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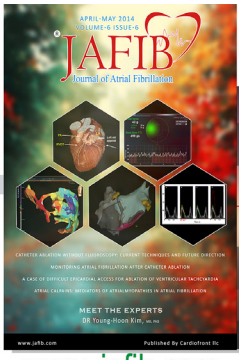

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Ventricular Rate Stabilization In Patients With Permanent Atrial Fibrillation And Single-Chamber Ventricular Pacemaker: RARE-PEARL Study

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Abstract

Background: In patients with permanent atrial fibrillation (AF) rate irregularity can cause symptoms and impair the pumping function of the heart. Ventricular pacing at a rate close to the mean spontaneous ventricular rate can result in a more stable ventricular rate. Specific algorithms for automatic Ventricular Rate Stabilization (VRS) were designed and implemented in commercially available pacemakers. To assess this dynamic rate control we designed the RARE-PEARL study: prospective, randomized, cross-over, double-blinded.

Methods: Patients with permanent AF, symptomatic episodes of brady-tachycardia, left ventricular ejection fraction (LVEF) >40%, NYHA class I/II/III, were eligible for enrolment. Each patient (n = 67) was implanted with a single-chamber VVIR pacemaker (models C20 or T20, Vitatron BV, The Netherlands) equipped with the VRS algorithm. At the end of a four week stabilization period, patients were randomized to VRS algorithm ON or OFF (2 months) and then crossed-over for the second phase (2 months). Primary endpoint was patient's preference.

Results: Sixty six patients ended the study: 19 (29%) had no preference; 15 (23%) preferred algorithm OFF, 32 (48%) algorithm ON ($p<0.0001$, algorithm ON vs OFF). In 58% of patients the algorithm ON caused an increase of ventricular pacing percentage > 10%. The ventricular pacing percentage was 82±10% with algorithm ON vs 59±26% with algorithm OFF ($p<0.0001$). Symptoms did not differ significantly.

Conclusions: The VRS algorithm significantly increases the ventricular pacing percentage in patients with permanent AF. This pacing function is preferred by the majority of patients implanted with a single-chamber VVIR pacemaker.

Introduction

Patients with permanent atrial fibrillation (AF) and an indication for VVI(R) stimulation account for about 16% of the total number of antibradycardia devices implanted per year in Italy.[1] It is easy to programme the lower rate of a pacemaker to prevent cardiac pauses, while it is difficult to determine the optimal pacing rate to stabilize the ventricular rhythm. To overcome this, a dynamic rate control algorithm was developed. A pacemaker equipped with this function can pace the heart so as to avoid pauses and to limit beat-to-beat variations in the cardiac cycles.[2-4]

AF can have detrimental hemodynamic effects: loss of atrial contribution, inappropriate increase in ventricular heart rate, and RR interval irregularity with short-long-short cycles that may for a 9%–12% reduction in cardiac output.[5,6] It has been proven that acute AF in humans causes a limited increase in coronary flow versus a more relevant increase in myocardial oxygen demand. Irregularity of the ventricular rhythm is one of the major factors negatively impacting cardiac output.[7]

Key Words:
Catheter Ablation of the Atrioventricular Node, Right Ventricular Pacing, Biventricular Pacing, Ventricular Tachycardia.

Disclosures:
Giorgio Corbucci was the study manager, employee of Vitatron Medical Italia (study sponsor). All other authors do not have any conflict of interest to declaret.

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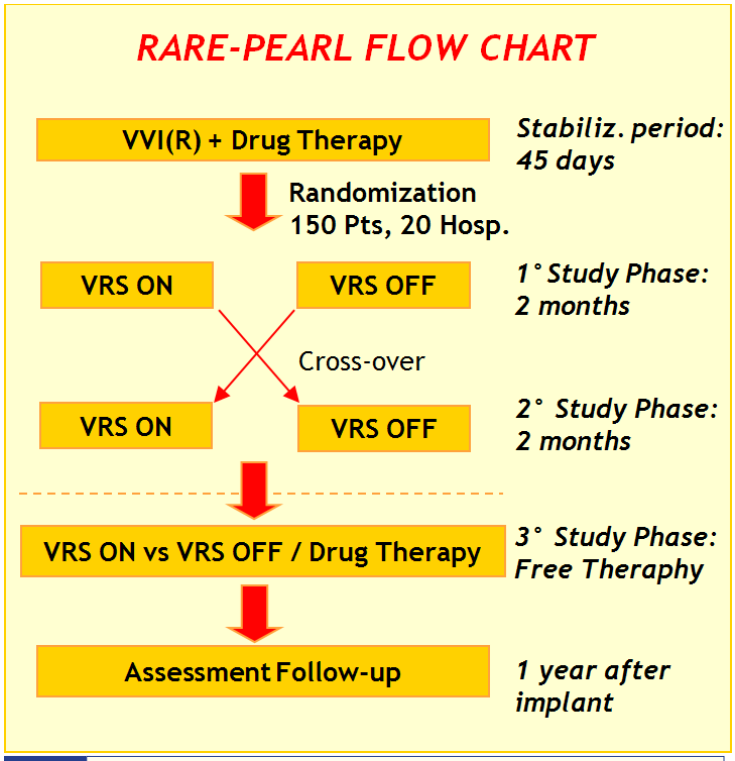

Figure 1 RARE-PEARL Study Flow chart

The aim of this prospective randomized cross-over study was to investigate the impact heart rate regularization in patients with permanent AF and indication to permanent single-chamber pacing.

