Atrial Resynchronization for Prevention of Atrial Fibrillation – Where Do We Stand Today ?

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Summary

Atrial fibrillation (AF) is an extremely heterogeneous cardiac rhythm disorder especially prevalent among the elderly population, and it is responsible for enormous health care costs. Interatrial conduction disturbance has been indicated as one of the factors which may play a role, both in the onset and the perpetuation of AF. Atrial resynchronization, a non-pharmacological therapeutic option of AF, using a right atrial lead and a coronary sinus lead for left atrial pacing, in order to compensate for the interatrial conduction delay, has therefore been proposed. Several studies have shown at least some benefit due to biatrial resynchronization. However, the general therapeutic success of a biatrial pacing therapy for AF prevention is not widely accepted. New pacing devices, specially adapted to the requirements of biatrial stimulation and featuring additional AF preventative therapies, may offer tools for a new era of AF preventative therapies. Future clinical trials will have to evaluate the potential benefits of a sophisticated atrial resynchronization therapy, which can be obtained using these devices, in selected patients.

Key Words

Atrial fibrillation, interatrial conduction, biatrial pacing, atrial resynchronization, overdrive pacing

Introduction

Paroxysmal atrial fibrillation (PAF) is one of the most common forms of arrhythmias and represents a significant management problem [1] due to the generally alarming onset of symptoms, the disability these symptoms produce, the possibility of thromboembolic complications and the often unsatisfactory results, or even undesirable effects [2] of drug therapy. The symptoms, especially in the presence of underlying heart disease, significantly deteriorate the quality of life for a large number of PAF patients. In Europe, it has been estimated that 1.6 to 2% of the general population (with the number greatly increasing after age 65) presents with atrial fibrillation (AF), and that 40% of these cases are PAF. Approximately 12% of PAF cases corresponding to about 396,000 patients (216,000 of them older than 65) present with severely symptomatic PAF that is refractory to multiple antiarrhythmic drug therapy [3]. A lot of interest is being directed towards this last patient group in finding ways to prevent or reduce the symptoms of this debilitating arrhythmia. The extremely heterogeneous nature of AF requires therapies that are specially adapted to the genesis of this in the individual case. This paper summarizes the theoretical expectations, first clinical experiences, and future strategies of atrial resynchronization therapy in patients with interatrial conduction disturbances.

Genesis of AF

The onset of the arrhythmia implies the presence of triggers that induce AF as well as a substrate that sustains it, since triggers without contributing factors do not cause AF. Triggers may include atrial premature beats (APB), tachycardia, bradycardia, sympathetic or parasympathetic stimulation, accessory atrio-ventricular pathways, and acute atrial stretch [4]. Ectopic activity originating from the pulmonary veins has been identified as a trigger for the origin of a very large percentage of PAF manifestations [5,6]. The ectopies seem to originate from "sleeves" of atrial tissue extending into these veins. Triggers propagating into the atria may initiate reentering wavelets, if the wavelength is sufficiently short. This can occur even in normal atria, if the effective refractory period (ERP) or conduction velocity is decreased. Persistence of AF may result from structural and electrical remodeling, which is characterized by atrial dilatation and a corresponding shortened ERP [4].

Paroxysmal AF has a tendency to evolve into progressively longer periods of generally non-self-terminating AF. While it initially responds to pharmacologic or electrical cardioversion, with time it tends to become gradually resistant to these therapies. However, prompt cardioversion reduces the time patients remain in AF and increases the interval between its recurrences. Consequently, timely sinus rhythm restoration could forestall progressive remodelling and decrease the frequency and duration of the AF episodes [4]. Therefore, prevention of PAF and/or its prompt termination is of particular clinical importance. Furthermore, measures directed at prevention, control, or a "cure" of AF or PAF should carefully consider the root cause of this extremely frequent arrhythmia, which is often a manifestation of various disease processes. Nevertheless, no obvious clinical cause is found in approximately half of the patients presenting with PAF (lone or idiopathic PAF). Therefore, it is very important to have different therapeutic approaches, which may permit individual strategies for AF prevention.

A disturbance of interatrial conduction is one possible substrate that can enable the initiation of AF and may benefit from special therapeutic approaches. Therefore, patients with interatrial conduction disturbances may be treated with specially designed therapies.

