the maintenance of high heart rates, besides being considered the leading cause of cerebrovascular accidents[1,2].

Multisite atrial stimulation has been used to prevent atrial tachyarrhythmias, as there are evidences that it not only suppresses automatic triggering sites, but it may also have a direct effect on the mechanisms of sustained AF[3-6] . DDDR stimulation with a minimum frequency programmed to 60 ppm, and a dynamic atrial overdrive algorithm (DAO) seem also capable of reducing symptomatic AF in patients with combined SND and AF[7,8]. On the other hand, dual-site atrial stimulation and conventional stimulation alone do not seem to be sufficient for the treatment of AF. The association of dual-site atrial stimulation with atrial overdrive algorithms and ß-blocker agents could be more useful than dual-site atrial pacing alone.

The objective of this study is to evaluate the effects of the hybrid therapy (HT) in preventing recurrent AF. The *primary endpoint* was set as the quantification of the recurrence rate of AF episodes, and the *secondary endpoints* were: quality of life, assessment of specific symptoms (syncope, palpitations, and dizziness), rate of hospital admissions, rate of electrical or pharmacological cardioversions, and thromboembolic cardiac events.

## Methods

Twenty-five consecutive patients were enrolled in this study, from November 2001 to May 2003, in accordance with the Helsinki Declaration guidelines, with the approval by the Ethics Committee of the University of São Paulo Medical School, and written informed consent obtained from all selected patients.

Age varied from 32 to 84 years (mean age was 63±13.8

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Manuscript received: August 11, 2005; revised manuscript received February 14, 2006; accepted on March 7, 2006.

years); 14 (56%) patients were females and 11 (44%) were males.

Inclusion criteria were: sinus node disease in its brady-tachycardia form (the tachycardia form was defined as chronic paroxysmal AF with at least three episodes during the first previous six months) or persistent chronic AF, both not responding to at least three anti-arrhythmic drugs, and a minimum of 18 years of age.

Exclusion criteria were: mitral valve disease with moderate or severe hemodynamic repercussions, congestive heart failure, acute cardiovascular disease over the last six months (unstable angina, acute myocardial infarction), severe liver or kidney disease, pregnancy, history of sustained ventricular tachyarrhythmia, and impossibility to be faithful in clinical follow-up.

The study was characterized as prospective, randomized, single-blinded, controlled, and crossover.

Initially, all patients underwent a cardiological evaluation consisting of: clinical examination, 12-lead electrocardiogram (ECG), 24-hour Holter monitoring, bidimensional Doppler transthoracic echocardiogram, and completion of the quality of life questionnaire (SF-36). Next, patients underwent dual-site pacemaker implantation: atrial (one electrode was placed on the right auricular appendage and another one close to the ostium of the coronary sinus) and ventricular. They were started on atenolol (dose adjusted as of 100 mg/day), and were randomly assigned to two groups according to the following criteria**:** group I - initially with the DAO (dynamic atrial overdrive) algorithm turned on for a three-month period, followed by three more months with the algorithm turned off; and group II – initially with the DAO algorithm turned off for three-months, followed by three more months with the algorithm turned on.

The total follow-up period was six months, and after the first three months, groups were crossed over. After a new clinical assessment, electronic evaluation of the pacemaker, 24-hour Holter, bidimensional Doppler echocardiogram and completion of the quality of life questionnaire (SF-36), the DAO algorithm status was switched (on/off). During the last three months (final follow-up phase of each group), the same sequence of assessments was performed again before the analysis of results. Figure 1 displays details of the follow-up sequence and schedule.

Table 1 shows the baseline characteristics of both groups with regard to age, gender, baseline cardiopathy, functional class, and the diagnostic tests patients underwent during the selection.

Table 2 shows detailed electrocardiographic characteristics of patients in each group as to sinus node disease and its brady-tachycardia syndrome, i.e., the arrhythmias that defined the inclusion of patients.

