Sinus Bradycardia and Sinus Pauses Immediately after Electrical Cardioversion of Persistent Atrial Fibrillation—What Do They Mean?

Dritan Poçi, M.D.,*† Britt-Marie Abrahamsson, R.N.,† Nils Edvardsson, M.D., Ph.D.,† and Lennart Bergfeldt, M.D., Ph.D.†

From the *Department of Cardiology, University Hospital Örebro, Örebro, Sweden, and †Department of Molecular and Clinical Medicine/Cardiology, Sahlgrenska Academy, University of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden

Background: To determine the role of sinus bradyarrhythmia (SB) immediately after electrical cardioversion of persistent atrial fibrillation (AF) on the short-term recurrence rate and long-term pacemaker need and all-cause mortality.

Methods: SB defined as sinus bradycardia (sinus rate <40 bpm for ≥ 2 consecutive cycles) and/or sinus pauses (>2 s), were recorded during 5 minutes immediately after successful DC cardioversion in 140 consecutive patients with persistent AF.

Results: SB was observed during the first minute of SR in 31 patients (22%). Sinus bradycardia was present in 27 patients, sinus pauses in 16 (>3 s in 10) patients, and both in 12 patients. Compared to patients without SB, the mean heart rate during the first minute after cardioversion was lower, 57 ± 13 versus 63 ± 11 bpm; $P < 0.05$, while the mean heart rates during the subsequent 4 minutes were not statistically significantly different. The AF recurrence rates were not significantly different at 1 week (45% vs. 40%), or at 3 months (68% vs. 53%) in patients with or without SB. After a mean follow-up of 86 ± 6 months the pacemaker implantation rate was 10% versus 11% (NS) and an all-cause mortality of 26 versus 18% (NS).

Conclusions: SB immediately after electrical cardioversion of persistent AF had no significant impact on the 3-month AF recurrence rate, the long-term need for pacemaker or all-cause mortality.

Ann Noninvasive Electrocardiol 2013;18(3):281–287

atrial fibrillation; sinus bradycardia; cardioversion; sick sinus syndrome

Sinus bradycardia and sinus pauses sometimes occur after spontaneous conversion of atrial fibrillation (AF) and are also features of the sick sinus syndrome (SSS).¹ If the sinus node is kept inactive due to an overdrive effect of shorter or longer episodes of AF, its recovery after sudden termination of AF may be slow and it is not possible to predict if or how soon the sinus rate will return to normal. If AF is a component of a SSS, which is the case in up to 50% of patients receiving a pacemaker because of SSS,² the sinus node can not be expected to react normally after

conversion. After cardioversion of persistent AF sinus bradycardia and pauses could imply pre-existing sinus node dysfunction, AF-induced SN remodeling or reflect normal variations, that could be more or less reversible over different periods of time. Sinus node dysfunction is limited to the sinus node and its closest atrial connections, while the initiation and maintenance of AF require participation of structures outside the sinus node area. Electrophysiological and electro-anatomical characterization of the atria in patients with SSS has pointed to a widespread pathological process, an

Address for correspondence: Dritan Poçi, M.D., Ph.D., Department of Cardiology, University Hospital, Örebro, Sweden.
E-mail: dritan.poci@orebroll.se

This study was supported by grants from the Gothenburg Medical Association, the Sahlgrenska University Hospital, and the Swedish Heart Lung Foundation.

idiopathic atrial myopathy.^{3,4} Atria in both patients with AF and without documented SSS, and in patients with SSS without documented AF seem to have important pathophysiological and structural properties in common.³

The purpose of the present study was to explore the prevalence of sinus bradycardia and/or sinus pauses immediately after successful electrical cardioversion of persistent AF and whether they were associated with recurrence of AF within the next three months. A second aim was to explore whether such patients were more prone than other patients to receive a permanent pacemaker during long-term follow-up.

