Prevention of Atrial Tachyarrhythmias by Cardiac Pacing

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Summary

In the short and impressive history of cardiac pacing, highly efficient therapies have been developed for the treatment of all forms of bradycardia, atrioventricular (AV) dissociation, hemodynamic insufficiency caused by chronotropic or dromotropic incompetency, and termination of ventricular tachyarrhythmia and ventricular fibrillation. The next frontiers will be prevention of atrial and ventricular tachyarrhythmias to reduce medical costs and improve the patients' quality of life, as well as to provide maximum hemodynamic and cardiovascular support in patients with advanced cardiomyopathy. This will require a refinement of the present multisite pacing techniques, where pacemaker leads are permanently placed in three or four cardiac chambers in order to resynchronize mechanical or/and electrical activity of the right and left sides of the heart, and development of even more sophisticated pacing algorithms for prevention of incipient tachyarrhythmias by original forms of electrical stimulation. These will be delivered upon detection of a dynamic substrate known to be preceding the tachyarrhythmias. This article will emphasize the importance of, and discuss the available and prospective methods for, automatic prevention of atrial tachyarrhythmias by implantable cardiac pacemakers.

Key Words

Prevention of atrial and ventricular tachyarrhythmias, multiside cardiac pacing

Atrial Tachyarrhythmias and Limitations of the Current Therapies

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with an incidence of 0.4% in the total adult population, 2% to 4% in people older than 60 years, and up to 13% in those older than 70 years [1,2]. It can be caused by virtually any structural cardiac disease, be precipitated by metabolic imbalance, and occur without any evident underlying cause [2,3]. In the latter case, functional factors such as autonomic tone may be involved in arrhythmogenesis. Atrial fibrillation episodes that occur and terminate spontaneously (paroxysmal) and enduring episodes that are unlikely to be terminated without medical treatment (sustained or persistent AF), or not even then (permanent or chronic AF), may have similar symptomatic consequences [2,4].

Atrial fibrillation causes a variety of symptoms related to an irregular and inappropriate ventricular rate and impaired cardiac output: exertion dyspnea, lassitude, lack of energy, palpitations, dizziness, and occasionally syncope, although many patients tolerate the arrhythmia remarkably well [2,5]. A fall in cardiac output can provoke ischemia in any organ whose perfusion is already impaired, and unstable angina can easily be provoked by AF, as a rapid ventricular response due to high sympathetic tone increases myocardial oxygen demand [2]. Patients with "diastolic" heart failure, in whom left ventricular relaxation is limited because of hyperthrophy or infiltration, are especially dependent on atrial systole to augment passive ventricular filling, as are patients with mitral stenosis. A rapid ventricular response is especially deleterious for the latter, because a long diastolic interval is needed for transmitral flow. Some authors found quality of life in patients with persistent symptomatic AF was less than that of patients recovering from myocardial infarction or with severe rheumatoid arthritis [5,6].

Most importantly, AF greatly increases the risk of stroke and thromboembolism, causing significant morbidity

and mortality. Thus, AF accounts for approximately 80,000 strokes per year in the United States, and patients with AF have a 1.5- to 1.9-fold higher risk of death than patients without AF [7]. The risk of thromboembolic complications in patients with AF is 5.6-fold higher than in matched controls in sinus rhythm, and the risk ratio is 12 to 17 when hypertension, heart failure, or mitral stenosis coexist with AF [5]. There is limited evidence that a sustained rapid ventricular rate during AF can, over long period of time, give rise to left ventricular dysfunction. Many patients with AF have cardiac failure, and often no clear independent cause for the failure is documented. It is suggested that in such patients AF should be considered as a potential cause of the heart failure rather than merely a consequence [2,5,8].

Recent studies reveal that enduring AF episodes result in electrical remodeling of the heart in a way that favors the induction and maintenance of AF ("atrial fibrillation begets atrial fibrillation") [5,9-11]. These data suggest that prompt restoration of sinus rhythm, both at the initial onset and after recurrences of AF, may be far more important in the long-term prognosis of the disorder than has previously been appreciated.