Interatrial Conduction Disturbances

Interatrial conduction is provided by muscle bundles, which are characterized by variability in both morphology and distribution. According to recent reports based on electroanatomical mapping of the atria, in patients without structural heart disease, these bundles provide two major inter-atrial activation routes, located anteriorly and posteriorly [7,8]. The anterior connection, described by Bachmann, when present, is usually a well-recognized circumferential muscle bundle, originating from the crest of the crista terminalis near the sinus node and crossing the roof of the right to the left atrium, where it diverges into fibers, passing through the left atrial appendage and between the pulmonary veins (Figure 1). Conversely the posterior route is not well-known, although consistent but variable connections have been documented between the coronary sinus and the left atrium [9]. However, these may not be the only inter-atrial conduction pathways [7]. These findings have been confirmed by a recent anatomical study designed to compare the difference in presence, site, distribution and dimensions of inter-atrial connections in postmortem studies of patients with and without a previous history of AF [10]. In particular, the study confirmed the apparent absence of Bachmann's anterior bundle in almost half of the patients and also found that the total number of connective bundles was smaller in the AF group. It advances the hypothesis that the marked morphologic variability, including the absence of Bachmann's bundle in half the patients and the potentially vulnerable posterior connections, may suggest also a variability of function in some patients, rendering them more predisposed than others to develop inter-atrial conduction disturbance and AF [10]. A disturbance of these conduction pathways leads to delayed left atrial activation, affecting cardiac hemodynamics. A widened P wave (> 120 ms) on the surface ECG can be used as an indicator of interatrial conduction disturbances, although also intraatrial conduction disturbances can cause

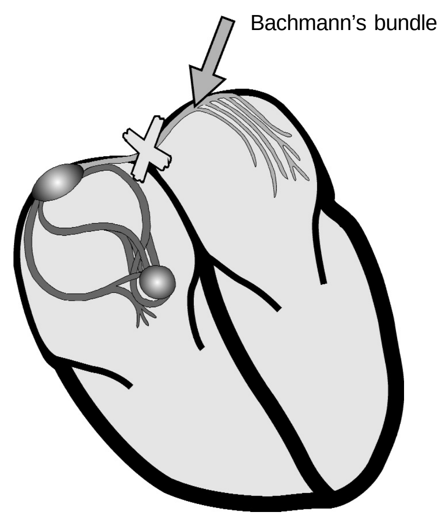

Figure 1. Interatrial conduction disturbances.

P wave widening. In this regard there are studies, which report significant conduction delays within the right atrium, specially related to delays in the activation of the coronary sinus ostium region. Interatrial and intraatrial conduction disturbances are known to enhance the risk of developing AF [11]. Therapies, aimed at preventing AF caused by disturbed conduction, should therefore compensate for conduction delays within the atrial conduction pathways.

Biatrial Pacing for Atrial Resynchronization

The theory that spatial dispersion of atrial refractoriness and/or conduction and the presence of APBs facilitates the onset of atrial arrhythmias, led to the development of synchronous biatrial (BiA) pacing by Daubert et al. [12] in 1989, with the objective of reducing atrial arrhythmias. This consisted of fixing a right atrial lead in the high right atrium (HRA) and a second lead in the coronary sinus (CS), either proximal, mid, or distal, for sensing and pacing the left atrium (LA). With a similar intent, Saksena et al. adopted a dual-site right atrial pacing technique some years later [13]. It consisted of fixing the second lead near the ostium of the CS, in the posterior part of the triangle of Koch, a zone crucial to the genesis of arrhythmias. Simultaneous activation of both atria was obtained by additionally pacing with a right atrial lead fixated to the anterior interatrial septum [14]. Moreover, pacing at the distal CS level appeared to suppress the propensity of right atrial extrasystoles to induce AF by limiting their precocity at the posterior part of Koch's triangle and most likely by blocking microreentries [15]. It therefore appears that BiA or multisite atrial pacing may contribute to arrhythmia prevention by correcting asynchrony and non-uniform activation (resulting from organic or functional conduction blocks), and by possibly preventing macroreentry events. Compared with spontaneous sinus rhythm and single-site right atrial pacing, this technique reduces the P wave duration [16] (Figure 2) and the activation delay of the crista terminalis region and of the CS ostium.

Although the general principle of biatrial pacing does not appear too complicated, more sophisticated devices are desirable that allow specific and separate programming of both atrial channels (e.g., pacing/sensing parameters, adjustable interatrial delays) in combination with new AF preventive algorithms to maximize therapeutic efficacy. It is important to have various tools that can be combined and specifically adapted to the individual patient's manifestations. Until very recently, most of these features were not implemented in cardiac pacemakers. The lack of these tools may account for the partially ineffective or disappointing attempts to prevent AF with biatrial pacing.