MATERIAL AND METHODS

Consecutive patients with persistent AF scheduled for elective electrical cardioversion (DC) were enrolled. Each patient was only included once. Patients with a permanent pacemaker or previously documented sinus node dysfunction were excluded. The baseline evaluation consisted of a medical history, including the number of previous cardioversions and the duration of the current AF episode, physical examination, 12-lead ECG (GE Marquette, General Electric, Waukesha, WI, U.S.A.), and chest x-ray. Laboratory evaluation included electrolytes, thyroid and liver function tests. Echocardiography was performed on clinical indications at the discretion of the AF clinic physician.⁵ All patients were treated with warfarin for at least 4 weeks before cardioversion with an international normalized ratio (INR) level within the target interval of 2.0–3.5. Patients who were on rhythm and/or rate controlling agents kept this medication unaltered for the duration of the study or until a change in medication was clinically indicated in case of AF recurrence. The cardioversion was performed as an outpatient procedure under brief general anesthesia with propofol. The defibrillator paddles were positioned above the apex of the heart and below the right clavicle. A maximum of four synchronized shocks, starting at 200J, were delivered, until SR was restored for at least 5 minutes or the procedure was considered a failure. The ECG was continuously recorded during the procedure and for at least 5 minutes after SR was restored. The patients were then monitored via telemetry until discharge and a 12-lead ECG was recorded before discharge from

the outpatient clinic ≤ 4 hours after cardioversion. Visits for rhythm control were scheduled at one week and 3 months. Warfarin therapy was to be continued for at least 3 months after cardioversion and then according to current guidelines. The ECG analysis of the first 5 minutes of SR was made manually on a beat-by-beat basis by one author (LB), who was not involved in the clinical patient care or informed about follow-up data. PP and RR intervals were measured; P waves were adjudicated as sinus or of ectopic origin. All premature atrial contractions were counted. Sinus bradycardia was defined as a sinus rate <40 bpm calculated from ≥ 2 consecutive P-P intervals and a sinus pause was defined as a PP interval >2 s.⁶ The indications for permanent pacemaker implantations were obtained via the Swedish Pacemaker Registry with complete national coverage.

Statistical Analysis

Mean (SD) and median (range) values were used for descriptive statistics. Fisher's exact two-tailed test was used for comparison of categorical data, and unpaired *t*-test for comparison of continuous variables. A difference was considered statistically significant at a $P < 0.05$.

RESULTS

In all, 151 patients (88%) were converted to SR. Eight of them relapsed into AF within 5 min, and 3 more had technically unsatisfactory ECG recordings. The study population therefore comprised 140 patients (Figure 1). Sinus bradycardia and/or pauses were present during the first minute after conversion in 31 patients (21 men; 22%, 95% CI: 15–29%) and for 14 of them (45%) this was their first DC cardioversion. Out of these 31 patients, 27 (87%) had sinus bradycardia and 16 (52%) sinus pauses ≥ 2 s (10 of them >3 s; 32%), while 12 (39%) had both. The clinical characteristics are presented in Table 1. Fifty-three patients had undergone at least one previous cardioversion. There was no significant difference in age, proportion of men versus women, duration of the index AF episode or in the prevalence of rhythm and/or rate control agents in patients with versus without SB. Patients with sinus bradycardia and/or sinus pauses had a significantly lower mean heart rate during the first minute after cardioversion (57 ± 13 vs. 63 ± 11

Figure 1. Patient flow chart. AF = atrial fibrillation; SB = sinus bradycardia and/or sinus pauses; SR = normal sinus rhythm.

bpm; $P < 0.05$), but the average rates during each of the subsequent 4 minutes and during the entire 5 minute period were not significantly different. The number of premature atrial beats during each minute varied among patients but the mean number was similar across the 5 minutes. There was no significant difference between patients with versus without sinus bradyarrhythmia (SB).

AF recurrence at 1 week and 3 months

The AF recurrence rate was 45% and 40% (NS) at one week as compared to 68% and 53% ($P < 0.01$) at 3 months, in patients with or without SB, respectively (Table 2). In the former group one patient with AF at one week was again DC cardioverted and remained in SR at 3 months. The recurrence rate in patients with SB was 28% at 3 months after cardioversion. We found no relation between AF recurrence and factors like age (>75 vs. ≤ 75 years), gender, and AF duration (>3 months vs. ≤ 3 months). Baseline

characteristics were compared in relation to AF recurrence at 1 week and 3 months without statistically significant differences between the two groups.

