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Pace and sotalol – three case reports of the benefits and potential hazards associated with sotalol administration in sinus node dysfunction

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Abstract. The sinus node dysfunction is associated with conduction system disease and supraventricular tachyarrhythmias (atrial fibrillation and atrial flutter). The only effective treatment for patients with chronic symptomatic sinus node dysfunction is pacemaker therapy. In tachy-brady syndrome patients, in addition to pacemaker therapy, the pharmacological treatment is necessary to avoid tachycardia episodes. Because of the frequent paroxysmal atrial fibrillation episodes a good choice to maintain the sinus rhythm is represented by sotalol. This article will present three patients that provide examples of beneficial effects of sotalol and also on the risk of severe adverse events in some cases.
Key words: sinus node dysfunction, atrial fibrillation, sotalol, pacemaker therapy.

Introduction. The sinus node dysfunction (SND) or sick sinus syndrome refers to abnormalities in sinus node impulse formation and propagation, and includes sinus bradycardia, sinus pause or arrest, chronotropic incompetence, and sinoatrial exit block. SND is associated with conduction system disease and supraventricular tachyarrhythmias (atrial fibrillation and atrial flutter), named "tachy-brady syndrome" (Epstein et al 2008).

SND is more prevalent in elderly patients related to senescence of sinus node, often accompanied with senescence of the atrium and conduction system (Dobrzynski et al 2007).

Atrial fibrillation (AF) is the most common serious arrhythmia with a prevalence estimated at 2.2 million people in the United States and 4.5 million in the European Union (Chugh et al 2001; Fuster et al 2006). Its incidence also increases progressively with age (Tse et al 2005). AF is associated with heart failure, hemodynamic impairment and symptoms affecting quality of life. Patients have an increased risk of arterial thromboembolic events, including stroke, resulting in significant morbidity, mortality and costs (Glotzer et al 2003; Flaker et al 2005).

The only effective treatment for patients with chronic symptomatic SND is pacemaker therapy. Many studies indicate that right atrial pacing decreases the incidence of AF, when compared with pacing of the ventricle, and it represents the optimal pacing mode (Rosenqvist et al 1986; Andersen et al 1997; Lamas et al 2002).

In tachy-brady syndrome patients, in addition to pacemaker therapy, the pharmacological treatment is necessary to avoid tachycardia episodes. Because of the frequent paroxysmal AF episodes a good choice to maintain the sinus rhythm is represented by sotalol – an antiarrhythmic drug with Class II (beta-adrenoreceptor blocking) and Class III (cardiac action potential duration prolongation) properties.

All antiarrhythmic drugs have potential proarrhythmic effects; these may range from simple sinus bradycardia to fatal ventricular arrhythmias especially in elderly patients with ischemic cardiac disease (Podrid 2001).

This article will focus on the beneficial effects of sotalol and also on the risk of severe adverse events in some patients.

Case report 1. The first case is a 62 year old female patient diagnosed with sick sinus syndrome, sinus bradycardia (40 bpm) and paroxysmal AF, in which an AAI pacemaker was implanted and programmed at 60 bpm. She received Sotalol 80 mg twice daily in order to prevent AF. After four years of treatment the AV node conduction is in the normal range and she is free of symptoms, the QTc interval was 440 msec (Figure 1).

