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Short communication

Heart rate distribution in paced and non-paced patients with severe recurrent reflex syncope and tilt-induced asystole: Findings from the BIOSync CLS study

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ABSTRACT

Background: Undiagnosed sinus or atrioventricular node dysfunction may bias estimation of the real efficacy of cardiac pacing in preventing vasovagal reflex syncope. We assessed this hypothesis in the BIOSync CLS trial which showed that dual-chamber pacing with closed loop stimulation (CLS) remarkably reduced recurrences of syncope.
Methods and results: In the study patients aged 40 years or older with ≥2 episodes of loss of consciousness in the last year and an asystolic response to Tilt-Table test were randomized to pacing ON (DDD-CLS mode) or pacing OFF (ODO mode). We utilized the available pacemaker diagnostic data in a total of 103 patients (52 pacing ON, 51 pacing OFF) to generate cumulative distribution charts for heart rate (HR) and percentage of pacing. At 12 months, we did not find evidence of suspected sinus or atrioventricular node dysfunction. Beats were similarly distributed between groups ($p = 0.96$), with an average HR of 76 ± 8 bpm (pacing ON) versus 77 ± 7 bpm (pacing OFF). In the active group, the median percentage of atrial and ventricular pacing was 47% and 0%, respectively. Intolerance to high pacing rates was reported in only one patient (1.6%) and was easily resolved by reprogramming the maximum CLS pacing rate.
Conclusions: We did not find evidence of suspected sinus or atrioventricular node dysfunction in the BIOSync CLS patients. The benefit of pacing should be ascribed to pacing prevention of pure vasovagal episodes. CLS algorithm modulated pacing rates over a wide frequency range, consistently competing with sinus node.

1. Introduction

Vasovagal reflex syncope significantly impairs quality of life when characterized by frequent unpredictable loss of consciousness [1]. Cardiac pacing has been investigated for decades as a potential therapeutic option with controversial results [2]. Identifying suitable candidates for pacing and avoiding futile implantations have always been the main concern [3]. The recent *Benefit of Dual-Chamber Pacing with Closed Loop Stimulation (CLS) in Tilt-Induced Cardioinhibitory Reflex Syncope* (BIOSync CLS) trial showed a 77% reduction in syncope attacks with DDD-CLS pacing mode for patients with recurrent vasovagal reflex syncope selected by asystolic tilt testing [4]. Although sinus bradycardia and any cardiac disease that may cause loss of consciousness were among the study exclusion criteria, it could be speculated that pacing may have prevented symptoms of previously undiagnosed intrinsic bradycardia or atrioventricular conduction dysfunction in some patients.

Abbreviations: bpm, beats per minute; CLS, Closed Loop Stimulation; DDD, dual-chamber sequential pacing mode; HR, heart rate; IQR, interquartile range.

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[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Table 1
Characteristics of the patients at baseline.

	All (n = 103)	Pacong Pacing ON (n = 52)	Pacing OFF (n = 51)	*p* Value
Age, years	63 ± 11	63 ± 11	63 ± 12	0.989
Male sex, n (%)	65 (63)	36 (69)	29 (57)	0.193
History of syncope				
No. of syncopes during lifetime	5 (3−10)	5 (3–10)	5 (3–8)	0.388
No. of syncopes during last year	2 (2–3)	2 (2–3)	2 (2–3)	0.639
Age at the time of first syncope, years	53 (25–65)	53 (23–65)	53 (28–68)	0.642
Heart rate, beats per minute	69 ± 10	68 ± 9	69 ± 12	0.985
Resting systolic blood pressure, mmHg	128 ± 13	129 ± 12	128 ± 14	0.789
Arrhythmias, n (%)				
First degree atrioventricular block	5 (5)	4 (8)	1 (2)	0.363
History of atrial fibrillation	11 (11)	5 (10)	6 (12)	0.724
Medical history, n (%)				
Hypertension	47 (46)	20 (38)	27 (53)	0.140
Diabetes	10 (10)	5 (10)	5 (10)	0.974
Hypertensive cardiopathy	26 (25)	12 (23)	14 (27)	0.609
Coronary artery disease	6 (6)	3 (6)	3 (6)	0.908
Valvular disease	3 (3)	2 (4)	1 (2)	1.000
Ejection Fraction (echo), %	60 (55–60)	60 (55–60)	60 (55–62)	0.623
Concomitant medications, n (%)				
ACE inhibitors	25 (25)	11 (21)	14 (27)	0.456
Angiotensin II Receptor Blockers	11 (11)	5 (10)	6 (12)	0.724
Alpha antagonists	8 (8)	4 (8)	4 (8)	1.000
Diuretics	11 (11)	6 (12)	5 (10)	0.776
Calcium antagonists	13 (13)	5 (10)	8 (16)	0.354
Beta-blockers	13 (13)	7 (14)	6 (12)	0.795
Tilt testing				
Syncope during passive phase, n (%)	19 (18)	13 (25)	6 (12)	0.083
Syncope during nitroglycerin phase, n (%)	84 (82)	39 (75)	45 (88)	
Maximum asystolic pause, *sec*	10 (6–20)	9 (6–20)	10 (5.5–18)	0.804
Sinus arrest, n (%)	92 (89)	48 (92)	44 (86)	0.358

Values are given as n (%) and continuous variables are given as mean ± SD or median (interquartile range [IQR]), as appropriate. ACE denotes angiotensin converting enzyme.

