Atrial tachyarrhythmia prevention and treatment by means of special pacing algorithms

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Pacing prevention algorithms have been introduced in order to maximize the benefits of atrial pacing in atrial fibrillation prevention. It has been demonstrated that algorithms actually keep overdrive atrial pacing, reduce atrial premature contractions, and prevent short-long atrial cycle phenomenon, with good patient tolerance. However, clinical studies showed inconsistent benefits on clinical endpoints such as atrial fibrillation burden. Factors which may be responsible for neutral results include an already high atrial pacing percentage in conventional DDDR, non-optimal atrial pacing site, deleterious effects of high percentages of apical ventricular pacing. Atrial antitachycardia pacing (ATP) therapies are effective in treating spontaneous atrial tachyarrhythmias, mainly when delivered early after arrhythmia onset and/or on slower tachycardias. Effective ATP therapies may reduce atrial fibrillation burden, but conflicting evidence does exist as regards this issue, probably because current clinical studies may be underpowered to detect such an efficacy. Wide application of atrial ATP may reduce the need for hospitalizations and electrical cardioversions and favorably impact on quality of life. Consistent monitoring of atrial and ventricular rhythm as well as that of ATP effectiveness may be extremely useful for optimizing device programming and pharmacological therapy.

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Introduction

Atrial fibrillation is the most common arrhythmia in clinical practice and its incidence is increasing due to the aging of the population. Atrial fibrillation represents the cardiac rhythm disorder that causes the highest number of hospitalizations[1] and is associated with higher mortality[2], major clinical complications, such as heart failure, acute myocardial infarction and stroke[3], and impaired quality of life[4]. Atrial fibrillation is frequently associated with ventricular tachyarrhythmias. It has been calculated that 20% of the patients with conventional indication for cardioverter-defibrillator implantation had atrial fibrillation before implant and that during the lifespan of the device more than 50% may develop atrial fibrillation[5,6]. Antiarrhythmic drugs have been widely used for cardioversion and maintenance of sinus rhythm, but they showed a limited and usually temporary efficacy[7]. As a consequence, several non-pharmacological therapies, including physiological pacing, pacing prevention algorithms, anti-tachy pacing therapies and low-energy internal cardioversion have been introduced to treat drug refractory patients and have been implemented in multifunction implantable devices[8].

Pacing prevention algorithms

Antiarrhythmic benefits of atrial and dual-chamber pacing versus single-chamber ventricular pacing in reducing atrial fibrillation recurrences and in preventing progression to permanent atrial fibrillation have been clearly demonstrated in large prospective trials enrolling either sinus node disease patients or unselected patients candidate for pacemaker implantation[9-11]. It has also been suggested that rate responsive availability may maximize the effect of physiological pacing[12]. Pacing prevention algorithms have been introduced in order to maximize atrial pacing preventive benefits. Specific mechanisms involved in atrial fibrillation prevention by pacing algorithms include premature atrial contraction suppression or conditioning, with fewer chances to initiate atrial fibrillation, short-long atrial cycle prevention and maintenance of a high degree of exit block from all natural subsidiary atrial pacemakers. Several algorithms have been introduced by the different manufacturers during the last years. To summarize, they may be classified as follows: 1) dynamic sinus rhythm overdrive, 2) premature atrial beat reaction (short-long cycle prevention and ectopy overdrive), 3) post-tachycardia overdrive to prevent early recurrence of atrial fibrillation, and 4) prevention of inappropriate rate fall after exercise. The atrial pacing preference algorithm was the first evaluated, before being implemented in market released devices, as a temporary software, named "consistent atrial pacing", which could be downloaded into a conventional dual-chamber pacemaker via telemetry using a custom research telemetry device. It included a diagnostic which could be interpreted by a special Microsoft Excel spreadsheet. Diagnostic data were available also when the algorithm was switched off (suspended). The reliability and effectiveness of such algorithm was evaluated in a prospective randomized pilot study in which 61 patients with brady-tachy syndrome were enrolled and implanted with a rate responsive dual-chamber pacemaker[13]. After downloading of the algorithm, patients were randomly assigned to algorithm programming "on" or "suspended", with crossover after 1 month. Consistent atrial pacing induced an increase in atrial pacing percentage from 77 to 96%, and was associated with an 80% reduction of premature atrial complexe number. Atrial fibrillation recurrences were not reduced in the overall population, but they significantly decreased by 42% when considering the patients in whom the atrial pacing percentage was < 90% during the algorithm "suspended" period. Algorithm tolerance was good with no severe adverse events.