Rhythm and Rate Control Medication

The prevalence of rhythm and rate control treatment was very similar in patients with and without SB. Sotalol was used by 23% in each group. Amiodarone was present in 6% and 12%, respectively. Disopyramide was present in 1 and 2 patients, respectively. Conventional beta-blockers were used by 52% in both groups and digoxin in 19% and 31%, and among them 13% and 11% of all patients had the combination of beta-blockers and digoxin. Verapamil was present in 3% and 6%, alone in one SB patient, otherwise in combination with sotalol ($n = 1$) or digoxin ($n = 6$). Three patients were treated with triple combinations: disopyramide+digoxin+beta-blocker (one in each group) and digoxin+beta-blocker+verapamil in three patients without SB.

Table 1. Clinical Characteristics of the Study Cohort (n = 140) Divided into the Two Subgroups with versus without SB; Proportions Expressed as Percent within Brackets

	SB n = 31	No SB n = 109	P
Age	69 ± 12	67 ± 12	Ns
Men/women	21 / 10	70 / 39	Ns
AF duration, index episode; months	10.2 ± 8.6	8.3 ± 7.2	Ns
Lone AF	8 (26)	33 (30)	Ns
Hypertension	11 (35)	22 (20)	Ns
IHD	9 (29)	27 (25)	Ns
Valve disease	4 (13)	5 (5)	Ns
DCM	-	9 (8)	
Heart failure	-	9 (8)	
Beta-blockade	16 (52)	57 (52)	Ns
Sotalol	7 (23)	25 (23)	Ns
Digoxin	6 (19)	34 (31)	Ns
Amiodarone	2 (6)	13 (12)	Ns
Calcium antagonist	1 (3)	7 (6)	Ns
PAC / 5 min	17 ± 15	15 ± 17	Ns
Mean HR/1st min	57 ± 13	63 ± 11	P < 0.05
Mean HR/5 min	60 ± 11	63 ± 14	Ns

AF = atrial fibrillation; DCM = dilated cardiomyopathy; IHD = ischemic heart disease; PAC = premature atrial contraction; HR = heart rate.

Pacemaker Implantation and All-Cause Mortality During Follow-Up

During an average follow-up period of 86 ± 6 months, 15 patients (11%) received a permanent

pacemaker on average 26 ± 18 (range 1–57) months after the cardioversion, 10% (n = 3) and 11% (n = 12) in patients with versus without SB. The indications that were entered into the Swedish Pacemaker Registry at the time of implant, were SSS in 8 (all patients receiving DDD pacemakers) and slow AF in 7 patients (VVI pacemakers). All 3 patients with SB post cardioversion had slow AF as pacemaker indication. The annual pacemaker implantation rate in the study cohort was on average 2.1% as compared to an annual implant rate in patients with diagnosed SSS in the same registry of ~1%. The annual mortality rate in our patient cohort was 2.8%. Twenty-eight patients died during follow-up, 8 (26%; one with pacemaker) with versus 20 (18%; two with pacemaker) without SB at the time of DC cardioversion (NS).

DISCUSSION

SB occurred in 22% of the patients during the first minute after successful electrical cardioversion, and sinus bradycardia was more common than sinus pauses. While a definition of sinus pauses of >2 s was chosen,⁶ the majority with pauses had a durations of >3 s. No statistically significant prognostic effect on the short-term AF recurrence, pacemaker implant rate or survival during long-term follow-up was observed. There was no difference in the predictability, if pauses were counted as >2 s or as >3 s. These results

Table 2. Atrial Fibrillation (AF) Recurrence at 1 Week and 3 Months Follow-up in Relation to Specified Subgroups