Methods

The RARE PEARL (Heart Rate Regularization in Patients with PErmanent Atrial FibRiLlation) study was a multicenter prospective, randomized, double-blinded, cross-over study.

The study protocol was approved by the local Ethics Committee and conducted in compliance with the protocol, in accordance with standard operating procedures and the Declaration of Helsinki. All patients enrolled in the study provided written informed consent.

Patient Population

Patients with standard indication to permanent VVI(R) pacing were enrolled in accordance with the inclusion and exclusion criteria. At the inclusion time (PM implant) all patients were on optimal drug therapy, including rate control.

Inclusion criteria

- Patient with permanent AF, standard indication for VVI(R) pacing and at least 1 symptomatic episode of high ventricular rate in the last month.
- NYHA Class I; II; III
- Patient has signed informed consent form
- Patient was able to comply with follow-up times and will comply with the protocol
- > 18 years

Exclusion criteria

- Paroxysmal AF.
- NYHA Class IV
- LVEF < 40%
- Patients with unstable angina
- Patients who have experienced an acute Myocardial Infarction or received a surgical coronary artery revascularization (CABG) or a coronary angioplasty (PTCA) within 3 months prior to enrolment
- Patient candidate for cardiac surgery, or coronary angioplasty (PTCA)
- Patients who experienced a cardiovascular accident with permanent disability or a transitory cerebral ischemia
- Life expectancy < 12 months due to other malignant medical conditions
- Pregnancy
- The patient was enrolled in any concurrent (drug and/or device) study

Study Objectives

The impact of heart rate regularization in patients' life was evaluated by the patient's mode preference and by the specific symptoms scale (Table 1).[8]

Secondary objectives of the study were: rate irregularity estimated by the percentage of ventricular pacing; number of patients subsequently submitted to atrio-ventricualr (AV) node radio-frequency (RF) ablation; side effects of pacing algorithms.

Study Design

The enrolled patients undergone pacemaker implantation, receiving a SSIR pacemaker (model C20 or T20, Vitatron BV, The

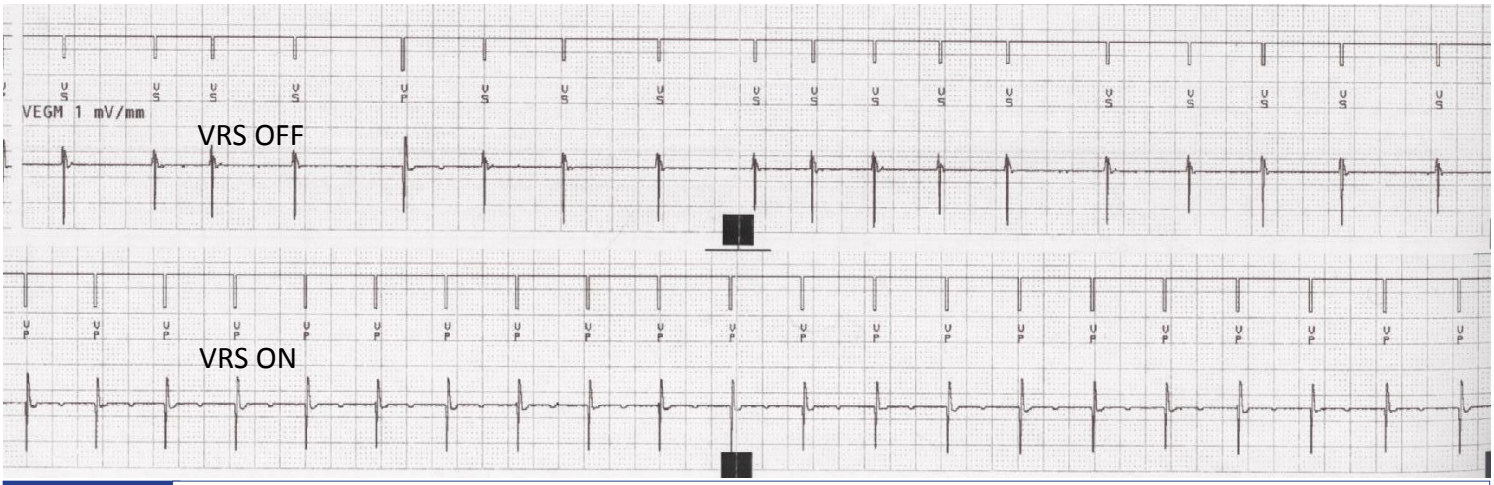

Figure 2: The "Dallas" epicardial lesion set. Blue lines indicate epicardial ablation lesions (Atricure). Red lines indicate surgical lines.