Statistical analysis - for the analysis of the qualitative variables, Chi-square and Fisher's exact tests were applied to those cases in which expected rates were below five. For the analysis of the quantitative variables, the hypothesis of normality was first verified for each variable, a necessary assumption for using parametric tests,. This hypothesis was evaluated using histograms, "box-plot" type charts, and

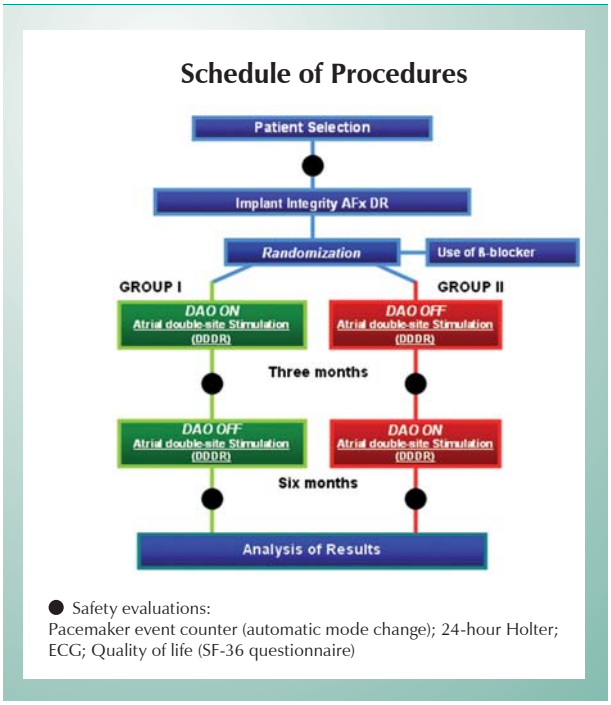



***Fig. 1 -*** *Sequence of evaluations performed during the study.*

asymmetry and kurtosis measurements.

For the variables that did not follow a normal distribution, the non-parametric Kruskall-Wallis test was employed.

T-Student and non-parametric Mann-Whitney tests were employed for the remaining comparisons between the groups – when the distribution was not characterized as normal. For comparisons within the same group, the paired t-test or the (non-parametric) Wilcoxon test was employed.

Pearson's and Spearman's correlation coefficients (non-parametric) were used to analyze the relationships between quantitative variables.

## Results

*Clinical evaluation – A) Palpitations, presyncope, syncope or precordial pain* - Over the three- and six-month follow-up periods, patients in groups I and II did not experience presyncope, syncope, or precordial pain.

A small number of presumable AF events, that is, frequent tachycardia palpitations with the stimulation algorithm turned on, was observed in group I (0.50 ± 0.23) or group II (0.60 ± 0.29). Comparison was made also with the algorithm turned off in group I (1.36 ± 0.38) and group II (1.11±0.61), with $p < 0.001$ and $p = 0.024$, respectively, using paired t-test.

*B) Functional class of congestive heart failure (NYHA)* - After three months of OAS therapy, 10 (83%) of the 12 patients in group I were classified as NYHA functional class I. After six months, the last three with the DAO algorithm turned off, only six patients (50%) remained in class I, whereas all others in class II. No patient in this group was classified as functional classes III or IV.

Among the 13 patients in group II who started the first

| Variable | Group 1 | Group II | |
|---|---|---|---|
| | n=12 | n=13 | p |
| Age (years) | 63.92 ± 12.76 | 63.92 ± 15.21 | 0.822 |
| Gender n (%) | | | 0.844 |
| Female | 6 (50.0%) | 8 (61.5%) | |
| Male | 6 (50.0%) | 7 (38.5%) | |
| Functional class (NYHA) | | | 0.466 |
| I | 4 (33.3%) | 7 (53.8%) | |
| II | 8 (66.7%) | 6 (46.2%) | |
| Baseline cardiopathy | | | 0.554 |
| Chagasic | 4 (33.3%) | 6 (46.2%) | |
| Hypertensive | 5 (41.7%) | 3 (23.1%) | |
| Ischemic | 0 (0.0%) | 3 ( 23.1%) | |
| Rheumatic | 1 (8.3%) | 1 (7.7%) | |
| Mitral valve prolapse | 1 (8.3%) | 0 (0.0%) | |
| Other | 1 (8.3%) | 0 (0.0%) | |
| 24-hour Holter echocardiogram | | | |
| Maximum heart rate (bpm) | 131.83 ± 53.80 | 155.62 ± 35.42 | 0.401 |
| Mean heart rate (bpm) | 56.00 ± 10.78 | 57.15 ± 9.42 | 0.384 |
| Minimum heart rate (bpm) | 38.67 ± 6.97 | 43.23 ± 5.95 | 0.299 |
| Total atrial extrasystoles (number) | 11360.83 ± 14225.28 | 5489.08 ± 8795.64 | 0.522* |
| Supraventricular tachycardia (number) | 94.17 ± 109.33 | 84.31 ± 107.35 | 0.971 |
| Heartbeats per TPSV episodes (number) | 14.67 ± 8.08 | 14.08 ± 8.73 | 0.773 |
| Echocardiogram | | | |
| Heart rate (bpm) | 62.8 ± 22.6 | 54.5 ± 8.1 | 0.257 |
| LV diastolic diameter (mm) | 50.5 ± 4.6 | 49.9 ± 4.2 | 0.122 |
| Final diastolic volume (ml) | 100.4 ± 31.0 | 100.9 ± 26.7 | 0.888 |
| LV ejection fraction (%) | 70.8 ± 4.7 | 69.2 ± 2.6 | 0.094 |
| LV diastolic diameter (mm) | 43.5 ± 4.7 | 38.6 ± 7.2 | 0.113 |