	SB 31 (22%; 15–29)		Normal SR 109 (78%; 71–85)	
	AF at 1 week	AF at 3 month	AF at 1 week	AF at 3 month
	14	21	44	58
	(45%; 27–64)	(68%; 48–83)	(40%; 31–49)	(53%; 44–62)
Age > 75 years	6	9	15	17
	(43%; 18–71)	(43%; 22–66)	(34%; 20–50)	(29%; 18–43)
Gender (F)	6	8	16	22
	(43%; 18–71)	(38%; 18–62)	(36%; 22–52)	(38%; 26–52)
AF duration > 3 months	11	17	25	37
	(79%; 49–95)	(81%; 58–95)	(57%; 41–72)	(64%; 50–76)
AA drug therapy	14	21*	39	40
	(100; 77–100)	(100%; 84–100)	(89%; 75–96)	(69%; 55–80)

Note: Proportions are presented with 95% confidence intervals within brackets. AA = antiarrhythmic; AF = atrial fibrillation; F = female; SB = sinus bradyarrhythmia; SR = sinus rhythm.

*P < 0.01 for comparisons between the subgroups at 3 months.

suggest that sinus bradycardia and/or sinus pauses in the immediate post cardioversion phase are benign in patients with no previous suspicion of SSS. However, the all-cause mortality was 44% higher (28 patients/26% vs. 20 patients/18%) in patients with SB at the time of DC cardioversion. At the same time, the very low number of pacemaker implants in patients who died may speak against that SB played a role but could also indicate that pacemaker implants were underprescribed in patients with SB.

The sinus node recovery time and the pattern of corrected return cycle lengths were assessed 5–20 minutes and 24 hours after internal cardioversion in a study of 37 patients with chronic AF of unknown duration and in 20 control subjects.⁷ The corrected sinus node recovery time was significantly shorter at 24 hours after conversion, suggesting reverse remodeling, and the results were not different after autonomic blockade. Patients who relapsed into AF within a month had a significantly higher density of PACs (159 ± 120 vs. 35 ± 37 per hour during the first 24 hours after conversion, $P = 0.001$). In another observation of 20 patients with paroxysmal AF for 100 ± 80 months and with sinus pauses ≥ 3 s after termination of AF, no sinus pauses ≥ 3 s were observed in ambulatory monitoring after catheter ablation of AF during the first week or at 1, 3, and 6 months in 19 patients.⁸ In these patients, without pharmacological agents believed to affect the sinus rate, the heart rate increased during maintained SR, from 44 ± 9 bpm in the first week to 79 ± 14 bpm, $P < 0.01$. One patient required a permanent pacemaker during 26 ± 18 months of follow-up.

Role of AF in the Development of Sinus Node Dysfunction and Vice Versa

Sinus node remodeling may be induced by short periods of rapid atrial pacing and longer periods of AF in animals and humans.^{7–10} Even in patients with paroxysmal AF and in SR for a long time, biatrial abnormalities characterized by structural change, conduction abnormalities and sinus node dysfunction have been demonstrated, compared to patients with left-sided accessory pathways.¹¹ While considerable knowledge has been acquired about the electrophysiological, contractile, and structural features of AF-induced atrial remodeling, its role in maintenance of AF and its reversibility,^{12–18} less is known about AF-induced

sinus node remodeling. While electromechanically detectable reversal of AF induced atrial remodeling seems to occur within days, reversal of structural remodeling, if at all possible, is a much slower process that can last for months. In a small study involving 11 patients with sinus pauses > 3 s after AF termination, and 25 patients with AF without evidence of sinus node dysfunction, all 11 patients became free of AF, sinus pauses and need of pacemaker after AF ablation during a 23 ± 14 month follow-up.¹⁹

In our study consecutive patients accepted for cardioversion of persistent AF differ in several aspects, reflecting the clinical reality. Our exclusion criteria were very few, but patients were not allowed to have documented sinus node dysfunction prior to the DC cardioversion. Theoretically, the 29 patients who did not obtain stable SR might represent a subgroup of patients who, at the time of cardioversion, had such an advanced sinus node dysfunction that restoration of stable SR was no longer possible, but more likely failed cardioversion depended on diffuse atrial electrical and/or structural deterioration. In those who converted to SR there are several options. They could have a preserved normal sinus node function and an AF duration that was not long enough to affect its function, which seemed to be the case in the majority of the patients. In the others, a continuous AF duration of several months could have caused some degree of electromechanical remodeling, where the sinus node might or might not have been involved. Also, the DC procedure might have been followed by transient stunning.