The atrial rate stabilization algorithm has been evaluated (alone or combined with consistent atrial pacing) in 16 patients with brady-tachy syndrome[14]. With regard to the effects on atrial fibrillation burden, 11 patients (69%) were found to benefit significantly from the consistent atrial pacing or atrial rate stabilization algorithms (reduction > 50% of atrial fibrillation burden). In detail, 7 patients were responders to both algorithms, 2 to consistent atrial pacing only, and 2 to atrial rate stabilization only.

The ability of the post-mode switching overdrive algorithm to stabilize the atrial rate after termination of treated atrial arrhythmias has been studied in 15 patients with structural heart disease and documented atrial and ventricular arrhythmias, receiving a Jewel AF device[15]. The algorithm was active in 41% of 600 spontaneous atrial tachyarrhythmia episodes. It was capable of driving and stabilizing the atrial rhythm in the presence of slow spontaneous atrial rhythm or premature atrial beats with normal atrioventricular conduction. In case of premature atrial beats with any degree of atrioventricular block, the algorithm stabilized the ventricular rate. The authors concluded that the algorithm is reliable and might be of benefit for atrial arrhythmia treatment.

Efficacy of preventive pacing algorithms has been confirmed by the preliminary results of the AF Therapy Study[16]. In 97 patients with a history of paroxysmal atrial fibrillation of at least 1 year, who had experienced at least three episodes during the last 3 months and were refractory to drug therapy, activation of four different preventive algorithms was associated with a significant improvement in all preselected endpoints: atrial fibrillation burden, average sinus rhythm duration, mean time in-between atrial arrhythmia episodes and number of patients free of atrial arrhythmias lasting > 1 min. All benefits were observed either in patients with or without conventional indication for pacing. Similarly, in the ADOPT trial[17], in which 320 patients were enrolled in a parallel design with randomization to algorithms on vs off, symptomatic atrial fibrillation burden was reduced by 25% in the treatment group. On the contrary, atrial fibrillation episode number, quality of life and hospitalizations did not differ between the two randomization arms. Concern about the actual effectiveness of prevention algorithms in improving clinical outcome has been raised by the conflicting results[18,19] of the most recently published studies in which arrhythmia burden was usually selected as the main endpoint. To explain that, the interaction with other critical factors has been claimed, first of all the atrial pacing site. It is well known that atrial pacing from the right atrial appendage is associated with a prolonged P wave duration with unfavorable effects on atrial conduction and refractoriness. Clinical studies suggest that combining prevention algorithms with interatrial septal pacing may lead to better clinical outcome[20]. Furthermore, the hemodynamic negative effects of unnecessary ventricular pacing in dual-chamber pacing systems may counterbalance the preventive role of pacing algorithms. Blanc et al.[21] demonstrated that pacing algorithms could reduce the atrial arrhythmia burden only in patients with ventricular pacing percentage < 70%. In the MOST study[22], in patients with sinus node disease, atrial fibrillation recurrences had reverse relationship with ventricular pacing percentage. Finally, due to high variability of atrial fibrillation recurrence patterns[23], published studies may be underpowered to demonstrate the true benefits of prevention algorithms.

Atrial antitachycardia pacing to treat atrial tachyarrhythmias

It has been demonstrated that rapid atrial pacing delivered for treating atrial tachycardia or atrial flutter may be effective in restoring sinus rhythm as highly as in 60-90% of patients[24]. Maximal effectiveness can be usually obtained by delivering antitachycardia pacing at a rate that is slightly greater than the atrial arrhythmia rate. Delivering of some extrastimuli following rapid pacing train may be more efficacious than overdrive atrial pacing at the same pacing cycle length in terminating atrial flutter[25]. High-frequency pacing may change atrial tachycardia in transient atrial fibrillation with later sinus rhythm restoration.

Appropriate detection of atrial tachyarrhytmias and efficacy of pacing therapies in patients receiving a dual defibrillator have been evaluated in large series. Adler et al.[26] reported on 537 patients with ventricular arrhythmia implanted with the Medtronic 7250 dual defibrillator (Medtronic Inc., Minneapolis, MN, USA) who were enrolled in the Worldwide Jewel AF Study and followed on average for 1 year. Seventy-four percent had a documented history of prior atrial tachyarrhythmias. Seventy-one percent of the patients had atrial therapies enabled at some time during the follow-up, allowing collection and analysis of 3500 atrial episodes from 167 patients. In the 7250 Dual Defibrillator Italian Registry[27], 105 patients were enrolled. Implant indication was represented by combination of ventricular and atrial tachyarrhythmias in 52% of patients, ventricular tachyarrhythmias only in 33%, and atrial tachyarrhythmias only in 14%. During a mean follow-up of 6 months, 863 treated atrial episodes were collected and analyzed. Gold et al.[28], on behalf of the Worldwide Jewel AF-Only Investigators, studied 146 patients with recurrent drug refractory atrial fibrillation without prior ventricular tachyarrhythmias, who were implanted with a dual defibrillator and were followed on average for 1 year. During the follow-up 4913 treated episodes were available for stored electrogram analysis and therapy efficacy evaluation.

