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Electrophysiological effects of biatrial pacing evaluated by means of signal-averaged P wave time-domain parameters. The significance of persistent atrial late potentials in right atrium during biatrial pacing

Andrzej Kutarski, Andrzej Głowniak, Dorota Szczęśniak and Piotr Ruciński

Department of Cardiology, Medical University of Lublin, Poland

Abstract

Background: *Atrial conduction disturbances are a known substrate of re-entrant atrial arrhythmia, and their detection is important for the selection of proper therapy. Time-domain analysis of P-wave in signal-averaged ECG (SA-ECG) recorded from chest leads is an accepted method evaluating inhomogeneity of atrial excitation, predictive for atrial arrhythmias. Biatrial (BiA) pacing created a new therapeutic option for patients with atrial arrhythmias. The aim of our study was to estimate the effect of BiA pacing on SA-ECG recorded from conventional external and from intraatrial leads.*

Methods: *Recordings were performed on 24 patients during BiA pacing system implantation. A surface SA-ECG was obtained from orthogonal leads, and intraatrial signals were recorded and averaged separately from the right and left atria at sinus rhythm and BiA pacing. We analyzed standard SA-ECG parameters (P/A wave duration, RMS20 and LAS5) and the presence of atrial late potentials (ALP-Pdur > 125 ms and RMS20 < 2.40 μV).*

Results and conclusions: *BiA pacing favorably modifies SA-ECG parameters in the right and left atrium. BiA pacing significantly shortens P duration, significantly increases RMS20 and reduces atrial late potentials (ALP) occurrence in most patients in comparison to sinus rhythm both atria. ALP are still present in 46% of patients in spite of effective BiA pacing, which can be observed mainly in the right atrium and is connected with increased risk of atrial fibrillation recurrence. This phenomenon suggests a limited effect of RAA-based BiA pacing on the synchrony of atrial activation, and a search is needed for another right atrial lead location for permanent BiA pacing.* (Cardiol J 2008; 15: 26–38)

Key words: signal-averaged ECG, biatrial pacing, intraatrial signal, atrial late potentials, atrial fibrillation

Address for correspondence:
Andrzej Kutarski, MD, PhD
Jaczewskiego 8, 20–954 Lublin, Poland
Tel./fax: +48 81 724 41 51
e-mail: a_kutarski@yahoo.com
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Introduction

In the recent years biatrial (BiA) pacing has become an accepted therapeutic option for atrial arrhythmia, in up-to-date textbooks listed under the "new indications" category [1–9]. BiA pacing is effective in about 80% of patients [1, 6–8, 10–12], and it can be anticipated that its antiarrhythmic effect should be inversely proportional to the underlying cause and severity of the arrhythmia. Surprisingly, Daubert et al. [6, 8], in a French Pilot Study, proved no such relationship. The pathomechanism of arrhythmia or technical problems with the pacing system may be of greater importance [7, 10–12]. Our previous study proved there to be no effect from factors such as age, type and severity of arrhythmia and degree of interatrial conduction disturbance upon the clinical antiarrhythmic effectiveness of BiA pacing systems in long-term follow-up [11]. The patients that did not benefit from BiA pacing were a little younger and had non-significant atrial dilatation. We suggested that a different pathomechanism of arrhythmia and its triggers might be the cause of the failure of BiA pacing, to prevent arrhythmia in those patients [11]. In the case of a focal AF triggered from pulmonary vein foci, BiA pacing may be ineffective [10, 12]. In 1997 Yu et al. [13] proved that premature extrastimuli from high right atrium (HRA) produced a markedly prolonged atrial potential recorded from the infero-posterior interatrial septum during HRA pacing, in comparison to coronary sinus (CS) pacing. During BiA pacing, the atrial potential recorded from the infero-posterior interatrial septum was significantly shorter, but not in all patients. What is most important, in patients without this effect, BiA pacing failed to prevent atrial fibrillation (AF). This study was followed by several others [14–17] concerning the mechanisms of atrial resynchronisation.

Our research on atrial resynchronisation, which commenced last year with the use of signal-averaging technique, demonstrated that BiA pacing significantly shortens atrial activation and increases its homogeneity compared to sinus rhythm, both in the external and intraatrial leads [18, 19]. In consequence, BiA pacing eliminates atrial late potentials in external and left-atrial recordings in virtually all patients while they are frequently still present in the right atrium. Preliminary results urged us to continue research on the electrophysiological effects of BiA pacing and to make an effort to find a relationship with its antiarrhythmic efficacy.