Benefit of pacing in vasovagal reflex syncope may thus have been overestimated [5]. To answer this question, we analyzed pacemaker data of the patients participating in the BIOSync CLS study.

2. Methods

Patients aged 40 years or older who had at least two episodes of unpredictable severe reflex syncope during the last year and a tilt-induced syncope with an asystolic pause >3 s were included. After pacemaker implantation, 63 patients randomized to pacing ON (DDD-CLS mode, 50 bpm basic rate and 120 bpm maximum pacing rate) experienced a 77% reduction in syncopal recurrence over 1 year as compared to 64 patients randomized to pacing OFF (ODO mode, only sensing functions and related pacemaker diagnostic data). The off-label use of the ODO mode allowed collection of long-term profiles of spontaneous heart rate (HR) for comparisons with the pacing ON group.

In the present analysis, we utilized the available pacemaker diagnostic data in a total of 103 patients (52 pacing ON, 51 pacing OFF) to generate cumulative distribution charts for HR and percentage of pacing up to 12 months post-implantation. HR distributions over ordered ranks of 10-bpm frequency bins are compared between study groups using mixed-effect models with random intercept at patient level. Frequency ranks (as linear and quadratic terms) and pacing group (ON/OFF) are included as fixed effects. With the available data and 10% standard deviation, we had 80% power to detect a minimum difference of 4 bpm in mean HR between groups with 0.05 alpha-error. All tests were considered significant with $p < 0.05$. Data were managed with the Stata/SE 11.1 (StataCorp LP, Texas, USA).

3. Results

The mean patient age was 63 ± 11 years and 63% were male with a median of five lifetime syncopal events. At enrollment, no statistically significant differences in clinical characteristics were found between the two groups (Table 1). At baseline, the resting HR was 68 ± 9 bpm (pacing ON group) and 69 ± 12 bpm (pacing OFF group) ($p = 0.98$).

At 12 months, beats were similarly distributed (Fig. 1), with most populated bins in the 60–80 bpm range and an average HR of 76 ± 8 bpm (pacing ON) versus 77 ± 7 bpm (pacing OFF), showing no significant effects of pacing on HR distribution ($p = 0.96$, mixed model analysis). In both groups, the median percentage of time at HR ≤ 50 bpm was 0% (interquartile range [IQR], 0%–0%).

In the pacing ON group, the median percentage of atrial pacing was 47% (IQR, 40%–57%), with similar prevalence across frequency bins (black bar portions in Fig. 1). The median percentage of ventricular pacing was 0% (IQR, 0%–2%). At multivariate logistic analysis, a higher incidence of atrial pacing (>50%) did not correlate with severity of syncopal burden: the age- and sex-adjusted odds ratio was 0.99 for any additional lifetime recurrence (95% confidence interval, 0.96–1.02; $p = 0.45$), and 0.98 for recent (<1 year) recurrences (0.90–1.06; $p = 0.59$).

One patient (1.6%) reported device-related palpitations, which were resolved by reprogramming the maximum pacing rate from 120 to 100 bpm.

4. Discussion

The HR distribution in our study cohort resembled that in the general healthy population [6]. During 1 year of follow-up, BIOSync patients had bradycardia ≤50 bpm only for a noticeably short time which excludes a possibility of an intrinsic sinus node dysfunction. Moreover, the patients with an active pacemaker had an exceptionally low proportion of ventricular pacing, ruling out a possibility of intrinsic atrioventricular conduction disease. Admittedly, we cannot exclude an increased susceptibility of sinoatrial and atrioventricular node to extrinsic vagal outflow in our cohort. Conversely, patients undergoing pacemaker implantation for assumed extrinsic sinus node dysfunction may require pacing occasionally, arousing suspicion of an autonomic component to their intermittent pauses/bradycardia. Since the electrophysiological properties of sinus and atrioventricular nodes are normal in cardioinhibitory reflex syncope [6], it is practically impossible to distinguish it from extrinsic sinus node dysfunction, and the two terms can be considered synonyms.

These findings are in line with the conclusion that most syncopal episodes were prevented by timely appropriate pacing, thereby improving quality of life. A remarkable 47% proportion of atrial pacing which was similarly distributed across frequency bins shown in Fig. 1 suggests that the CLS algorithm yields a pacing rate that is similar to normal sinus rate. Since CLS-based pacing rate is calculated continuously according to variations in right ventricular impedance sampled during systole [7], any change in myocardial contraction speed resulting from a variety of conditions preceding impeding syncope (increase in HR, reduced pre load, etc.), may elicit immediate CLS response and prevent vagally-induced drop in HR and blood pressure [8,9].