The available therapeutic options for termination and prevention of AF have a limited success rate. While external DC cardioversion can restore sinus rhythm in 70%-90% of patients, and internal cardioversion may additionally improve this score [12], AF recurs in the majority of patients within a year. Prophylactic antiarrhythmic drug therapy doubles the number remaining in sinus rhythm [2,5,13,14]. However, proarrhythmia and an increased risk of sudden death are a concern [2,5,13,15]. Atrial fibrillation may be cured by catheter ablation chiefly in cases when accessory pathways or automatic atrial foci contributing to AF are clearly identifiable [2,7,16,17]. Ablation of the AV node may reduce patient symptomatology related to excessive ventricular rate during AF, but this procedure creates a new disease (partial or complete AV block) for the rest of the patient's life [2,7,18-20]. Surgical techniques aimed at curing AF, so called "corridor" and "maze" procedures and their later modifications [18], require open chest surgery with all its attendant risks and complications. Implantable atrial defibrillators, resembling ventricular cardioverter-defibrillators, have recently become available [7,22,23]. Their application is still in the experimental phase and clinical experience has been limited. As concerns still exist with respect to the sensitivity and specificity of AF detection by implantable atrial defibrillators and safety of AF cardioversion (the danger of triggering more lethal ventricular arrhythmias by the atrial defibrillation shock must be ruled out), implantable atrial defibrillators have not yet been endorsed by the ACC/AHA Task Force [24].

Prevention of Atrial Tachyarrhythmias by Cardiac Pacing

AV synchronization

The maintenance of AV synchrony is important for the prevention of AF. A number of studies have indicated a significant increase in the prevalence of AF in patients implanted with ventricular demand pacemakers for sinus node disease compared with patients in whom atrial (AAI) or dual-chamber (DDD) pacemakers are used [2,25-27]. These data also showed that ventricular pacing was associated with an increased incidence of heart failure and thromboembolism, and with a trend to higher mortality. Although AV synchronous pacing was initially introduced to improve the hemodynamic benefits of cardiac pacing by increasing cardiac output up to 25% [28-32], the antiarrhythmic effects of AV synchronous pacing were promptly recognized. Wherever possible, the atrium should be paced prior to the ventricle, or the ventricle stimulated synchronously to the intrinsic atrial activity.

Atrial pacing

It has been found that some forms of bradycardia-induced AF may be abolished by conventional atrial pacing. Increasing the atrial rate should theoretically be expected to reduce susceptibility to AF by increasing the homogeneity of atrial conduction and repolarization, and suppressing ectopic beats that initiate arrhythmia. Constant "overdrive" temporary pacing can be used to prevent both atrial and ventricular arrhythmias in the acute setting, and there is some evidence that implanted pacemakers can suppress the pause-related and vagal forms of AF in selected patients [2,33-35]. New algorithms, permanently pace the atrium up to 10 beats above the intrinsic rate [36]. There are indications that specific forms of pacemaker rate modulation preserving the sympatho-vagal balance, such as Closed Loop Stimulation (CLS), may reduce the incidence of paroxysmal AF for which autonomic imbalance is responsible. Namely, CLS pacing

systems optimize the pacing rate based on the assessment of sympathetic activity that is, inter alia, influenced by the baroreceptor reflex [37,38]. This will prevent intensive sympathetic activity caused, for instance, by pathologically low heart rates. While conventional rate-adaptive systems using "open loop sensors" may misinterpret current circulatory demands and give rise to sympatho-vagal imbalance due to an attempt of the organism to compensate for the inappropriate heart rates, CLS systems are incorporated into the cardiovascular control loop and guided to an optimal pacing rate by continuous control of the circulatory centers [39-41]. Prospective clinical studies assessing CLS success in prevention of paroxysmal AF remain to be organized, and patient selection criteria and end-points of such studies to be defined.

