

# Therapy of Atrial Tachyarrhythmia by Cardiac Pacing

M. SCHALDACH

Department of Biomedical Engineering, University of Erlangen-Nuremberg, Erlangen, Germany

## Summary

*The discussion on atrial fibrillation (AF) is increasingly focussing on the understanding of pathophysiological mechanisms, leading to advanced therapeutic concepts, rather than the various methods of treatment, if AF already occurred. Since a high risk of embolic complications requires the avoidance of sustained episodes of AF, preventive therapy of AF should be the central effort for future developments. This paper summarizes concepts for preventive therapy of atrial tachyarrhythmias using pacemakers. Several mechanisms underlying AF like intra-atrial conduction disturbances or inhomogenous refractoriness can be preventively treated using biatrial pacing without significant side effects. Additionally, literature reports that atrial stimulation at elevated rates may reduce the occurrence of AF. Both methods for preventive AF therapy using pacemaker, biatrial and overdrive pacing, are used on permanent basis. Furthermore, it is supposed that atrial arrhythmias are caused by sympatho-vagal imbalance. Since vagally and adrenergic mediated rhythm disturbances may result from unsuitable support of the cardiovascular system, an appropriate stimulation rate helps to prevent AF. Integration of the pacing system into the natural cardiovascular regulation system provides an optimal and physiologic control of hemodynamic parameters. For further refinement of preventive therapy, a consequent extension of correspondence between therapeutic tool and the body-own regulation processes will provide prediction of AF and therefore, suitable therapy is initiated on demand.*

## Key Words

Atrial fibrillation, bifocal pacing, overdrive stimulation, Closed Loop Stimulation, natural regulation

## Introduction

Atrial fibrillation (AF) has become a subject of increased interest and intensive clinical research in recent years since it is a major cause of embolic events [19]. Various studies emphasize the clinical relevance of AF. The Framingham study reports an incidence of AF from 0.5 % for subjects aged between 50 and 59 years up to 8.8 % for subjects 80 years and older [4, 17]. Several therapy strategies are applied aiming primarily on prevention of embolic complications and control of ventricular rhythm. Prevention of stroke can be performed by anticoagulation therapy with Warfarin or a high dosage of Aspirin [19]. Conversion from AF back to sinus rhythm is performed using the antiarrhythmic drugs Flecainide and Propafenone with and without additional therapy of beta-blockers or electrical cardioversion [19]. Both therapy approaches require treatment for prevention of recurrences of AF. Recurrences without therapy are reported for 44 to 85

% within 12 months following cardioversion which could be reduced to 17 % with preventive therapy. This indicates the importance of preventive therapy of AF using antiarrhythmic drugs. Pacemaker therapy is not primarily indicated if the patient suffers from AF but may be required for rhythm control. Indications for pacemaker implantation are the therapy of bradycardia due to sinus node pause or drug induced atrioventricular block and optimization of hemodynamics e.g. for patients suffering from AF with congestive heart failure (CHF) [19]. Pacemaker therapy for prevention of AF is still under evaluation but clinical results indicate that methods like biatrial pacing or atrial stimulation at elevated rates reduce the prevalence of AF [9, 19, 25].

Based on the analysis of the arrhythmogenic processes the preventive effects of pacemaker therapy are discussed with respect to clinical results.

### **Mechanisms Underlying AF**

In a healthy atrial myocardium the refractory period, characterized by the impossibility of re-excitement, shortens homogeneously from the sinus node to more distal parts of the atrium, commonly termed "dispersion of refractoriness". Dispersion of refractoriness exceeding the physiologic range is usually regarded as favoring inducibility and persistency of atrial fibrillation [20]. Additionally, areas of atrial myocardium with abnormally slow or high conduction velocities hold arrhythmogenic potential when recently activated myocardium is re-excited (reentry circuit) [1]. The wavelength concept [2] elucidates the role of conduction velocity and refractory period, the product of which is labeled wavelength. It describes the minimum circuit length allowing activation without running into the refractory period that was created by the previous excitation. The wavelength hypothesis was proved using several experimental methods. Rapid stimulation, local acetylcholine applications, severe vagal maneuvers, and Isoprenaline infusions have been known to induce AF through their influence on the action potential duration, refractory period or conduction velocity. All these interventions lead to abnormally delayed or inhomogeneously conducted atrial activation - setting the stage for reentry circuits [21].