Sinus node dysfunction may be associated with increased dispersion of atrial refractoriness and areas of slow conduction, which promote the development of AF.^{4, 11, 20, 21} Furthermore, atrial pacing reduced AF recurrences in patients with as well as without SSS,^{21, 22} and was associated with improved survival as compared to ventricular pacing.^{22, 23} If postcardioversion SB would be part of a previously unrecognized SSS, atrial pacing might reduce the risk of AF recurrence. The present study, however, did not test the effect of atrial pacing on AF recurrence, but patients with SB did more frequently relapse into AF. We also did not reevaluate the sinus function, and can therefore not confirm or exclude that reversal of electromechanical properties actually took place, which would have decreased the likeliness of a

significant manifest SSS. However, the fact that maintenance of SR at 1 and 3 months was frequent also in patients with initial SB, might indicate a reversal and stabilization of electrical and/or mechanical properties.

Criteria of Sinus Node Dysfunction

Indicators of disturbed automaticity and/or sinoatrial conduction have been used as markers of sinus node dysfunction, but limited sensitivity is a problem.⁶ Our criteria of SB had, in other clinical settings, a specificity for sinus node dysfunction in the range of 90–95%^{4,6,10,24} In the present study the proportion of patients with SB was 22% (95% CI: 15–29%), which is comparable to 27% (10 patients with CSNRT >525 ms) in the study by Manios et al.⁷ In the study by Hocini et al. 42% had CSNRT ≥500 ms, but they were selected because of sinus pauses >3 s after AF episodes.⁸ However, in our study, 10 of the 16 patients with sinus pauses >2 s had, in fact, pauses >3 s. Thus, it seems that SB after conversion of AF in most cases is more benign than when appearing in other settings.

Role of Concomitant Medication

Ideally, patients should be off all medication when the sinus node function is investigated. However, patients are frequently medicated before a planned cardioversion with the hope that immediate relapses can be reduced and the chance of maintaining SR increased. In the present study, patients continued with their ongoing medication, since it was felt unethical to stop treatment. It can not be excluded that the medication may have had some influence on the sinus node function, but the proportions of patients treated with rhythm and rate controlling agents were similar in patients with and without bradyarrhythmia at baseline and among the patients maintaining SR at three months. In addition, the proportions of SB were similar in patients with and without rhythm and rate controlling medication further supporting that drug effects on the sinus node function were not the major reason for the occurrence of SB.

Limitations

At long-term follow up, all-cause mortality was 26% in patients with SB versus 18% in patients without, representing a difference of 44%. A larger

number of patients would have been needed for a statistically significant difference in mortality.

CONCLUSIONS

Sinus bradycardia and sinus pauses, alone or in combination, occurred in one fifth of AF patients converting to SR. They were rapidly reversible, did not seem to be caused by concomitant medication, and can be regarded as benign in the absence of prior suspicion or documentation of sinus node dysfunction.

Acknowledgments: We are grateful for the skilful help of Lotta Backman, RN, in data management. There are no disclosures to be made in relation to this study.