Biatrial pacing

Theoretically, the most appealing concept for prevention of AF is multisite atrial pacing [42]. It was demonstrated that AF can be locally entrained over a substantial area [2,3]. This implies that if a sufficient proportion of the atrial myocardium can be captured by simultaneous pacing at several sites, a critical mass will no longer be available to sustain the fibrillatory process [2]. Several electrophysiologic studies conducted in acute settings have demonstrated the therapeutic potential of multisite atrial pacing in preventing AF [43-45]. Some forms of AF have been demonstrated to emerge from interatrial conduction block (IACB), which is often caused by a major conduction defect in the right atrial upper wall and the interatrial septum, resulting in delayed and retrograde activation of the left atrium. In the surface ECG, the IACB is characterized by a P-wave duration of 120 ms or more, a broad and notched configuration of the P-wave in lead I, and a biphasic (positive-negative) configuration in leads II and III, with an isoelectric interval between the two components [28,35,46]. In addition to the impairment of the hemodynamic situation [29], left atrial contraction against a closed mitral valve results in atrial stretching which may trigger premature atrial beats and facilitate dilatation of the left atrium. Electrical resynchronization of the opposite atrial parts in IACB is expected to shorten atrial conduction times and homogenize refractoriness, thereby decreasing the vulnerability of the atrium to premature beats and preventing the subsequent tachycardia genesis. Permanent multisite pacing was first introduced by Daubert et al. in 1990 in the form of simultaneous or synchronous pacing from the right atrial appendage and the left atrium (via the coronary sinus) for the treatment of IACB in patients with sick sinus syndrome [30,35,46,47]. Atrial resynchronization improved hemodynamics by providing a more appropriate mechanical AV delay on the left side of the heart, but it also reduced or prevented atrial tachyarrhythmias.

In patients without AV block, Daubert et al. used a single-chamber or dual-chamber device programmed to the AAT mode. In patients with AV block, biatrial and unifocal ventricular pacing was performed with a conventional dual-chamber pacemaker, which is called triple-chamber pacing [35,46]. In parallel with the investigations of Daubert, Kutarski et al. gained sound experience in prevention of atrial tacharrhythmias using a variety of biatrial pacing configurations (with respect to the paths of pulse propagation), or using high-energy coronary sinus pacing without right atrial pacing [48].

In 1997, Witte and co-workers [49] commenced investigation of the benefits of biatrial pacing in patients with lone AF and IACB (P wave ≥ 120 ms). These patients had frequent drug-refractory paroxysmal AF, normal left atrial size (left atrial diameter < 40 mm), and normal left atrial ejection fraction (≥ 50%). As in the earlier studies of Daubert et al. and Kutarski et al., Witte and co-workers demonstrated a significant decrease in the prevalence of AF following biatrial pacing system implantation.

Technological Aspects of Biatrial Pacing and Handling

Left atrial access via coronary sinus

Current approaches focus on the insertion of the lead via the right atrium into the coronary sinus [49-51]. Using this technique, Daubert et al. [30] reported a failure of lead insertion into the coronary sinus in only one out of 40 patients (2.5%), and an identical result was obtained by Witte et al. in the same number of patients [49]. Kutarski et al. [50], however, reported on 100% implantation success in their last series of 44 patients, as contrasted with 90% implant success in the first series of 100 patients in 1995. Mean fluoroscopy exposure time during selective catheterization of the coronary sinus ostium was less than 5 minutes in 50% of the patients, and up to 10 minutes in an additional 38% [48,50].

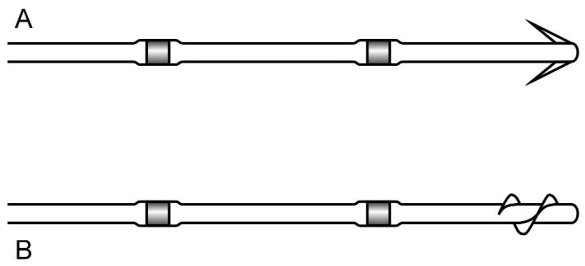

Figure 1. Coronary sinus leads (Biotronik, Germany) with soft tines (A) or a silicone thread (B) for fixation in the distal portion of the coronary sinus. In either model, two rings for bipolar pacing and sensing will likely be located in the mid or proximal coronary sinus where pacing thresholds and sensing values are usually of the best quality.