Structural changes in the atrial tissue may be one of the underlying factor for increased dispersion of refractoriness or reduced conduction velocity. Other factors involved in the induction or maintenance of AF include premature beats, the interaction with the autonomic system, atrial stretch and aging process [19]. Enhanced automaticity involving one or more foci firing rapidly is another reported mechanism for AF [19]. The interaction of the autonomic tone with AF became a central topic of discussion in recent years. Literature reports vagally and adrenergically mediated AF [7].

#### *Vagally mediated atrial fibrillation*

Vagally mediated AF is characterized by a close relationship between a relative bradycardia and the onset of AF. Additionally, it occurs predominantly at night, at rest, or during the digestive periods. The atrial vulnerability to vagal input depends mainly on the shortening of the refractory period, which then favors macro reentry circuits and leads to atrial flutter and

fibrillation. Holter recordings usually show a progressive slowing of the sinus rate, clearly suggesting the increasing predominance of the vagal over the sympathetic drive [7]. Clinical results are confirmed in animal models. Stimulation of the parasympathetic fibers or application of acetylcholine on the atrial wall consistently induces AF. The essential point behind these maneuvers is that the action potential and the refractory period of the atrial cells are shortened. Two mechanisms appear to be involved in triggering vagally mediated AF. First, prolonged intra-atrial conduction times can be observed, supporting reentry circuits in some patients. Second, it is known that the vagal effect is non-uniformly distributed within the atrium, provoking a non-homogeneous character of atrial repolarization and harboring potential for AF genesis [6].

#### *Adrenergically mediated atrial fibrillation*

In clear contrast to AF forced by vagal influence, the adrenergically mediated type of AF usually occurs during the daytime and is closely related to stress or exercise [7]. The onset of the latter type of AF is preceded by heart rate acceleration and an increase in low frequency heart rate variability-an indication of a predominantly sympathetic drive. Unlike vagally mediated AF, the adrenergic form usually occurs in a diseased myocardium. The question whether AF is simply triggered by elevated heart rates or by direct adrenergic influences on the myocardium, provoking premature beats, enhanced automaticity, or inadequately increased contractility, is still under discussion.

### **Concepts for Preventive Therapy of AF using Pacemaker**

The analysis of the mechanisms underlying AF leads to several concepts of preventive pacemaker therapy for AF. First of all, structural disease have to be avoided e.g using AV-synchronous pacing instead of VVI therapy [31]. Secondly, dispersion of refractoriness has to be reduced. Lowered conduction velocity or even intraatrial conduction block can be treated using biatrial pacing, firstly investigated by Daubert et al. [11]. Finally, sympathovagal balance shall be maintained to avoid vagally or adrenergic mediated AF

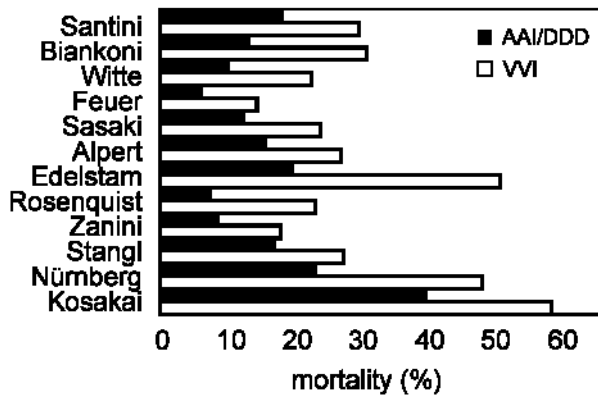


Figure 1. Mortality rate in SSS patients paced with AAI/DDD versus VVI modes (accumulated statistics of retrospective studies covering follow-up periods from 2 to 8 years.)