**non-parametric test. LV- left ventricle.*

**Table 1 - Clinical-epidemiological characteristics according to patient distribution in randomized groups (I and II)**

three months with the DAO algorithm turned off, 7 (53.8%) remained in NYHA functional class I, 5 (38.4%) remained in class II, and 1 (7.6%) in class III. After six months, the last three with OAS, 12 patients (92.3%) were classified as functional class I, and 1 patient (7.6%) asfunctional class II. Only one patient was classified as class III at the beginning of the treatment, and no one was classified as class IV.

*C) Hospitalizations due to AF, and pharmacological and electrical cardioversions* - The number of hospitalizations due to AF in group I before the treatment was 3.83±2.44, and after six months of pharmacological treatment (atenolol) and non-pharmacological (dual-site atrial pacing and DAO algorithm turned on or off), the number of events decreased significantly (1.83±1.00, p=0.008).

The number of hospitalizations due to AF in group II before randomization was 3.23±1.79, and after six months of pharmacological and non-pharmacological treatment, a significant decrease in the number of events was observed (1.08±1.22 and p=0.001).

The number of pharmacological and electrical cardioversions in group I before randomization was 1.75±1.06 and 1.33±0.98, respectively. After six months, the number of interventions was simultaneously reduced to 1.00±0.62 and 1.00±0.55 (p=0.001).

The number of pharmacological and electrical cardioversions in group II before randomization was, respectively, 1.77±0.93 and 1.62±1.33. This number decreased after six months of treatment with atenolol and dual-site atrial pacing (DAO algorithm turned off and then on) to 1.00±1.11 (pharmacological, p=0.003) and 0.56±0.76 (electrical, p=0.007).

*D) Thromboembolic cardiac events, and use of anticoagulants*

| Variável | Grupo I n=12 | Grupo II n=13 | Teste X2 |
|---|---|---|---|
| Bradicardia sinusal com FC entre 40-60 bpm | 7 (58,3%) | 6 (46,1%) | p=0,562 |
| Bradicardia sinusal com FC < 40 bpm | 5 (41,6%) | 7 (53,8%) | p=0,511 |
| Bloqueio sino-atrial | 9 (75%) | 10 (76,9%) | p=0,674 |
| Pausas sinusais >3,0 seg. | 4 (33,3%) | 5 (38,4%) | p=0,897 |
| Presença de FA paroxística | 7 (58,3%) | 10 (76,9%) | p=0,418 |
| Presença de FA persistente | 5 (41,7%) | 2 (15,4%) | p=0,166 |

*HR- : AF- atrial fibrillation.*

**Table 2 - Characteristics of the arrhythmias recorded during patient selection**

*and platelet antiaggregants* - In the first month of follow-up, after having the pacemaker implanted and being randomized to group I, one female patient experienced an episode of transient ischemic cerebrovascular accident, which was diagnosed clinically and by craniocerebral tomography. The patient was hospitalized and after 15 days her clinical status progressed without any sequelae. Pacemaker programming was not altered at any moment, since the clinical treatment alone was sufficient for the patient to finish the protocol six-month follow-up. No one thromboembolic cardiac event was observed among the other 24 patients over the six-month follow-up period.