Biatrial Resynchronization – Previous Results

Paroxysmal AF

D'Allonnes et al. reported that 64% of their patients (n = 86) with drug refractory AT and intra-atrial conduction delay, who were treated with BiA synchronous pacing, remained in sinus rhythm at the end of the follow-up, and were taking a significantly reduced amount of antiarrhythmic drugs [17]. The SYNBIA-PACE study compared RA pacing with BiA pacing by implanting one lead in the right atrium and another into the CS. The results of this trial were not statistically significant [18]. Only a trend towards a prolonged time to AF recurrence was reported. However, technical problems and limitations seem to be one potential reason for the failure of this study to show beneficial

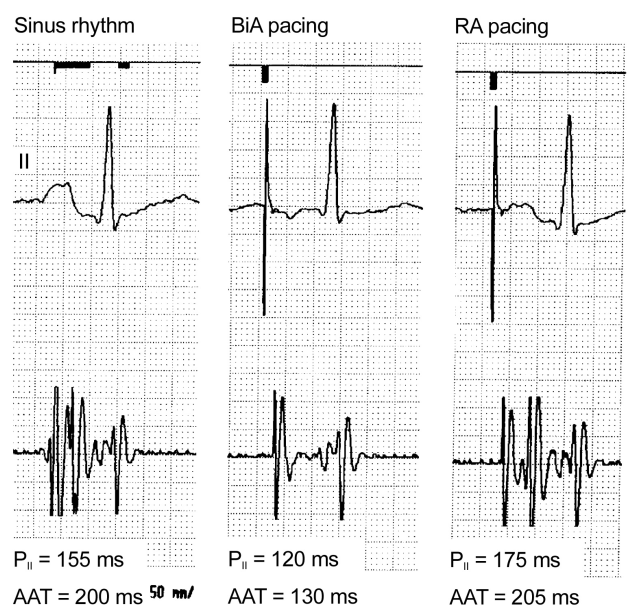

Figure 2. Shortening of the P wave by biatrial pacing (BiA) in relation to sinus rhythm and conventional right atrial (RA) pacing [16].

effects of BiA pacing [19]. Recently, the results of a smaller study (19 patients) were published by Mirza et al. [20], comparing RA pacing, coronary sinus (CS) pacing and BiA pacing (for 3 months each). The greatest reduction in PAF episodes was seen during biatrial pacing, especially with leads implanted at the high right atrium and distal CS (p-value < 0.005).

Likewise, dual-site right atrial pacing combined with pharmacological therapy in unselected patients with previously drug refractory atrial flutter and fibrillation significantly increased the percentage of patients free of AF recurrence to 89% [21]. Furthermore, Leclercq et al. demonstrated the superior efficacy of dual versus single-site AP, in modifying the natural history of patients with prolonged P wave and sinus node dysfunction [22]. Finally, preliminary results of the DRAPPAF study, comparing recurrences of AF during dual and single-site right atrial pacing, showed a similar arrhythmia-free interval in both groups, but a significantly lower incidence of electrical cardioversions in those switching from single to dual-site pacing [23].

Right atrial septal pacing is another promising therapeutic approach leading to atrial synchronization. In a randomized, multicenter trial by Bailin et al. with 120 patients, RA appendage pacing was compared with septal pacing in the region of the Bachmann's bundle [24]. Those patients who were paced at the region of the Bachmann's bundle had a higher rate of success in remaining free of chronic AF (75%), as compared to patients with RAA pacing (47%) after 1 year.

Post-Operative AF

It is well-known that open-heart surgery is associated with post-operative AF in approximately 40% of cases. Temporary biatrial pacing has been tested to prevent AF after open-heart surgery. Several studies have proven a clear benefit of biatrial pacing. For example, Fan et al. [25] examined 132 patients after coronary artery bypass surgery, randomized into a BiA, RA, LA, or control group. Atrial overdrive pacing was temporarily performed for 5 days. In the control group, 41.9% of patients developed AF; 33.3% in the RA group, 36.4% in the LA group, and only 12.5% of patients in the BiA group developed post-operative AF. Therefore, BiA pacing reduced the number of patients suffering from post-operative AF by 62.5% compared to standard right atrial pacing. Although post-operative AF cannot be directly compared with "common" paroxysmal AF, this interesting result can be viewed as evidence of the benefit of biatrial pacing in this subgroup of patients.

Combining Atrial Resynchronization with AF Preventive Algorithms

Although some studies have shown biatrial resynchronization to be beneficial, there are no published data available that test a combined therapy consisting of BiA pacing in conjunction with AF preventative algorithms such as dynamic overdrive pacing. Padeletti et al. [26] examined the effect of RA appendage or septal pacing (= atrial synchronization) in combination with overdrive pacing in 46 patients with paroxysmal AF and sinus bradycardia in a crossover design regarding overdrive ON vs. OFF. This study showed that septal pacing was more effective than RA appendage pacing. However, no additional benefit of overdrive pacing was observed. Care must be taken when study results on overdrive pacing are discussed. For example, it has been shown that a high intrinsic rate may reduce the benefit of atrial overdrive pacing in the same manner as a high percentage of ventricular pacing. Within the scope of the PIPAF study, the effect of overdrive pacing was compared in 111 patients. The analysis demonstrated that overdrive was beneficial only in those patients with a percentage of ventricular pacing less than 50% [27].