REFERENCES

1. Ferrer MI. The sick sinus syndrome. *Circulation* 1973;47:635–641.
2. Kusumoto FM, Goldschlager, N. Cardiac pacing. *N Engl J Med* 1996;334:89–97.
3. Roberts-Thomson KC, Sanders P, Kalman JM. Sinus node disease: An idiopathic right atrial myopathy. *Trends Cardiovasc Med* 2007;17:211–214.
4. Sanders P, Morton JB, Kistler PM, et al. (2004) Electrophysiological and electroanatomic characterization of the atria in sinus node disease: Evidence of diffuse atrial remodeling. *Circulation* 2004;109:1514–1522.
5. Poçi D, Abrahamsson B-M, Bergfeldt L, et al. Burden and timing of premature atrial contractions after electrical cardioversion of persistent atrial fibrillation do not predict its recurrence. *Clin Cardiol* 2008;10:492–497.
6. Benditt D, Milstein S, Goldstein M, et al. (1990) Sinus node dysfunction: Pathophysiology: clinical features, evaluation, and treatment. In: Zipes DP, Jalife J (eds.): *Cardiac Electrophysiology: From Cell to Bedside*. (pp. 708–734). Philadelphia, W.B Saunders Co.
7. Manios EG, Kanoupakis EM, Mavrikakis HE, et al. Sinus pacemaker function after cardioversion of chronic atrial fibrillation: Is sinus node remodeling related with recurrence? *J Cardiovasc Electrophysiol* 2001;12:800–806.
8. Hocini M, Sanders P, Deisenhofer I, et al. Reverse remodeling of sinus node function after catheter ablation of atrial fibrillation in patients with prolonged sinus pauses. *Circulation* 2006;108:1172–1175.
9. Elvan A, Wylie K, Zipes DP. Pacing-induced chronic atrial fibrillation impairs sinus node function in dogs. *Electrophysiological remodeling*. *Circulation* 1996;94:2953–2960.
10. Hadian D, Zipes DP, Olgin JE, et al. Short-term rapid atrial pacing produces electrical remodeling of sinus node function in humans. *J Cardiovasc Electrophysiol* 2002;13:584–586.
11. Stiles MK, Wong JB, Kuklik P, et al. Paroxysmal lone atrial fibrillation is associated with an abnormal atrial substrate: Characterizing the “second factor.” *J Am Coll Cardiol* 2009;53:1182–1191.
12. Allesie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovasc Res* 2002;54:230–246.
13. Schoonderwoerd BA, Van Gelder, IC, Van Veldhuisen, DJ, et al. Electrical and structural remodeling: Role in

- the genesis and maintenance of atrial fibrillation. *Prog Cardiovasc Dis* 2005;48:53–168.
14. Everett TH, Wilson EE, Verheule S, et al. Structural atrial remodeling alters the substrate and spatiotemporal organization of atrial fibrillation: A comparison in canine models of structural and electrical atrial remodeling. *Am J Physiol Heart Circ Physiol* 2006;291:H2911–H2923.
 15. Hobbs WJ, Fynn S, Todd DM, et al. Reversal of atrial electrical remodeling after cardioversion of persistent atrial fibrillation in humans. *Circulation* 2000;101:1145–1151.
 16. Neuberger HR, Schotten U, Blaauw Y, et al. Chronic atrial dilation, electrical remodeling, and atrial fibrillation in the goat. *J Am Coll Cardiol* 2006;47:644–653.
 17. Pandozi C, Bianconi L, Villani M, et al. Electrophysiological characteristics of the human atria after cardioversion of persistent atrial fibrillation. *Circulation* 1998;98:2860–2865.
 18. Raitt MH, Kusumoto W, Giraud G, et al. Reversal of electrical remodeling after cardioversion of persistent atrial fibrillation. *J Cardiovasc Electrophysiol* 2004;15:507–512.
 19. Miyanaga S, Yamane T, Date T, et al. Impact of pulmonary vein isolation on the autonomic modulation in patients with paroxysmal atrial fibrillation and prolonged sinus pauses. *Europace* 2009;11:576–581.
 20. Luck JC, Engel TR. Dispersion of atrial refractoriness in patients with sinus node dysfunction. *Circulation* 1979;60:404–412.
 21. Miyamoto K, Nakao K, Seto S, et al. Abnormal right atrial electrograms predict the transition to chronic atrial fibrillation in paced patients with sick sinus syndrome. *Pacing Clin Electrophysiol* 2004;27:644–650.
 22. Andersen HR, Nielsen JC, Thomsen PE, et al. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. *Lancet* 1997;350:1210–1216.
 23. Wiberg S, Lönnnerholm S, Jensen SM, et al. Effect of right atrial overdrive pacing in the prevention of symptomatic paroxysmal atrial fibrillation: A multicenter randomized study, the PAF-PACE study. *Pacing Clin Electrophysiol* 2003;26:1841–1848.
 24. Brignole M, Alboni P, Benditt D, et al. Guidelines on management (diagnosis and treatment) of syncope. *Eur Heart J* 2001;22:1256–1306.