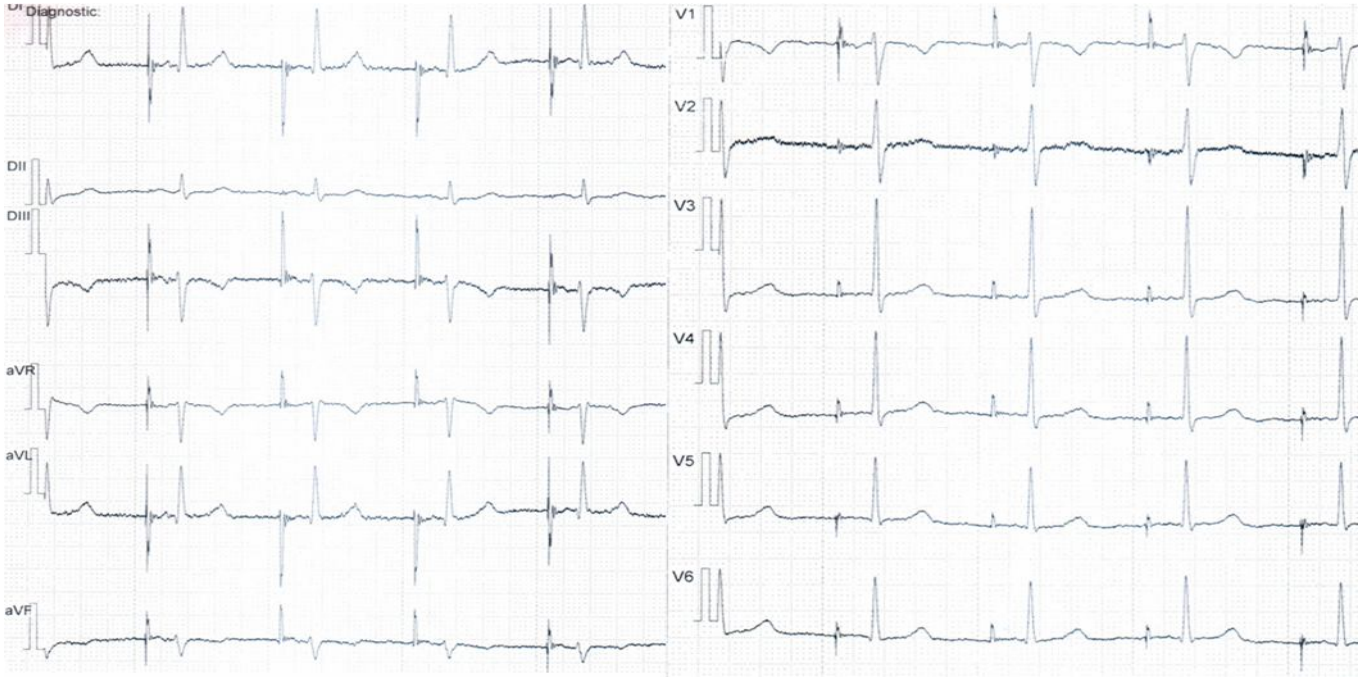

Figure 1. M. A., 66 years old; EKG - AAI paced rhythm, 60 bpm, QTc=440 msec.

Case report 2. The second case is a 71 years old man diagnosed with sick sinus syndrome and paroxysmal AF. On conversion from atrial fibrillation to sinus rhythm, he presented a prolonged sinus pause (more than 3 sec). For this reason a DDD pacemaker was implanted and a treatment with Sotalol 80 mg twice daily was prescribed. The pacemaker was programmed with a long A-V delay to avoid right ventricular apical pacing (therefore the atrial stimulation was maintained most of the time). In two years of treatment he didn't presented episodes of AF or other atrial tachycardias. At the latest visit, in December 2010, the QTc interval on the EKG was mildly prolonged – 475 msec (Figure 2).