Netherlands). After pacemaker implantation, a 45 days stabilization period was respected, to stabilize the lead and the drug therapy. During the stabilization period following the implant, the final programming was performed and sensing and pacing parameters were optimized. No additional changes have been made during the randomized phase of the study and in the drug therapy as well.

At the end of the stabilization period the patient was randomized to have Ventricular Rate Stabilization (VRS) algorithm switched either ON or OFF. The 1st Study Phase ended after 2 months. Then cross-over took place: VRS algorithm was switched respectively OFF or ON and the 2nd Study Phase was started. Also the 2nd Study Phase ended after 2 months. The randomization was centralized.

The physician (co-investigator) administering the specific symptoms scale questionnaire (Table 1) was blinded (and the patient too) about the status of the VRS algorithm setting. He did not perform the pacemaker telemetric interrogation. Only the principal investigator knew the about the programming of the VRS algorithm. The cumulative score of symptoms was compared during baseline, stabilization period, VRS ON and VRS OFF phases for each patient.

Pacemaker Implantation and Algorithm

The pacing system was implanted according to standard clinical procedures, usually applied by the investigator. The ventricular leads were bipolar to guarantee optimal sensing. The leads were implanted in the right ventricle in accordance with the standard of each centre. All routine measurements, such as pacing threshold, endocardial sensing and impedance were performed in accordance with the local clinical practice. All adverse events encountered during the implantation procedure were documented. At discharge lower rate was set at 10 bpm below the spontaneous rate of the patient. The spontaneous rate of the patient was evaluated through a one minute ECG recording at rest.

VRS algorithm is designed to limit variations in R-R intervals during AF. Ventricular pacing slightly above the mean ventricular rate eliminates long intervals resulting in a more stable ventricular rate. The pacemaker increases the pacing rate after two consecutive ventricular sensed events, but not above the maximum therapy rate (programmed at 120 min-1 in the study). After each ventricular paced event, the pacemaker decreases the pacing rate until it detects a new ventricular sensed event or it reaches the lower rate. Figure 1 shows how the ECG of the same patient is with and without the algorithm activated.

Post-Stabilization Follow-Up

This visit marked the end of the 6 weeks stabilization period. At this stage VRS was switched ON or OFF in accordance with the randomization assigned. If VRS was ON, the relative upper-rate limit was set at 120 bpm.

Table 1: **Specific Symptoms Scale Questionnaire for patients with AF: the patient has to quantify by means of a score scale (0=absence, 10=maximum score) each of the following symptoms that occurred during the previous month (8). The cumulative score was used for statistical analysis.**

Symptoms	Score
Palpitations	(0 – 10)
Effort dyspnea (shortness of breath during physical activity)	(0 – 10)
Rest dyspnea (shortness of breath at rest)	(0 – 10)
Exercise intolerance (fatigue during mild physical activity)	(0 – 10)
Easy fatigue at rest	(0 – 10)
Chest discomfort	(0 – 10)
Cumulative Score	(0-60)

Statistics

Results were expressed as mean values ± standard deviation (SD) or as numbers and percentages, as appropriate. The Mann–Whitney U test was used if normal distribution criteria were not met. Alternatively the Student's T-test was used. Z-test was used for proportions. A P value <0.05 was considered statistically significant. All analyses were performed by means of the SPSS (SPSS Inc., Chicago, USA) software package.

Results

Sixty seven patients (80 ± 6 years aged; 49 M,18 F) were enrolled and randomized at the end of the post-implant stabilization period: 34 patients to VRS ON and 33 patients to VRS OFF.

One patient with VRS ON was lost to follow-up at the end of the first phase, so 33 patients per group (66 patients in total) crossed over and ended the study. One patient was submitted to AV node RF ablation at the end of the study. No adverse effects related to the VRS algorithm were reported by the patients.

Patient's Preference

At the end of the study 32 patients (48%) preferred VRS ON versus 15 patients (23%) who preferred VRS OFF (p<0.001 ON versus OFF). Nineteen patients (29%) did not have any preference.

Pacing Percentage

The ventricular pacing percentage was 82 ± 10 % with algorithm ON versus 59 ± 26 % with algorithm OFF (p<0.0001). In 58% of patients the algorithm ON caused an increase of ventricular pacing percentage > 10%.