#### AV-synchronous versus ventricular pacing

The most obvious advantage of AV-synchronous pacing when compared with ventricular pacing is the avoidance of atrial contractions against closed valves, which thus prevents inadequate mechanical stress of the atrial myocardium. Moreover, the atrial contribution to ventricular filling leads to a more efficient pumping function, providing additional long-term benefits for the heart. A literature review covering a considerable number of patients (VVI: 347, AAI: 321) with sinus node disease revealed that atrial fibrillation occurs much more commonly (22.3%) in ventricular pacing (VVI) than in atrial demand pacing with DDD or AAI (3.9%) over the course of a 2 ½ year observation period. The reduction in arrhythmia incidence achieved by atrial demand pacing coincides with a significant reduction in systemic embolism (1.6% vs. 13%) [30]. Further studies investigated the influence of cardiac pacing modes on cumulative survival rates of the patients [15, 24, 31] (see Figure 1). Mortality was consistently lower in the DDD group, indicating the systematic benefit of AV-synchronous pacing for the patient. Overall, it can be concluded from these studies that pacing modes maintaining atrial activity and normal AV-synchrony significantly lower the risk of permanent fibrillation and cardiovascular mortality.

#### Batrial pacing

Atrial fibrillation often appears with a varying combination of anatomical and histological abnormalities, ranging from atrial enlargement to

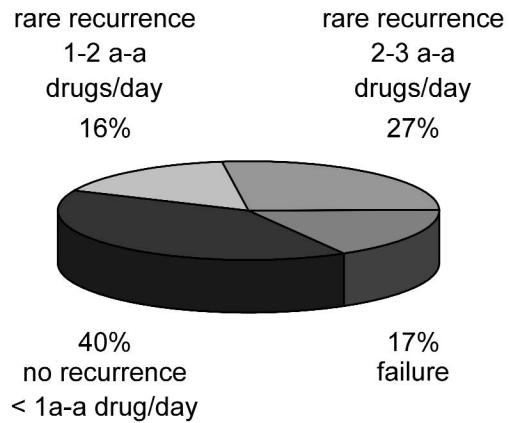


Figure 2. Batrial pacing reduces the recurrence of AF (adapted from [18]).

myocardial fiber disruption and tissue fibrosis. These pathological structures favor slow conduction velocities, which manifest as prolonged P waves of the surface ECG. Based on the wavelength theory it can be concluded that such diseased atrial myocardium is susceptible to developing complex reentrant patterns typical of AF. Single-site atrial pacing has not been efficient in reducing the P-wave duration, neither from the right atrium or via the coronary sinus nor during intraoperative investigations [11] and permanent pacing [18, 23]. However, dual-site pacing in the high right atrium and near the coronary sinus ostium shortened the P wave, as compared with the sinus rhythm, significantly in 20 patients with paroxysmal atrial flutter or fibrillation by an average value of 17 ms [23]. Similar to AV synchronous pacing which limits the occurrence of AF, batrial pacing is supposed to be a suitable therapy in the case of an inter-atrial conduction block. Triggered by intrinsic right atrial events the left atrium is paced via a coronary sinus lead. This approach bypasses conduction disturbances in the right atrium as well as in the atrial septum. This was clinically investigated in 64 patients with pacing by one lead in the right atrium and another lead which was inserted into the coronary sinus for left atrial pacing. On average, the P-wave duration shortened from 150 ms during sinus rhythm to 100 ms with batrial pacing [18]. Furthermore, batrial pacing has been reported to reduce the recurrence rates of atrial flutter and fibrillation in patients with severe atrial conduction disturbances (Figure 2) [9]. Overall, it can be concluded that batrial pacing is efficient and, thus,

indicated in patients with prolonged P waves and disturbed intra-atrial conduction.

#### *Atrial overdrive pacing*

Permanent atrial pacing at an increased rate may reduce the occurrence of atrial fibrillation [6, 10, 22, 25]. Since up to now clinical results are reported only from small patient populations, this method is still under discussion. The most obvious mechanism has its roots in the completely different spatial and temporal spread of paced contractions compared with intrinsic contractions. Therefore, pacing may occasionally suppress arrhythmogenic foci which are active in case of sinus activity. Moreover, overdrive pacing leads to an increased temporal portion of atrial refractoriness (during which no reentry excitation can take place), reducing the probability of atrial tachyarrhythmia. Additionally, atrial pacing at increased rates forces more homogeneous frequency profiles and leads to a more uniform dispersion of refractory period and conduction velocity with antiarrhythmic consequences. Myocardial re-modeling is discussed as being supported by stabilized atrial rates over long periods of overdrive pacing [22]. Finally, overdrive pacing may reduce the sympathetic tone, because the heart rate is maintained slightly above the rate the sinus node would adapt. In connection with a continuous monitoring of the sympatho-vagal balance the overdrive pacing can be realized on demand, leading to a typical closed loop regulation.