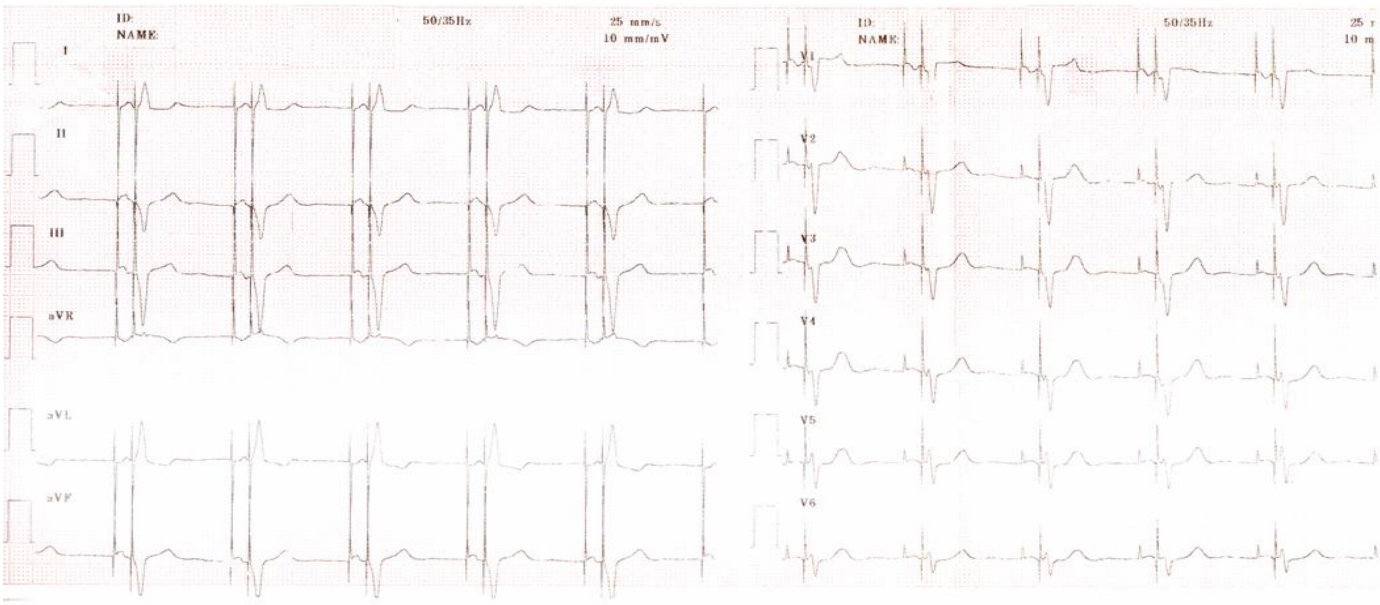

Figure 2. A. I., 73 years old; EKG - DDD paced rhythm, 60 bpm, QTc=475msec.

Case report 3. The third case is similar to the second one. This time it is a female patient, 60-year old, with a history of sinus node dysfunction, paroxysmal AF and atrial flutter which was regarded as inadequately controlled by antiarrhythmic drug therapy. A complex procedure of AF ablation by pulmonary veins isolation and cavotricuspidian isthmus ablation was performed in December 2007 in a cardiology hospital in France. She also presented a strong family history of sinus node disease (her mother and her older sister both received a pacemaker for sick sinus syndrome). Over the next few months, she experienced recurrent dizzy spells, which became increasingly severe. She was admitted in our hospital in November 2008. The EKG revealed severe sinus bradycardia with a heart rate of 38-40 bpm and sinus pauses of more than 3 seconds (Figure 3).

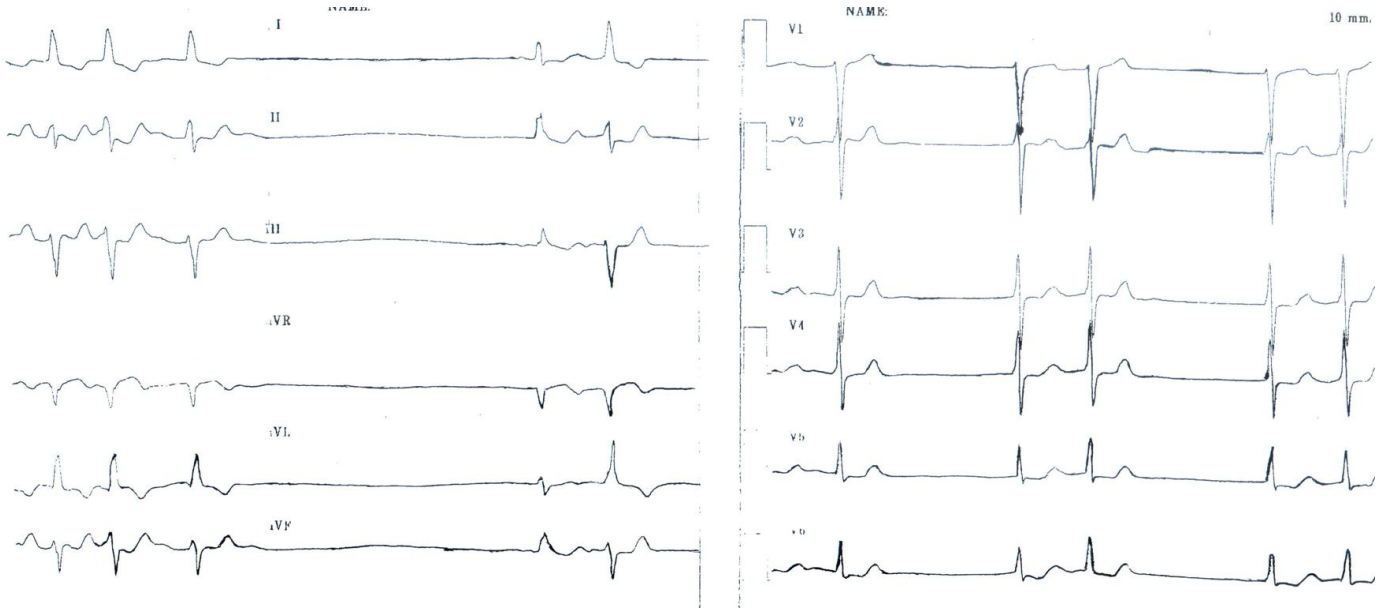

Figure 3. C. V., 58 years old; EKG - sinus rhythm, sinus pause of 3 sec.