In group I, 30.7% (4 patients) received an oral anticoagulant, and 23.1% (3 patients) received a platelet antiaggregant throughout the six-month follow-up. In group II, 35.7% (5 patients) received an oral anticoagulant and 42.9% (6 patients), received a platelet antiaggregant.

*Electronic evaluation of the stimulation system* – A) Sample total time retrieved by telemetry, percentage of atrial and ventricular stimulation.

A1) Group 1 - the sample total time between the first phase (three months) with the optimized therapy, and the second phase with the dual-site atrial pacemaker and the algorithm turned off, were statistically similar (p=0.609) as measured by the Wilcoxon test. The percentage of atrial stimulation was greater in the phase with the algorithm turned on (p=0.003), whereas the percentage of ventricular stimulation was, on average, smaller (p=0.09).

A2) Group II - The sample total time was similar with the DAO algorithm turned off and on (p=0.117). The percentage of atrial stimulation was significantly greater with the DAO turned on as per the evaluation performed at six months (p=0.001). The percentage of ventricular stimulation measured in each one of the phases (DAO turned on and turned off) was smaller with the algorithm turned off, even including a statistical difference between them. (p=0.02).

*B) Automatic mode shift (AMS) values*- Table 3 displays data about the study phase in group I (comparison with DAO turned on) during which patients remained three months with the overdrive algorithm turned off, followed by six more months with the algorithm turned on. Values were, on average, greater with the DAO algorithm turned off (p=0.004).

Table 4 displays data about the study phase in group II during which patients remained three months with the overdrive algorithm turned on, followed by six more months with the algorithm turned off. Values were also, on average, greater with the DAO algorithm turned off (p=0.019).

*Quality of life assessed by the SF-36 questionnaire* - A. Group I: comparison between baseline data and those of the first phase in group I (DAO turned on during three months) revealed a significant improvement in all physical and mental components of the SF-36 questionnaire.

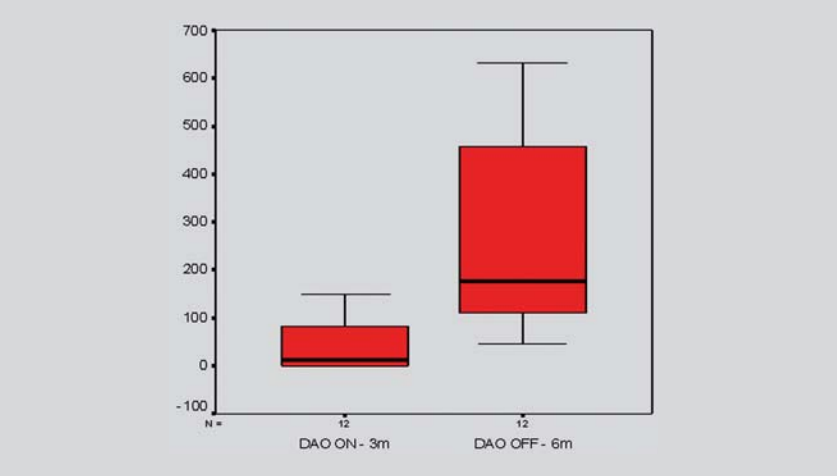
With the algorithm turned on, a statistically significant improvement was observed in the following variables: physical strength (PF) (p=0.038), physical capacity (RP) (0.028), vitality (VT) (p=0.011), and overall physical component summary (PCS) (p=0.034).

B) Group II – a significant improvement in most variables was observed by comparing data recorded after three months of dual-site atrial stimulation, atenolol, and DAO algorithm turned off, and baseline data collected before randomization. For some variables, the differences between the groups were not significant at a 5% level, such as RP (p=0.077), RE (p=0.068), and MCS (p=0.070). However, considering the size of the sample, these differences (with *p* between 0.05 and 0.10) may be equally important.

After three months of dual-site atrial stimulation, use of atenolol, and DAO algorithm turned off, and three more months with the algorithm turned on, the only variable to show statistically significant improvement was RP (p=0.027).