The aim of the study was to assess the homogeneity of extinction of right atrial activation and the influence of BiA pacing upon it. An additional aim was to analyse the relationship between the presence of atrial late potentials (ALP) in the right atrium and the antiarrhythmic effects of BiA pacing in long-term follow up, as this may have major clinical implications.

Methods

Patients

The study was conducted on a group of 24 patients (15 female, 9 male, mean age 68.8 ± 9.97 years) eligible for permanent BiA pacing. In seven patients (29.2%) sporadic AF, in eight patients (33.3%) recurrent AF and in nine patients (37.5%) frequent AF (according to Kingma et al. paradigm [20]) was identified. Due to the high arrhythmia burden, the ongoing medication was not modified — discontinuation of treatment could provoke AF episodes, thus impeding the measurement of pacing and sensing conditions. During the pacemaker implantation procedures five patients were treated with one drug (amiodarone or propafenone), eight were on two drugs (propafenone and sotalol//amiodarone) and eleven patients (46%) had no ongoing antiarrhythmic medication.

Procedures

1) 12-lead ECG with 100 mm/s speed 80 mm/1 mV gain; 2) The internal electrogram (IEGM) recording from right atrial appendage (RAA) and CS, simultaneously with ECG lead II; 3) SA-ECG recording from external orthogonal leads; 4) SA-IEGM recording from the right and left atrium separately. Intraatrial signals were obtained with standard bipolar pacing leads introduced during the pacemaker implantation procedure, subsequently employed for permanent pacing.

External SA-ECG recording and processing

Equipment constructed in the National Institute of Cardiology (Warsaw) was applied for signal recording and processing. It consisted of a micropotential amplifier (noise $< 1.5\ \mu$V in 0.1–300 Hz bandwidth, CMRR > 130 Db), 12-bit A/D converter, 486 CPU PC and software designed for signal-averaging and subsequent analysis of data. Standard Ag/AgCl electrodes were applied on cleansed chest skin. The P wave was derived from three bipolar orthogonal (Frank) leads. The signals (from each lead) were amplified (×1000), passed through a band-pass filter (cut-off frequency 0.1–300 Hz) and digitized by the A/D converter with a 12-beat accuracy. The signal-averaging process was triggered

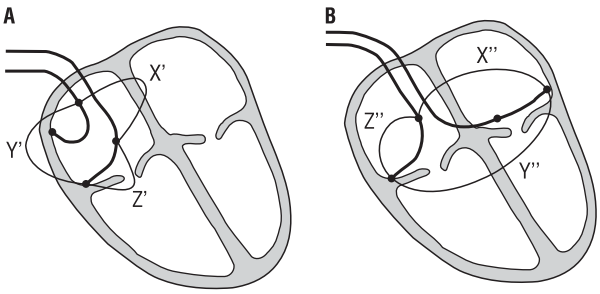

Figure 1. The scheme presents the connections of intracardiac leads to obtain right atrial (X′, Y′, Z′) and left atrial (X′′, Y′′, Z′′) signals.

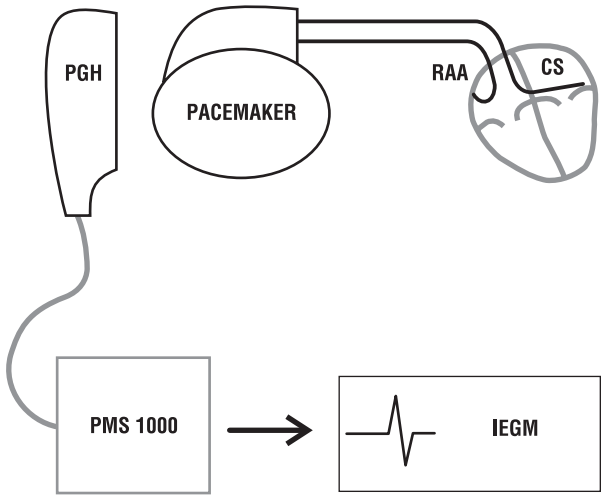

Figure 2. The internal electrogram (IEGM) was recorded from the right atrial appendage (RAA) and coronary sinus (CS) leads connected to a dual-chamber pacemaker via telemetry.

by the R wave during sinus rhythm and the pacing spike at BiA pacing. Ectopic beats, if present, were identified and rejected. Approximately 50 beats were averaged and stored on PC HD. The process was described previously [21].