Coronary sinus lead fixation and dislocation rate

Coronary sinus lead fixation requires the development of new techniques: the trabecular structure that facilitates passive lead fixation in the ventricular apex is not available in the coronary sinus, while the increased vulnerability of the vessel compared to the myocardium permits no active fixation mechanism to be applied. The requirements for distal fixation and proximal pacing may be both fulfilled if the point of fixation and the electrodes are separate. Two novel lead models are designed to meet these requirements (Figure 1). In the first model (Figure 1A), the lead tip is equipped with soft tines similarly to standard passive fixation leads, but without an active electrode tip. Instead, two ring electrodes are used for bipolar pacing and sensing from the coronary sinus. The distal and proximal rings are situated about 6 cm and 9.5 cm from the lead tip, respectively. The alternative design from Figure 1B features a silicone thread tip for fixation in a side branch of the coronary sinus and two rings similar to those in Figure 1A. It has been generally accepted that usage of a bipolar lead in the coronary sinus instead of a unipolar lead is beneficial with respect to the improved electrode-wall contact within the coronary sinus due to the higher lead rigidity [35].

Preliminary results with the lead from Figure 1A were obtained from 44 patients in a single center with a long experience in coronary sinus lead implantation. The dislocation rate was as low as 2.3%, since only one of 44 leads dislodged after the wound closure [50]. The lead from Figure 1B was studied in 50 patients in a center with comparatively less experience in coronary sinus pacing. The lead could not be successfully fixated in three patients (6%) and early lead dislocation occurred in additional four patients (8%) [49]. Extraction of coronary sinus leads is occasionally performed due to removal of the therapy or adverse events. The extraction carried out within 6 months after implantation is chiefly uncomplicated, while later attempts may fail due to partial encapsulation of the lead by the coronary sinus wall [49,50,52]. The lead models shown in Figure 1 are also aimed at facilitating the lead extraction procedure by omitting bulbous or nonisodiametric portions of the leads that usually make the extraction difficult [53,54].

Electrophysiologic values for coronary sinus leads

Due to the increased distance between the coronary sinus electrode and the excitable myocardium (they are separated by the vascular wall) and a lack of firm fixation of the electrode, it is impossible to obtain pacing thresholds within the coronary sinus that are as good as for conventional atrial and ventricular pacing sites. While conventional pacing via passive fixation leads exhibits mean acute thresholds ranging from 0.25 to 0.65 V (at 0.5 ms pulse width), depending on the lead design, acute thresholds within the coronary sinus are typically > 1 V. In particular, the leads from Figure 1 exhibited mean acute thresholds of 2.04 ± 0.94 V and 1.57 ± 0.86 V (at 0.5 ms), respectively, in the bipolar configuration, and similar or slightly worse values in any form of unipolar stimulation [49,50]. Earlier, conventional tined leads positioned in the coronary sinus resulted in a 2.93 ± 1.87 V acute bipolar threshold (at 0.5 ms). The observed threshold improvement in the leads from Figure 1 is believed to be a consequence of the ring- instead of tip-pacing (the ring is usually closer to the excitable myocardium and less sensitive to the orientation of the lead) and of a more favorable location of the rings (mid and proximal coronary sinus) as compared to the tip location (usually distal coronary sinus) [48,50].

In addition to conventional bipolar and unipolar pacing configurations, biatrial pacing offers the possibility of a unique "split bipolar" pacing configuration [35]. Namely, a simultaneous stimulation of the right and left atria may be achieved not only by delivering two separate pulses - one via the right atrial lead and the other via the coronary sinus lead - but also by using a single impulse propagating from the right atrial lead tip to the coronary sinus lead tip (or ring), thus exciting

both sides of atria. Although split bipolar configuration features a high pacing threshold (the mean acute value is about 3.5 V, the chronic threshold 4 to 6 V), it offers a favorably high pacing impedance of about 700 Ω due to the serial connection of the lead tips (or tip and ring), as compared to a 200 to 350 Ω total impedance value for the parallel stimulation of the right and left atria using two distinct circuits. Therefore, the split bipolar configuration usually results in slightly lower battery energy consumption than the separate right and left atrial stimulation.

Finally, the sensing performance of the coronary sinus leads was found to be satisfactory, providing good initial position and sufficient lead fixation had been attained. Kutarski et al. reported 2 to 3 mV mean amplitudes sensed by the coronary sinus leads (A-wave) in a variety of configurations and designs, and the values were stable during the follow-up [48]. Daubert et al. [35] measured a mean acute A-wave amplitude of 3.5 ± 2.1 mV, as compared to the mean far-field R wave amplitude of 2.1 ± 1.2 mV (which was present in all subjects). Yet in all cases, it was possible to achieve a ratio > 1 between A-wave and R-wave amplitudes and thus allow proper sensing in the left atrium, despite a slight decrease in chronic A-wave amplitudes (on average by 23%). Witte et al. [49] reported better acute A-wave amplitudes in the coronary sinus (3.6 ± 1.4 mV) than in the right atrial appendage (2.5 ± 0.9 mV).