*Two-channel 24-hour Holter monitoring* - Table 5 displays data comparing Holter monitoring in patients in group I and in group II before the pacemaker had been implanted (patients' baseline data), and the comparison between the follow-up phases, that is, DAO on-off (group I) and DAO off-on (group II). The comparison between baseline data before randomization and those collected during the first three months and last six months of therapy showed that the number of isolated atrial extrasystoles, episodes of non-sustained atrial tachycardia (NSAT), and heartbeats during the episodes of NSAT decreased significantly in both groups.

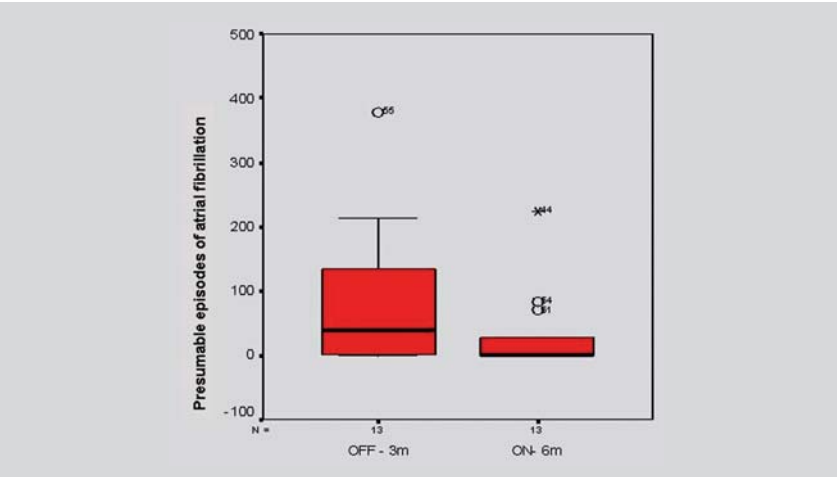
*Bidimensional Doppler echocardiogram* - With the exception of heart rate measured during the test, most variables, i.e., left ventricle diastolic diameter, final diastolic volume, ejection fraction, and left atrium diameter did not show statistically significant differences in either group when




| Variable | N | Mean | Standard deviation | Median | Minimum | Maximum | p |
|---|---|---|---|---|---|---|---|
| DAO on (three months) | 12 | 40.83 | 55.276 | 13 | 0 | 151 | |
| DAO off (six months) | 12 | 276.42 | 211.417 | 174 | 45 | 633 | p= 0.004 |

*DAO- dynamic atrial overdrive.*

**Table 3 - Rate of AMS activations – comparison between two phases in Group I (DAO on and off)**




| Variable | N | Mean | Standard deviation | Median | Minimum | Maximum | p |
|---|---|---|---|---|---|---|---|
| DAO off (three months) | 13 | 85.62 | 117.238 | 39 | 0 | 379 | |
| DAO on (six months) | 13 | 32.23 | 64.499 | 1 | 0 | 225 | P=0.019 |

*DAO - sobreestimulação atrial dinâmica.*

**Table 4 - Rate of AMS activations – comparison between two phases in Group II (DAO OFF and ON)**

compared with baseline data and with the three and six-month follow-up phases, whether the DAO algorithm was turned on or off.