High-gain SA-ECG P wave parameters time-domain analysis

The first stage was to combine filtered (Butterworth bidirectional filter) and averaged signals from three leads (X, Y and Z) to a spatial vector magnitude $(X^2 = Y^2 + Z^2)^{1/2}$. The onset and offset of P wave were defined as the points at which the atrial signal exceeded and returned to the 1.5 μV level, respectively. The following parameters were measured and calculated automatically: 1) filtered P wave duration (Pdur); 2) root mean square voltage of the final 20 ms of filtered P wave (RMS20); 3) duration of low amplitude signal < 5 μV (LAS5). Atrial late potentials were considered positive with Pdur > > 125 ms and RMS20 < 2.4 μV [21].

Intracardiac SA-IEGM recording and processing

Three bipolar pacing leads were used. A standard "J" shaped lead implanted into the right atrial appendage (RAA) and the second lead was introduced into CS. The third lead (for permanent ventricular pacing) was temporary placed in the left atrial appendage (LRA) position. The same equipment described above was employed for signal recording and processing. To obtain right and left atrial signals, intracardiac leads were attached to the micropotential amplifier via sterile connectors according to the scheme shown in Figure 1. Right atrial electrogram was recorded from three combined intraatrial leads X', Y', Z' and left atrial electrogram — from leads X'', Y'', Z''. The signal from each lead was augmented and filtered in the same mode as during external signal recording. The averaging process was triggered by the A wave during sinus rhythm and the pacing spike during BiA pacing, and the obtained parameters were analyzed in the same way as the external SA-ECG. The employed technique was described previously [18, 19, 22] (Fig. 1).

Interatrial conduction evaluation with IEGM recordings

The internal electrogram (IEGM) was recorded from the RAA and CS leads connected to a dual-chamber pacemaker via telemetry (Fig. 2), and simultaneously with lead II ECG. The following timing parameters were determined: 1) P wave duration in lead II or III in high resolution ECG (P_{II}); 2) interatrial conduction time (IACT) measured from the onset of A wave in RAA signal to the onset of A wave in CS signal; 3) total atrial activation time (TAAT) measured from the onset of P wave in lead II ECG to the end of atrial activation in CS signal.

Follow-up visits were performed monthly for six months after the implantation. History concerning arrhythmic episodes (onset, duration, termination) was taken from each patient together with data obtained from the pacemaker memory. The comparison of arrhythmia severity before the implantation and comprehensive analysis of follow-up data led to the estimation of the efficacy of BiA pacing (Table 1).

Statistical analysis

The significance of differences between all the groups was evaluated by the F variance test, and

Table 1. Utilized methods for evaluation of antiarrhythmic effectiveness of permanent biatrial pacing (BiA) during 6-month follow-up.

Severity of AF before and during BiA	Class of AF severity	How did we evaluate the effectiveness of BiA?		Class of improvement
No arrhythmia	1	Improvement by 2 classes	Excellent	1
Sporadic (monthly)	2	Improvement by 1 classes	Good	2
Frequent (weekly)	3	Improvement in the same class	Weak	3
Incessant (daily)	4	Lack of effect or permanent AF	No effect	4

AF — atrial fibrillation

specific differences between the groups were analyzed by LSD test. The results are presented as mean ± standard deviation. Statistical significance of differences between the groups was evaluated by the Student's t-test and chi-square test. Correlation was estimated using Pearson's r-test for parametric values and Spearman's rank R-test for nonparametric values. A p level of < 0.05 was accepted as statistically significant.

The study was approved by the Bioethical Committee of the Medical University of Lublin (approval KE-0254/70/2003). Informed consent was obtained from each patient.

Results

The results are presented in Table 2.

The average P wave duration in high resolution ECG was 158 ms at sinus rhythm and only 118 ms with BiA pacing. Moreover, BiA pacing significantly changed total atrial activation time (182 *vs*. 108 ms), external SA-ECG P wave duration (156 *vs*. 120 ms) and intraatrial SA-IEGM A wave duration in the right (175 *vs*. 137 ms) and left atria (175 *vs*. 137 ms). Additionally, there was a favourable modification of LAS5, which was decreased by BiA pacing in external SA-ECG (6.7 *vs*. 5.2 ms), as well as in intraatrial SA-IEGM in the right (12.9 *vs*. 9.8 ms) and left atria (9.1 *vs*. 6.2 ms). Root mean square voltages of the final 20 ms of atrial activation (RMS20) was also favourably altered in external SA-ECG (2.2 vs. 3.0 ms), and intraatrial SA-IEGM in the right (1.8 *vs*. 2.7 ms) and left atria (2.3 *vs*. 3.4 ms).