The first experiences with overdrive stimulation were gained by applying atrial demand pacing at increased rates [6]. Successful long-term suppression or reduction of AF was achieved in five of six patients. A more specialized pacemaker algorithm aims at suppressing premature atrial contractions (PAC) which are known for triggering atrial tachyarrhythmia [22]. In the event of a PAC, the atrial pacing rate is increased by a certain percentage. This algorithm has been proven to decrease the occurrence of PACs significantly, the incidence of AF, however, was not reduced, thus indicating that AF is not very closely related to the preceding PACs.

#### *Therapeutic and preventive aspects of preserving the sympatho-vagal balance using CLS therapy*

With respect to the discussed mechanisms, avoiding sympatho-vagal imbalances, e.g. by an increase of pathologically low heart rates is the method of choice

for efficient preventive therapy. Especially, in cases of chronotropic incompetence, increased cardiac output during exercise sequences must be primarily provided by changes in the myocardial contractile force. This effort of the circulatory system leads to significantly increased sympathetic tones in load situations. The inotropic reserves are exhausted in their full range to provide a sufficient perfusion of the organs as long as possible. Hence, bradycardic patients require increased heart rates, an indispensable prerequisite for reducing the incidences of atrial fibrillation. On the other hand, pacing at inappropriately high heart rates is disadvantageous as well. Thus a method for supporting suitable pacing rates in every situation has to be found. The detailed knowledge of the natural mechanisms for providing appropriate heart rates is an indispensable prerequisite for the development of a therapy tool avoiding sympatho-vagal imbalances. The natural cardiovascular regulation is a highly developed and complex closed-loop control system. The total peripheral vascular resistance and cardiac output—the product of stroke volume and heart rate—affect the arterial blood pressure (the controlled variable). The most important short-term regulation process to preserve stable blood pressure (BP) is the baroreceptorreflex. Triggered by every change of blood pressure the baroreceptorreflex ensures stable BP by appropriate reaction of the cardiovascular control mechanisms with respect to the recognized blood pressure shift [8, 27].

Only the natural cardiovascular regulation system with its coupling to the nervous system is able to provide an optimal and physiologic control of the hemodynamic parameters. Thus, a therapy tool, considering the autonomic balance, must be based on the incorporation of the pacemaker system into the natural regulation. By this way the pacing rate is under continuous control of the circulatory centers. To integrate the pacemaker into the natural cardiovascular control loop, one has to monitor a cardiac parameter which reflects the influence of the circulatory centers and to adjust therapy accordingly [13, 26]. Based on that, e.g. the pacing rate is part of the balancing of different cardiovascular parameters.

As the control of the circulatory centers is incessant, a continuous feedback loop between them and the implant is established. I.e., the pacing rate is adjusted beat to beat according to the cardiovascular demand. If the pacing rate is too high, it would be lowered by the

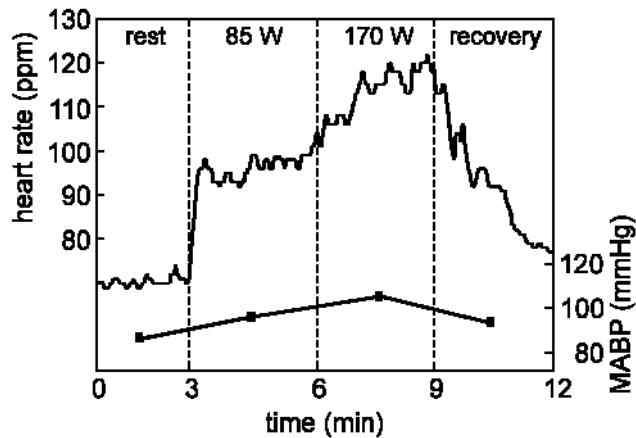


Figure 3. CLS heart rate of a young, athletic, but chronotropically incompetent patient during ergometry [14].

circulatory centers and vice versa, i.e. it closely follows the 'would be' sinus rate.

In case of the pacemakers with CLOSED LOOP Stimulation (CLS) the integration into the natural feedback loop is realized by monitoring changes in the myocardial contraction dynamics. This has been theoretically elaborated [18] and clinically validated [3, 5].