Pacemakers and pacing modes in biatrial pacing

A significant portion of candidates for biatrial pacing will require conventional ventricular pacing and sensing, as AV conduction abnormalities are observed in 80% of patients with severe IACB [46]. While today's pulse generators are equipped with a maximum of two connector outlets, one for the atrium and one for the ventricle, pacemakers for a true multisite pacing should have at least three separate channels, allowing stimulation and sensing of two or more sites in the same cardiac chamber in a traditional unipolar or bipolar fashion. Triple-chamber pacing (biatrial + right ventricular) is currently achievable with dual-chamber pacemakers with the aid of several types of "Y-connectors", but with less programming flexibility than would be ideal [35,47].

Another option for sole biatrial pacing is to utilize a dual-chamber pacemaker instead of a single-chamber unit and avoid implantation of a Y-connector. In this solution, the right atrial lead is connected to the atrial pacemaker port, to allow prompt sensing of sinus beats, and the coronary sinus lead is attached to the ventricular port. Furthermore, optimal performance may be expected using dual-chamber pacemakers that allow a 0 ms AV delay (i.e., 0 ms AA delay) in order to maximally shorten total atrial activation time. While most dual-chamber devices allow a minimum AV (AA) delay of 30 ms, the Logos DS pacemaker (Biotronik, Germany) permits the 0 ms AV (AA) delay.

Clinical Outcome

Two indicators are used to evaluate the effectiveness of biatrial pacing. One is comparison of P-wave morphology and duration in biatrial stimulation versus single right atrial pacing and single left atrial pacing (coronary sinus lead) at the same pacing rate. The other indicator that usually serves as the end-point of a study is a demonstration of a significant decrease in the incidence of atrial tachyarrhythmia recurrences in highly symptomatic and drug refractory patients.

Reduction of atrial activation time

Daubert et al. [46] were initially encouraged to institute biatrial pacing in patients with IACB after observing a dramatic decrease in P-wave duration and a normalization of P-wave morphology in three patients in the acute settings, using temporary endocardial leads.

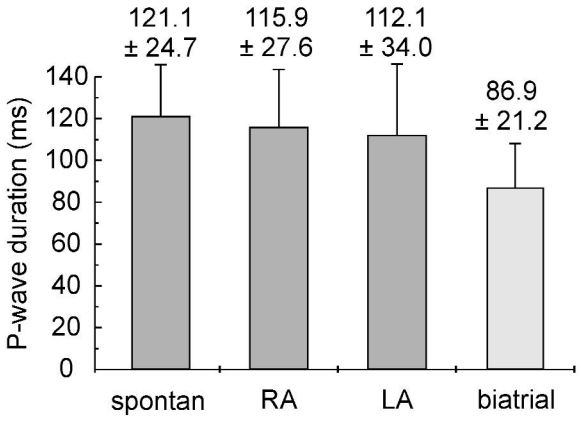

Figure 2. P-wave duration during sinus rhythm, right atrial (RA) pacing, left atrial (LA) pacing using a moderate energy level, and biatrial stimulation. Mean values ± standard deviations are shown. The investigation was conducted in 50 patients in the course of a biatrial pacing system implantation.

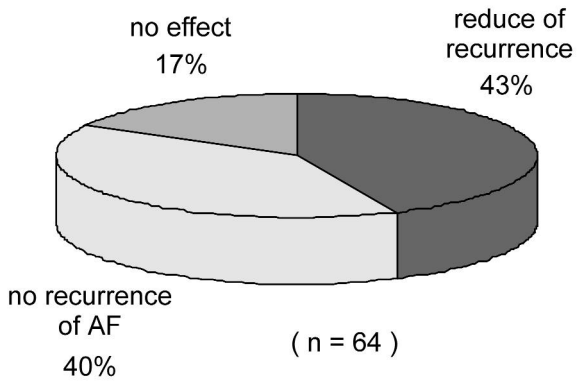

Figure 3. Incidence of AF after biatrial pacing system implantation in 64 patients. The patients had conventional indications for pacing. Biatrial pacing was undertaken due to IACB associated with frequent (at least once weekly), drug-refractory AF.