Atrial tachyarrhythmia detection was very good in all the studies with a positive predictive value of atrial detection ranging from 91 to 99%. The most common reasons of inappropriate detection were represented by far-field R-wave oversensing during sinus rhythm or cluster of premature atrial contractions. Reprogramming of atrial sensitivity allowed in some case avoidance of inappropriate detection due to far-field R-wave oversensing. Sensitivity of atrial tachycardia and fibrillation detection and validation of continuous detection of atrial tachyarrhythmias have been specifically addressed by Swerdlow et al.[29] who performed 80 Holter recordings with telemetered atrial electrograms in 58 patients, implanted because of combination of atrial and ventricular arrhythmias. Continuous detection of atrial tachyarrhythmia could be demonstrated in 96% of patients with spontaneous episodes. Atrial sensitivity for arrhythmia detection was 100%.

It is worthwhile to stress that the atrial arrhythmia detected at very early onset was very commonly a well organized atrial tachycardia. Among 2380 episodes in the worldwide series, 63% were classified as atrial tachycardia (mean atrial cycle 278 ± 56 ms) and 37% as atrial fibrillation (mean cycle 204 ± 35 ms). In the Italian Registry, among 863 atrial episodes, 53% were automatically classified by the device as atrial tachycardia and 47% as atrial fibrillation. After revision of the stored data, among 843 appropriately detected episodes, 55% were clinically classified as atrial fibrillation and 45% as atrial tachycardia. In the AF-Only group, among 3116 episodes treated by antitachycardia pacing, 67% were classified as atrial tachycardia.

Efficacy of antitachycardia pacing therapy in the three series is reported in table I[26-28]. The efficacy was estimated in two ways: 1) crude estimate, defined as the proportion of successful terminations out of the total number of treated episodes; 2) adjusted estimate, using the generalized estimate equation method[30] which allows adjusting estimate for multiple episodes within a patient through a correlation structure between episodes and patients.

In the worldwide study a subanalysis performed to compare the efficacy of burst+ vs ramp therapy for atrial tachycardia did not find any significant difference between the two therapies. A history of atrial flutter was the only independent predictor of pacing efficacy for atrial tachycardia, while no independent predictors could be identified for atrial fibrillation. No comparison was feasible between burst+ or ramp and high-frequency burst because the last was usually applied after unsuccessful delivery of burst+ or ramp therapy.

Pooling all antitachycardia pacing therapies (burst+, ramp and 50 Hz burst), their efficacy consistently increased as far as atrial arrhythmia cycle lengthened. As a matter of fact, in the Italian Registry, while the relationship between efficacy of atrial burst+ and ramp vs atrial cycle length was very high ($r^2 = 0.85$, $p < 0.001$), the relationship between efficacy of 50 Hz burst and atrial cycle length was very poor, with a trend toward a reverse correlation ($r^2 = 0.31$, $p < 0.05$). Such a difference could be explained by taking into account the action mechanisms of different antitachycardia pac-

Table I. Efficacy of antitachycardia pacing on spontaneous atrial tachyarrhythmias.

	Atrial tachycardia (%)			Atrial fibrillation (%)		
	CE	AE	95% CI	CE	AE	95% CI
Adler et al.[26]	58.5	45.4	39.4-51.5	29.8	25.7	19.5-33.0
Ricci et al.[27]	70.9	58.4	42.6-72.7	24.3	12.5	5.9-24.5
Gold et al.[28]	48.7	37.9	31.5-44.7	22.7	18.0	12.8-24.7

AE = adjusted estimate; CE = crude estimate; CI = confidence interval.

ing techniques. During overdrive pacing, the wavefront of pacing stimulus enters the reentrant pathway in the antidromic and orthodromic direction. The antidromic wavefront blocks by collision the arrhythmia wavefront, while the orthodromic wavefront may either reset the tachycardia or stop it, when early enough to be blocked in a refractory area.