Symptoms

Symptoms were assessed by the Specific Symptoms Scale (Table 1): the cumulative score was significantly different at baseline compared to any phase of the study, but it did not differ significantly among VRS ON, VRS OFF and the Stabilization periods (Table 2).

The lowest value of the cumulative score was achieved with VRS ON.

Discussion

The aim of the ventricular rate stabilization (VRS) algorithm is to prevent symptoms due to rate irregularity and this might have an impact also on the episodes of high ventricular rate. The first finding of this randomized cross-over study is that VRS algorithm significantly increases the ventricular pacing percentage in patients with permanent AF. This can impact the rate regularization since pacing intervals do not show beat to beat variations comparable with those during spontaneous heart beats in AF. Second, this pacing feature was preferred by the majority of patients implanted with a single-chamber VVIR pacemaker, but symptoms did not show statistically significant differences.

Table 2: **Symptoms were collected as cumulative score (see table 1) for comparison.**

	Baseline	Stabilization Period	VRS ON	VRS OFF
Symptoms score	18 ± 10	10 ± 11	9 ± 9	10 ± 8

Legend: VRS = Ventricular Rate Stabilization.
Statistical evaluation: Baseline vs Stabilization Period: p<0.0001; Baseline vs OFF: p<0.0001; Baseline vs ON: p<0.0001; VRS ON vs VRS OFF: p=0.862 (ns); VRS ON vs Stabilization Period: p=0.197 (ns); VRS OFF vs Stabilization Period: p=0.484 (ns).

Other studies have addressed the topic of rate regularization with dedicated and automatic algorithms.[9-11] However, this is the first study evaluating patient preference, together with objective assessment of symptoms and objective assessment of rate regularization through pacing percentage.

Tse et al[9] showed that an automatic algorithm can regularize the ventricular rate during AF without increasing the mean ventricular rate, thereby reducing the severity of AF-related symptoms in patients with persistent AF. It is relevant that this pacing modality could increase rate regularity without increasing the mean heart rate, so we can assume that this pacing modality does not have a negative effect on heart rate itself. However, the same study showed that rate regularization did not improve general quality of life (Medical Outcomes Study 36-item Short-Form General Health Survey), the performance of routine activities (Duke Activity Status Index), or functional capacity (hall walk) in patients with AF.

Simpson et al[10] showed that ventricular rate regularization using a rate-smoothing ventricular pacing algorithm might reduce symptoms and improve the quality of life (QOL) in patients with symptomatic AF despite adequate rate control.

Ciaramitaro et al[11] showed that a ventricular rate regularization algorithm effectively stabilizes rate, without increasing pacing rate above spontaneous rhythm and helps achieving a more favourable autonomic balance, improving rate recovery after exercise. The rate stabilization was assessed by comparing the heart rate variability that was significantly lower with the algorithm ON.

Our study confirms that a rate regularization algorithm can increase regularity and also confirmed that it does not have an impact on symptoms, as measured with standard methods. The hypothesis is that the stabilization algorithm might also prevent high rate episodes and related symptoms: symptoms score takes it into consideration. On the other hand, the majority of patients preferred the period corresponding to the activation of the algorithm.

We can conclude that rate regularization per se does not add relevant clinical benefit in patients with permanent AF chronically paced with VVIR pacemaker. The big benefit comes from the implantation of the pacemaker itself, as demonstrated by the important improvement in symptoms during the stabilization phase compared to the pre-implant period. Subsequent phases did not add statistically significant benefit. On the other hand the preference of the patient, collected in a double-blinded way, tells us that regularization may bring something positive; but between the first and the second randomization phase was not observed a wash out period, in order to avoid residual or carryover effect, but this is a limit of our study. Probably rate regularization may add objective clinical benefit in patients with impaired left ventricular function, such as patients with permanent AF and low ejection fraction; during the study period we didn't perform an echocardiographic evaluation finalized to monitor left ventricular function. It would make sense to check this hypothesis by implanting a CRT system in such a patients, activating the rate regularization algorithm to maximize the delivering of biventricular pacing therapy and increase rate stability and monitoring the subsequent ventricular function evolution.

Besides a very short follow-up period, the principal limitation of the study was that the real efficacy of VRS algorithm has been evaluated through a subjective assessment of the wellbeing and preference of the patient, not through an accurate analysis of objective parameters (echocardiographic, radiological and lab findings). The state of well-being warned by patient may be the result of multiple conditions (drug therapy, the evolution of underlying heart disease, psychological factors, clinical condition at the beginning of follow-up, etc.).

Conclusions:

Automatic rate regularization significantly increased the ventricular pacing percentage in patients with permanent AF. This pacing function was preferred by the majority of patients implanted with a single-chamber VVIR pacemaker, but symptoms did not show significant differences.

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