They considered it as a direct proof of a significant correction of interatrial and intra-atrial (in the same compartment) asynchrony. In the patient population that was later treated by permanent biatrial pacing at their clinic (most patients had severe IACB), P-wave duration was measured manually on amplified ECG bipolar precordial leads. During permanent pacing, the mean value decreased from 209 ± 38 ms (range 160-300 ms), as measured during right atrial pacing, to 108 ± 13 ms (range 90-130 ms) following synchronous biatrial pacing. In a patient subgroup with normal sinus rhythm, P-wave duration was reduced from 181 ± 28 ms (sinus rhythm) to 116 ± 12 ms (biatrial pacing) [46]. Thus, the average reduction of P-wave duration in biatrial pacing compared with conventional right atrial pacing or sinus rhythm was 48% (101 ms) and 36% (65 ms), respectively. Daubert et al. [46] reported that sole coronary sinus pacing did not reduce P-wave duration and interatrial asynchrony compared with single right atrial pacing but only reversed the order of asynchrony. Figure 2 illustrates the most recent results provided by Witte et al. [updated reference 49], confirming that a significant reduction of P-wave duration is obtainable also in patients with moderate IACB.

Decrease in the incidence of atrial tacharrhythmias

In the patient group studied by Daubert et al. [35], most of the patients free of arrhythmia after biatrial system implantation had interrupted or reduced antiarrhythmic drug therapy. Figure 3 summarizes the experience of Kutarski et al. [48] in preventing AF by using biatrial pacing concepts. The therapy was ineffective in 17% of patients, fully effective in 43%, and partly effective in 40%. Figure 4 illustrates results of Witte and colleagues, who attempted to prevent AF in patients with lone AF and IACB [49]. The patients had frequent drug-refractory paroxysmal AF, no conventional indications for pacing (ventricular lead was unnecessary), normal left atrial size (left atrial diameter < 40 mm), and normal left atrial ejection fraction (> 50%). A biatrial pacing concept using a dual-chamber device with

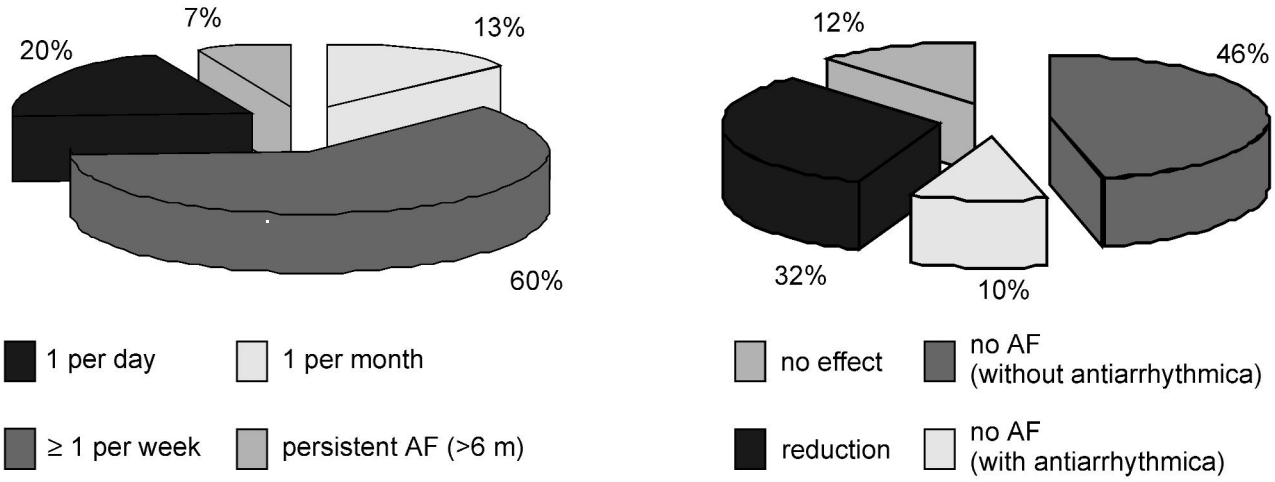

Figure 4. Incidence of AF before and after biatrial pacing system implantation in 50 patients with lone AF and IACB. The mean follow-up period was 7.2 months.