Clinical experience shows, that the reaction of the integrated closed-loop system to sympathetic and vagal influences is reflected in the resulting regulation behavior during various situations. The CLOSED-LOOP Stimulation pacemaker supports the sympathovagal regulation mechanisms while considering their pathologically caused limitations. Results of blood pressure and stimulation rate in a patient with coronary heart disease and CLS therapy show constant blood pressure and distinct variations in heart rate, but a naturally caused limitation of stimulation rate (no values higher than 92 bpm are reached during exercise) [29]. In sequences of considerable physical exercise, an increase in sympathetic tone is the principle mechanism for the increase in cardiac output via chronotropic and inotropic mechanisms. Analyzing the heart rate and blood pressure of a chronotropically incompetent patient with an implanted closed-loop pacemaker shows the sympathetic influence through significantly increased heart rates and slightly increased blood pressure during ergometric exercise (Figure 3). Vagal mechanisms are reflected in the heart rate responses of patients supported with closed-loop pacemakers as

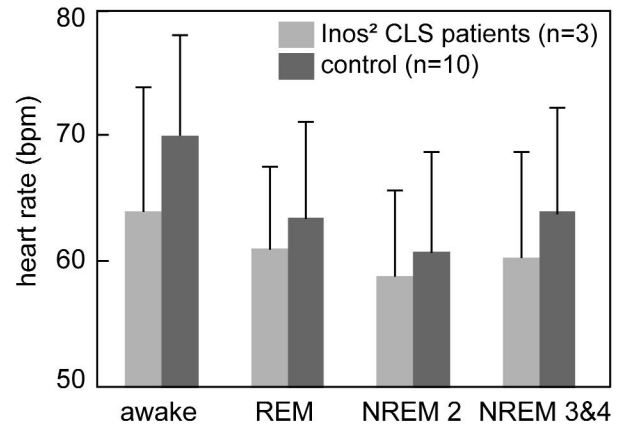


Figure 4. The pacing rate of the patient group (Dr. Lang, Tübingen, Germany) shows the same relation as the sinus rate of the control population [20] during different sleep stages.

well. Heart rate trend recordings during sleep demonstrate the correlation between heart rate variation and various sleep stages (Figure 4).

Hence, with the closed-loop pacemaker, the stimulation rate is linked to the circulatory centers, and adequate perfusion is enabled under various conditions. A stimulation rate that is physiologically appropriate is ensured, and baroreceptor sensitivity remains intact and provides the essential feedback to the circulatory control system. This autonomic reflex with a fast change in heart rate limits BP variability and therefore, avoids mechanical stress on the myocardial wall and, thus, provides a good prognosis for the patient and reduced incidence of arrhythmia. This correlation between ability of heart rate to react fast and adequate to blood pressure shifts and the prognosis of patients for arrhythmia was investigated clinically [12].

Additionally, recordings of stimulation rate and blood pressure indicate that even during sleep elevation of cardiac output demanded by cardiovascular system has to be compensated by stimulation rate. The CLS therapy takes care of the contractile reserves because an increased demand of cardiac output is also compensated by elevated rate and, thus, should decrease the incidence of arrhythmias.

## Conclusion

In the meantime, cardiac pacing plays a legitimate role in treating atrial tachycardia. Present pacemaker

developments aimed at the therapy of both idiopathic diseases of the heart and those associated with pathological influences of the autonomous nervous system. Depending on the underlying cardiac disturbance, biatrial and overdrive pacing have been proven to lower the incidence of atrial fibrillation significantly. Additionally, atrial overdrive pacing involves aspects of influencing the autonomic control of the heart, leading to the avoidance of arrhythmogenic sympatho-vagal imbalance.

The demands placed on the circulatory control system increase in patients with atrial bradyarrhythmia. Myocardial contractility and peripheral vascular resistance are heavily burdened with compensating for the lacking contribution usually afforded by the appropriate heart rate. This means automatic imbalance as well as additional stress to the myocardium and, therefore, an increased potential for pathological changes of the myocardium, including tachyarrhythmias. Monitoring the contractile myocardial state enables the cardiac pacemaker system to support the patients' own blood pressure regulation with adequate heart rates. This support of the cardiovascular system utilizes afferent information from the autonomous nervous system and keeps efferent autonomous signals in balance. For further refinement of preventive therapy, a consequent extension of correspondence between therapeutic tool and the body-own regulation processes may provide prediction of AF and therefore, suitable therapy can be started on demand.

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