The management strategy was the same: DDD pacemaker implantation and Sotalol 80 mg twice daily for the next year. Also, in this case, the pacemaker was programmed with a long A-V delay to avoid right ventricular apical pacing and to favour the AAI mode. One

year later she presented frequent episodes of rapid palpitations. The Holter monitor showed episodes of polymorphic nonsustained ventricular tachycardia (Figure 4) associated with sotalol administration, which was discontinued and she was started on propranolol. The QTc interval was severely prolonged 540 msec. Until the latest control in December 2010 she didn't experienced new recurrent episodes of rapid palpitations.

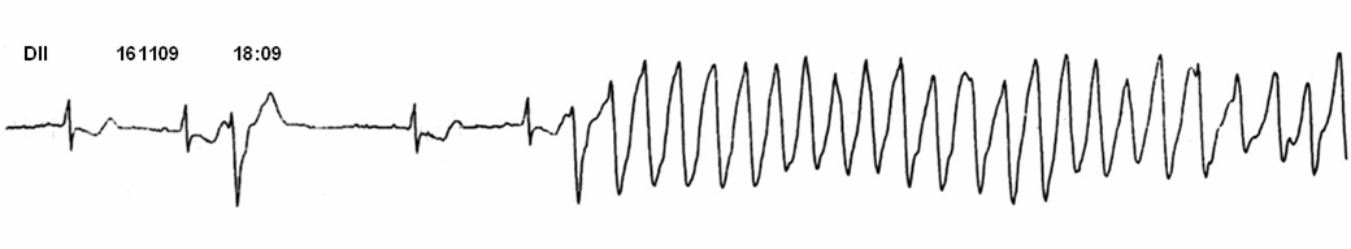

Figure 4. C. V., 59 years old; telemetry monitoring showing polymorphic nonsustained ventricular tachycardia.

Discussion. These three cases provide examples of the benefits and potential hazards associated with the sotalol administration.

In patients with SND and normal atrioventricular (AV) conduction, physiological pacing can be accomplished with either a single chamber atrial pacemaker AAI/R or a dual chamber pacemaker DDD/R. For dual chamber devices have been developed new algorithms in order to minimize ventricular stimulation. However, a single-chamber atrial pacemaker in AAI mode is an acceptable therapy in patients with SND and normal AV conduction as the overall incidence of complete heart block is very low. In patients with SND and known AV conduction abnormality (including bundle branch block and bifascicular block), a DDD pacemaker should be used because of the high risk of AV block (Brandt et al 1992). In the first case presented, the AAI pacing was enough because the AV interval (conduction) remained constant during the five years of follow-up. The other two cases needed DDD pacemakers due to advanced age (Case 2) and to first degree AV block (Case 3).

The AF recovery to sinus rhythm will result in hemodynamic improvements by restoration of atrial systole and improvement of ventricular filling at rest and during exercise (Ueshima et al 1993; Yigit et al 2003; Singh et al 2005, 2006). In patients with SND low heart rates will facilitate atrial ectopies, which if are very early can induce paroxysmal AF (Wallmann et al 2003). For this reason rapid atrial pacing significantly decreases the rate of AF recurrence (Flammang et al 2005). Also, there are retrospective studies indicating that right atrial pacing decreases the incidence of AF compared with pacing in the ventricle (Rosenqvist et al 1996). Andersen et al (1997) demonstrated significant benefit for single chamber right atrial pacing vs. single chamber right ventricular pacing in patients with sick sinus syndrome, with a decreased incidence of AF, thromboembolic events, congestive heart failure and improved survival, especially after long-term follow-up.

Sotalol, by his high degree of beta-adrenoreceptor blocking effect (synergistic with atrial pacing), reduces the atrial ectopies and maintains the sinus rhythm (Plewan et al 2001). But this ß-adrenergic blocking activity through the sinus bradycardia may represent a major limitation concerning the use of sotalol in patients with SND or AV block unprotected by a backup pacemaker. Contrary to this situation, in patients with pacemaker, sotalol can be used for its class III effects in order to prevent the AF recurrence. In our patients the double strategy "pace and sotalol" managed to maintain free of supraventricular arrhythmias (especially AF) along the follow-up period.

The SAFE-T study demonstrated that the effects of sotalol and amiodarone on long-term maintenance of sinus rhythm are similar (Singh et al 2005). The SOPAT study demonstrated that antiarrhythmic therapy with Sotalol is as effective as the fixed combination of Quinidine - Verapamil in the reduction of the recurrence rate of

symptomatic paroxysmal AF with a low but definite risk of severe side-effects (Patten et al 2004).