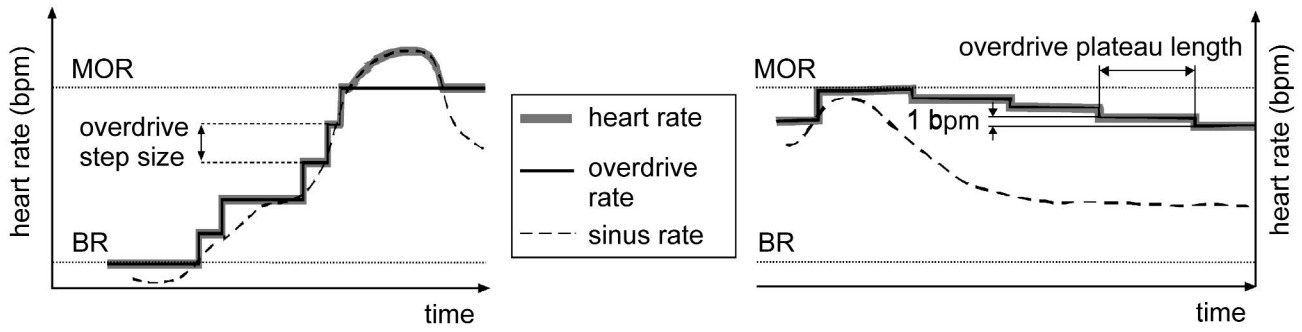

Figure 5. Illustration of the DDD+ pacing mode for suppression of spontaneous atrial activity. Upon a sensed event in the atrium (left panel), a pacing rate will ensue that is faster than the average rate of the previous four heart beats by an "overdrive step size" (programmable parameter, default value 10 bpm). In the absence of spontaneous atrial activity (right panel), the pacing rate will decrease slowly by 1 bpm.

the right atrial lead connected to the atrial port and the coronary sinus lead connected to the ventricular port, as described in the previous section, was used. The therapy appeared to be without effect in 12% of patients, was fully effective in 56%, and partly effective in 32%.

Permanent Overdrive of Sinus Rhythm

As mentioned in the section "Atrial Pacing", some forms of AF may be prevented by constant or frequent atrial pacing at rates higher than the sinus rate. In the following, one such algorithm that has been recently investigated in a multicenter clinical trial will be described. The algorithm can be downloaded into the random access memory of the Inos^2 CLS pacemaker at any time after pacemaker implantation. When the algorithm is activated, pacing occurs in the so-called DDD$^+$ mode. In this mode, every atrial sensed beat will be followed by an increase in pacing rate that will surpass the intrinsic heart rate within 1 to 3 seconds (Figure 5, left panel). The physician defines how fast the pacing rate will increase by programming the parameter "overdrive step size". Thereafter, the pacing rate will decrease slowly in decremental steps of 1 bpm, and each step will last for a period of time that equals the "overdrive plateau length" parameter (Figure 5, right panel). The DDD$^+$ pacing mode is supposed to minimize the incidence of spontaneous atrial activity and, thus, homogenize atrial depolarization and repolarization patterns, suppress arrhythmogenic foci (which may be active in case of sinus activity), reduce sympathetic tone, and facilitate so-called myocardial remodeling (converting remodeled atrium due to AF to normal status).

The ongoing multicenter clinical study with this algorithm is designed to be a randomized cross-over study. All participating patients with a history of paroxysmal AF are randomized to group I (starting in the DDD mode) or group II (starting in the DDD$^+$ mode). Six months later, the modes are crossed. The follow-up controls are scheduled for 3, 6, 9, and 12 months after patient enrollment. The incidence of atrial tachyarrhythmias in each mode is evaluated based on the pacemaker diagnostic functions: standard event counters and histograms; counters of sustained and non-sustained AF episodes; the total time in sustained AF, non-sustained AF, and without AF; and the mode-switch history (date/time). The hypothesis of the study is that the DDD$^+$ mode will result in a decreased number of AF episodes and increased percentage of AF-free time compared with the DDD mode. Antiarrhythmic therapy will be unchanged during the study.

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