De Voogt et al. showed a beneficial effect of combining septal and overdrive pacing [28]. The effect of RA appendage or septal pacing with and without dynamic overdrive was compared in 125 patients. During RA appendage pacing, overdrive pacing reduced the AF burden from 89.3 ± 32.9 min/day down to 44.7 ± 42.5 min/day (p-value = 0.031). During septal pacing, additional overdrive reduced AF burden even more, from 88.3 ± 27.7 min/day (without overdrive) to 27.1 ± 16.5 min/day. This suggests that septal pacing was not beneficial compared to RA appendage pacing; however, used in combination with overdrive pacing, it reduced the AF burden by 40%. Despite contradictory reports by Mabo et al. [29], the results obtained by BiA or multisite atrial pacing have been generally favorable in both included and excluded patients. The possibility of testing additional beneficial electrophysiologic effects of this pacing technique combined with an overdrive algorithm or other AF preventive algorithms on a well-defined group of patients is particularly challenging and might offer new insights.

Figure 3. The Stratos LA (Biotronik, Germany) biatrial pacemaker.

Biatrial Resynchronization – Future Strategies

The technique of biatrial pacing has some promising aspects. However, new technical devices are needed that are specially adapted to the requirements of an optimal atrial resynchronization therapy. Although interatrial conduction delays are known to be a substrate for the onset and perpetuation of AF, trigger mechanisms such as ectopic activity or atrial premature beats, which play an important part in AF genesis, also have to be taken into account. The activation of AF preventive algorithms, such as overdrive pacing, or algorithms preventing short-long sequences in combination with alternative pacing sites, such as atrial septal pacing or biatrial pacing, would be a promising approach. It is desirable to have several technical features that allow the detailed and separate programming of right and left atrial pacing and sensing parameters. To optimize hemodynamics, it is necessary to individually adjust the AV delay as well as the interatrial delays.

In the past, biatrial pacing was often achieved by splitting the atrial channel using a Y-adapter. Of course, this technique does not allow any specific, separate programming of the right and left atrial channels. A new, "real" triple-chamber pacemaker, the Stratos LA (Biotronik, Germany, see Figure 3), will soon be available. This device allows the independent programming (pulse amplitudes, pulse width, polarities) of all three channels with separate unipolar/bipolar sensing in the right and left atrium. It permits the adjustment of interatrial delays after sensing and pacing in freely programmable increments between 0 and 30 ms. Stratos LA synchronizes on right or right and left atrial extrosystole (AES) and also on early and/or late AES. This innovative pacemaker has separate right and left atrial statistics (event counter, event episodes, histograms, etc.) and separate right and left IEGMs. In addition to these multisite features, Stratos LA provides three different AF preventative algorithms that can be activated separately or jointly. In addition to the well-known dynamic atrial overdrive (DDD+) mode, the device features an algorithm that prevents short-long sequences (post-AES pacing) and an algorithm that prevents sudden rate drops (rate fading) that might occur in some patients after exercise.

This means that a device for biatrial/bifocal pacing will be available, offering totally new possibilities with regard to atrial resynchronization therapy. The option of additionally activating AF preventative algorithms could further enhance the therapeutic success. Hopefully, this will lead to new clinical data, providing clearer evidence about the possibilities of a sophisticated atrial resynchronization therapy by biatrial pacing in selected patients. Using this new device together with the Corox LA lead (Biotronik) for coronary sinus-based, left atrial pacing, a controlled international multicenter clinical trial called MISSION (Multisite Stimulation and Overdrive Pacing for Prevention of Atrial Arrhythmias) will be conducted. Within the scope of MISSION, the AF preventative effect of BiA pacing with and without preventative algorithms will be compared to standard RA pacing with and without preventative algorithms in patients who suffer from interatrial conduction disturbances (P wave > 120 ms) and have a documented history of paroxysmal AF. Hopefully, this new clinical study will illuminate the potential benefits of atrial resynchronization therapy.

Conclusion

Although the first attempts at atrial resynchronization by biatrial pacing are now 13 years old, the results of this approach have, to some extent, been discordant. However, a large amount of clinical data has shown a beneficial effect of atrial resynchronization with respect to AF prevention. These data should stimulate intensification of research efforts in this therapy. New pacing devices, providing novel, powerful tools should enable high-quality clinical trials to study the possibilities of clinical benefit of biatrial pacing in specially selected patients.

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