## Discussion

Our study showed a significant reduction in the number of episodes of recurrent AF, assessed indirectly by the number of activations of the automatic mode shift (AMS). The initial improvement in the condition, mainly in group I, led to a significant reduction in the rate of recurrent AF due to the additions to the treatment (DAO algorithm) (p=0.004). At the same time, in group II, with patients remaining three months with the optimized atrial therapy, and then being reprogrammed with the DAO algorithm turned off, a significant reduction was also observed in the rate of recurrent AF (p=0.019). Therefore, with regard to the number of AMS activations and, consequently, the rate of recurrent AF episodes, we observed that optimized atrial stimulation proved to be more effective in reducing the AF rate. In the DAPPAF study, the group submitted first to conventional stimulation and then to dual-site atrial stimulation, had also a smaller number of AF events, and reduced need for cardioversion.[9] Hybrid therapy is a new and promising tool to prevent AF, as it enhances tolerance to antiarrhythmic drugs by eliminating the bradicardy they induce and reducing their side effects. In this study, the use of atenolol in all patients selected could be considered an adjuvant factor in reducing the number of AF events, either by increasing tolerance or synergism with DAO. Interestingly, in the DAPPAF study, only those patients who were on antiarrhythimic medication benefited from this approach[10]. On the other hand, the study PROVE that also evaluated DAO algorithm in patients with bradicardy and chronic AF, did not report satisfactory clinical results, despite the reduced action of atrial triggers during AF[11]. The STADIM study, characterized as a prospective, randomized, controlled, single-blind and cross-over study, included patients with paroxysmal or persistent AF and indications for dual-chamber stimulation. In the STADIM study, the same pacemaker as the one used in our study, with the same *St. Jude Medical Inc*. DAO algorithm™ and two atrial electrodes (one placed at the appendage and the other at the ostium of the coronary sinus) were used. The study's preliminary results confirmed our own, showing a positive trend towards the prevention of AF in those patients with stimulation at the OCS with the DAO algorithm on[12].

This study showed a unique finding compared to similar studies: a clinical-functional correlation with changes in patients' quality of life. Indeed, especially when patients underwent the optimized therapy with the DAO algorithm on, as well as when the groups with dual-site atrial stimulation were compared to baseline data recorded before randomization, a significant improvement in all physical and mental components surveyed (through SF-36 questionnaire) corroborated the clinical improvement. When the DAO algorithm was switched off, only three variables of the physical

| | N | Pre-implantation | 3 Months | P* | 6 Months | P** |
|---|---|---|---|---|---|---|
| Maximum HR | | | | | | |
| Group 1 | 12 | 131.8 ± 53.8 | 106.8 ± 14.3 | 0.105 | 123.8 ± 21.9 | 0.086 |
| Group II | 13 | 155.6 ± 35.4 | 131.0 ± 18.0 | 0.027 | 108.3 ± 15.3 | 0.019 |
| Mean HR | | | | | | |
| Group 1 | 12 | 56.0 ±10.8 | 72.3 ± 8.5 | <0.001 | 76.9 ± 13.3 | 0.266 |
| Group II | 13 | 57.2 ±9.4 | 76.5 ± 6.6 | <0.001 | 70.0 ± 6.8 | 0.065 |
| Minimum HR | | | | | | |
| Group 1 | 12 | 38.7 ±7.0 | 59.6 ± 1.8 | <0.001 | 60.8 ± 5.5 | 0.545 |
| Group II | 13 | 43.2 ±6.0 | 61.1 ± 2.1 | <0.001 | 61.7 ± 6.2 | 0.872 |
| Atrial extrasystoles | | | | | | |
| Group I | 12 | 11360.8 ±14225.3 | 6.8 ± 12.7 | 0.002 | 105.8 ± 141.2 | 0.002 |
| Group II | 13 | 5489.1 ±2546.0 | 81.8 ± 112.1 | 0.001 | 13.9 ± 15.8 | 0.011 |
| Non-sustained atrial tachycardia | | | | | | |
| Group I | 12 | 94.2 ±109.3 | 13.7 ± 12.1 | 0.017 | 2.0 ± 1.9 | 0.002 |
| Group II | 13 | 84.3 ±107.4 | 8.5 ± 3.8 | 0.004 | 2.1 ± 2.8 | 0.002 |
| Number Heartbeats | | | | | | |
| Group I | 12 | 14.7 ±8.1 | 2.8 ± 4.5 | 0.002 | 8.6 ± 6.8 | 0.013 |
| Group II | 13 | 14.1 ±8.7 | 11.5 ± 12.2 | 0.480 | 1.7 ± 2.7 | 0.007 |

** Baseline x 3 m; ** 3 m x 6 m.*

**Table 5 - Comparison between baseline data and follow-up results at three and six months, according to randomized groups**

and overall mental components showed improvement. The comparison between baseline data and the dual-site atrial stimulation showed improvement in a greater number of variables, mainly in physical and overall health aspects.

Finally, this study showed that hybrid therapy, i.e., OAS associated with the administration of a ß-blocker, reduced the rate of recurrent AF and improved the clinical-functional status of patients with symptomatic bradycardia.

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