Slower tachycardias, due to a wider excitable gap, may be more easily terminated in this way. Termination of atrial tachyarrhythmias by high-frequency pacing is typically preceded by tachycardia acceleration, which becomes unable to be sustained, so resulting in arrhythmia end and sinus rhythm restoration. It has been hypothesized that high-frequency pacing induces a new faster reentrant circuit which is unable to sustain itself[31]. This mechanism looks independent of the arrhythmia cycle.

Looking at individual patients, random and wide distribution of median atrial cycles at onset during the follow-up was observed in the majority of them. A subgroup showed a narrow Gaussian distribution along either a fast (200 ms) or a slow band (250 ms). Antiarrhythmic drugs have been demonstrated to be capable of modifying atrial cycle profile. Antiarrhythmics may modify the electrophysiological properties of the atria and the arrhythmia organization pattern by lengthening the mean atrial arrhythmia cycle and by widening the temporal excitable gap[32-34]. Dijkman and Wellens[35] demonstrated that atrial arrhythmias in defibrillator patients with structural heart disease, receiving class III antiarrhythmic drugs, frequently had longer cycle lengths than atrial fibrillation. In fact, among 600 spontaneous episodes, atrial fibrillation was diagnosed in 19%, fast polymorphic atrial tachycardia in 20%, fast monomorphic atrial tachycardia in 57%, and slow atrial tachycardia in 4%. Drug-induced atrial cycle length changes may impact on atrial antitachycardia pacing therapy efficacy. In spite of that, in the AF-Only series there were no drugs that were independent predictors of therapy efficacy.

Finally, increasing the delay from arrhythmia detection to therapy delivery was associated with a significant reduction in efficacy. Optimal delay has been identified in less than 5 min in the Worldwide Study and in less than 1 min in the Italian Registry. That was probably due to the fact that the majority of atrial tachyarrhythmias accelerated in few minutes after onset. Considering that slower arrhythmias can be more easily treated by pacing techniques, a short delay in therapy delivery should be recommended.

The efficacy of 50 Hz burst on atrial fibrillation may be a matter of debate. Wide local capture of atrial fibrillation has been documented[36]. Data from canine studies suggested that high-frequency pacing could accelerate the local atrial fibrillation cycle length and destabilize the reentrant rhythm so that destabilized atrial fibrillation could be converted to sinus rhythm in some cases. Anyway, in humans termination of persistent atrial fibrillation by high-frequency pacing could never be demonstrated[37,38]. High-frequency pacing may terminate induced atrial fibrillation during electrophysiological study with a 33% efficacy rate[31] and atypical atrial flutter with a 60% efficacy rate[38]. In selected cases, local capture of new-onset atrial fibrillation and entrainment of a relatively large area of the atria[39] could have destabilized the arrhythmia by reducing the number of wavelets of the random reentry, so preventing the arrhythmia to sustain. Anyway, considering that arrhythmia classification is based on atrial activity at atrial lead site, misclassification of atrial tachycardia as atrial fibrillation may not be excluded. Furthermore, some episodes may have terminated spontaneously after therapy delivery[40].

Safety of antitachycardia pacing therapy was excellent since no ventricular arrhythmia induction was observed in any case after antitachycardia pacing delivery.

Conclusions

Pacing prevention algorithms actually do work. They reduce atrial fibrillation triggers such as premature atrial complexes and prevent short-long cycle phenomenon. Clinical studies showed inconsistent clinical benefits of the algorithms. Factors which may be responsible for neutral results include: 1) high atrial pacing percentage in conventional DDDR, 2) non-optimal atrial pacing site, 3) deleterious effects of high percentages of ventricular pacing, and 4) inappropriate study design and endpoint selection. Variability of atrial arrhythmia recurrence patterns and onset mechanisms suggest individual programming of prevention algorithms by using data stored in the device memory.

Atrial antitachycardia pacing is an effective tool to treat atrial tachyarrhythmias and it may stop nearly 50% of arrhythmia episodes. Delivery of atrial therapies early after arrhythmia onset and on more organized arrhythmias may improve success rate. Association of antiarrhythmic drugs, mainly propafenone and flecainide, may further increase effectiveness by lengthening atrial arrhythmia cycle. Effective antitachycardia pacing therapies may reduce atrial fibrillation burden, but conflicting evidence does exist as regards this issue, probably because current clinical studies may be underpowered to detect such an efficacy. Consistent monitoring of atrial and ventricular rhythm as well as that of antitachycardia pacing effectiveness may be extremely useful for optimizing device programming and pharmacological therapy. Clinical endpoints should be further investigated and privileged in future studies.

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