Intolerance to inappropriately high pacing rates is a possible side-effect of CLS. With the pacemaker setting used in our study, this side-effect was reported in only one patient and was easily resolved by reprogramming the maximum pacing rate.

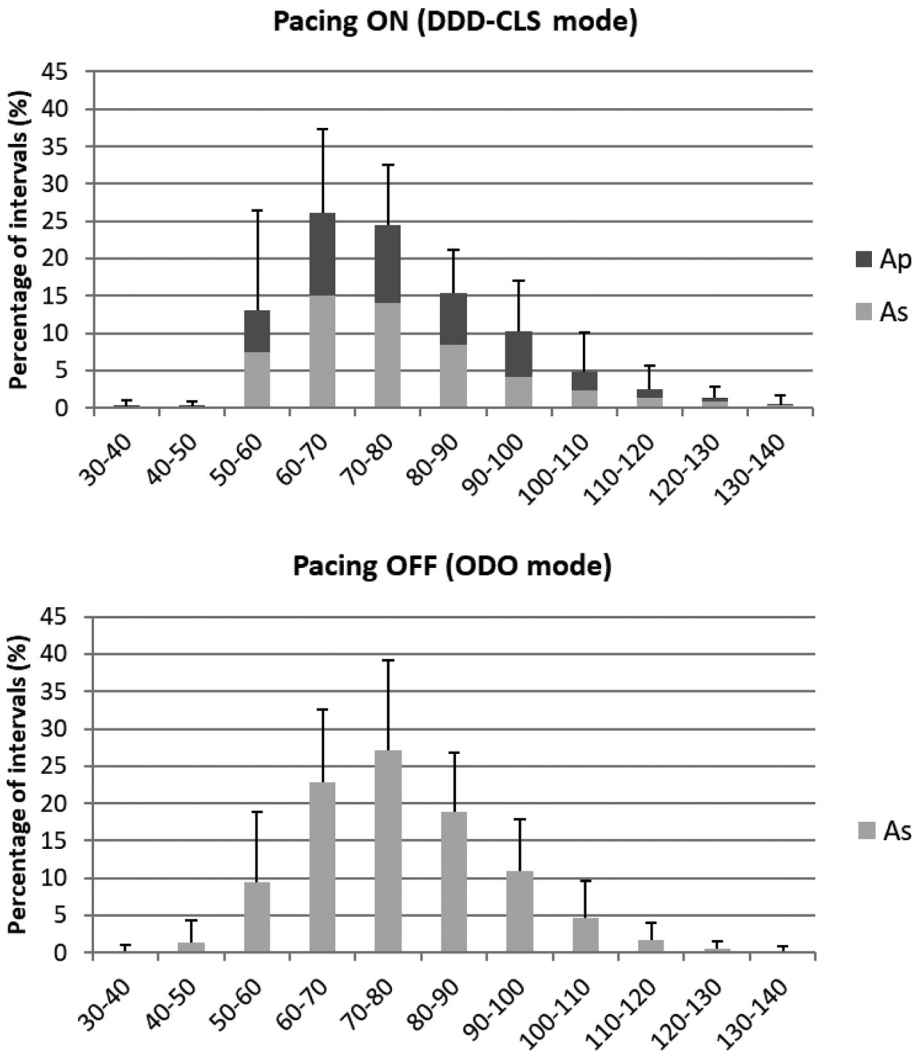

Fig. 1. Heart rate distributions based on device-reported atrial intervals. Bars and error bars denote average values and standard deviations, respectively. Black portions in the upper graph are relative to the proportion of atrial paced (Ap) intervals in each 10-bpm frequency bin; grey bars are relative to atrial sensed intervals (As). Distributions were compared between the two study groups with mixed-effect models with random intercept; linear and quadratic terms of frequency ranks and study group were used as fixed effects. Model coefficient estimates of the frequency terms were statistically significant for both linear and quadratic terms ($p < 0.0001$). The term relative to the study group (pacing ON vs. OFF) was not significant ($p = 0.96$).

5. Conclusions

We did not find evidence of intrinsic sinus or atrioventricular node dysfunction in the BIOSync CLS patients. Thus, the benefit of pacing should be ascribed to pacing prevention of pure vasovagal episodes. CLS algorithm modulated pacing rates over a wide frequency range, consistently competing with sinus node. This observation may be important to fully understand the role of CLS in syncope prevention.

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Conflicts of interest

A.G. and D.G. are employees of BIOTRONIK Italia, an affiliate of Biotronik SE & Co. KG, sponsor of the study. The other authors have no conflict of interest to declare.

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