Pure class III antiarrhythmic agents are characterized by their action potential duration–prolonging effect as the sole electrophysiological mechanism. Besides this effect the sotalol and amiodarone possess also additional electrophysiological effects (Hohnloser et al 1994; Singh 1994).

All antiarrhythmic drugs have potential proarrhythmic effects which may range from simple sinus bradycardia to fatal ventricular arrhythmias (especially in patients with significant structural heart disease) and might exceed the benefit of the drug (Wellens et al 1992). Class Ia drugs and class III antiarrhythmic drugs induce early after-depolarizations and determine polymorphic ventricular tachycardia (Borggrefe et al 1992).

The QT interval is prolonged by a variety of drugs. The class III antiarrhythmics are the major examples and exert their therapeutic effect by affecting potassium ion channels, reducing outward, repolarizing current and prolonging action potential duration and the QT interval respectively. These drugs are used for conversion and maintenance of sinus rhythm in patients with recurrent AF and they may induce a potentially fatal arrhythmia - torsade de pointes (TDP) (Jackman et al 1998). The incidence of this form of proarrhythmia is ranging between 1.8 – 4.8% for d,l-sotalol (Lehmann et al 1996; Haverkamp et al 1997). The *d*-sotalol may be less likely to provoke TDP compared with *d,l*-sotalol because of the lack of drug-associated bradycardia (Touboul 1993). However the exact incidence of TDP induced by *d*-sotalol is not yet established. The likelihood of occurrence increases with the use of higher doses (Hohnloser et al 1992; McNeil et al 1993). In several studies, the authors demonstrated that sotalol was more effective than placebo in maintaining sinus rhythm and TDP did not develop if drug doses were adjusted to renal function and the QT interval was monitored (Brachmann et al 1993; Benditt et al 1999). The reduction of outward currents and the enhancement of inward currents during phase 2 and 3 of the action potential determine its prolongation in the ventricular myocytes, which in turn prolongs the QT interval on the EKG. The ventricular repolarization is determined by the intrinsic transmural heterogeneity in the density of the various ion channels. The reduction of outward current and the increase in inward current facilitates the development of early afterdepolarizations due to reactivation of the L-type calcium current and to activation of the sodium-calcium exchange current during the action potential plateau (Burashnikov et al 1998; Viswanathan et al 1999). A marked increase in dispersion of repolarization increases the likelihood that early afterdepolarization-induced extrasystoles will trigger reentry and TDP (Verduyn et al 1997; Antzelevitch et al 1999).

Patients who develop drug-induced long QT syndrome may have subtle genetic defects which make them more susceptible to arrhythmias when drugs that can cause prolonged QT intervals are administrated. The acquired abnormal QT prolongation may be due to a reduced repolarization reserve and the TDP's occurrence secondary to a repolarization prolonging drug represents a patient-specific response (patients who develop new episodes of TDP after exposure to another repolarization prolonging drug different from the initial one who caused the arrhythmia) (Haverkamp et al 2000). This response specific to each patient does not necessarily imply an abnormal QT prolongation and TDP every time when he/she is exposed to a repolarization prolonging stimulus and the intervals between the initiation of the therapy and the occurrence of arrhythmia are highly variable. Studies of congenitally long QT syndromes (LQTS) demonstrated a genetic heterogeneity which implies multiple genes (Keating et al 2001). These genetic studies have identified families with very low penetrance (individuals with genetic mutations but without clinical phenotype) and suggested that such individuals may be at increased risk for TDP during the administration of QT-prolonging drugs (Donger et al 1997; Priori et al 1999; Napolitano et al 2000; Sesti et al 2000; Yang et al 2002). Furthermore the *HERG* gene was identified not only in LQTS disease but also as the predominant target of most drugs inducing TDP (Sanguinetti et al 1995).

In two of our patients (Case 1 and 2) the QT interval was slightly prolonged without ventricular arrhythmias. Conversely, the third case presented a QT prolongation

with frequent polymorphic ventricular tachycardia considered a major complication of the sotalol therapy. After sotalol discontinuation she was free of ventricular arrhythmias. Furthermore, her paced QRS complex was very large (200 msec) vs. her native QRS (100 msec) that can be explained by o possible cardiomyopathy or by depolarization troubles in the left ventricular mass. Also the family burden of SND may suggest a genetic predisposition or a possible channelopathy.

In conclusion, the "pace and sotalol" strategy is a good therapeutic alternative in patients with SND in order to maintain the sinus rhythm. Nevertheless, although the sotalol is generally well tolerated by the majority of patients, the need for individualized careful dose titration and the QT interval monitoring, particularly in patients with structural heart disease, is required by the observation of drug-associated serious arrhythmic adverse events.

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