The comparison and statistical evaluation of the above data is presented in Table 3.

Biatrial pacing significantly improves most of the SA-ECG/IEGM parameters except for LAS5 values in external SA-ECG and left atrial SA-IEGM; however, a positive tendency can be observed. The switch to BiA pacing significantly shortened P wave duration (–40 ms), TAAT (–75 ms), SA-ECG P wave duration (–36 ms) and SA-IEGM A wave in the right (–38 ms) and left (–48 ms) atria. Both the quantity and significance of differences lead to a general

Table 2. ECG, IEGM, SA ECG and SA RA and LA IEGM atrial potential parameters during sinus rhythm and biatrial pacing.

Parameters	Sinus rhythm						Biatrial pacing					
	N	Aver.	Median	Min.	Max.	SD	N	Aver.	Median	Min.	Max.	SD
High resol. ECG Pdur	24	157.7	159.0	125.0	199.0	16.0	24	117.8	119.0	90.0	160.0	18.2
TAAT (IEGM)	24	181.5	182.0	144.0	225.0	22.4	24	108.0	105.0	89.0	138.0	13.7
Ext. SA ECG Pdur	24	156.2	155.4	119.3	186.8	16.8	24	120.5	121.3	90.5	153.9	13.9
Ext. SA ECG RMS20	20	2.17	1.96	1.09	3.69	0.76	24	2.95	2.78	1.62	5.32	0.86
Ext. SA ECG LAS5	24	6.68	5.50	0.00	26.70	7.48	24	5.17	4.70	0.00	12.60	3.13
Int. RA IEGM SA Adur	24	174.8	168.8	144.4	224.5	24.1	24	136.8	133.6	100.5	189.4	19.7
Int. RA IEGM SA RMS20	23	1.77	1.69	0.75	3.46	0.72	23	2.72	2.47	0.75	4.59	1.33
Int. RA IEGM SA LAS5	23	12.91	11.00	0.00	33.00	7.91	23	9.83	9.40	0.00	33.00	7.52
Int. LA IEGM SA Adur	23	175.3	169.6	138.2	237.1	26.7	24	127.8	126.9	103.6	187.8	18.4
Int. LA IEGM SA RMS20	15	2.33	1.78	0.98	4.81	1.19	23	3.43	3.35	1.28	5.75	1.24
Int. LA IEGM SA LAS5	15	9.01	9.40	0.00	18.80	6.17	23	6.21	6.30	0.00	14.10	3.81

Table 3. Interatrial conduction and high gain SA P and A wave parameters during sinus rhythm (SR) and biatrial pacing (BiA). Comparison and statistical evaluation.

Parameters	Rhythm	N	Aver.	SE	p
High resol. ECG Pdur	SR	24	157.7	15.99	0.000
	BiA	24	117.8	18.16	
TAAT (IEGM)	SR	24	181.5	22.46	0.000
	BiA	24	108.0	13.72	
Ext. leads SA Pdur	SR	24	156.2	16.84	0.000
	BiA	24	120.5	13.86	
Ext. leads RMS20	SR	20	2.17	0.76	0.000
	BiA	20	2.99	0.92	
Ext. leads LAS5	SR	24	6.68	7.48	0.520
	BiA	24	5.17	3.13	
Int RA leads SA Adur	SR	24	174.8	24.10	0.000
	BiA	24	136.8	19.76	
Int RA leads RMS20	SR	16	1.47	0.44	0.000
	BiA	16	2.60	1.44	
Int RA leads LAS5	SR	16	15.42	7.68	0.293
	BiA	16	11.29	8.19	
Int LA leads SA Adur	SR	23	175.3	26.66	0.000
	BiA	23	127.8	18.78	
Int LA leads RMS20	SR	12	2.09	0.93	0.000
	BiA	12	3.29	0.86	
Int LA leads LAS5	SR	12	9.82	5.59	0.436
	BiA	12	7.06	3.45	

assumption: that BiA pacing radically shortens atrial activation. Furthermore, BiA pacing increased the homogeneity of the extinction of atrial activation, reflected by the RMS20 values in external SA-ECG P wave (+0.8 μV), SA-IEGM A wave in the right (+1.1 μV) and left (+1.2 μV) atria. Biatrial pacing shortened the duration of low amplitude signals $< 5\,\mu$V (LAS5) in all leads; however, the change was statistically significant in the right atrial SA-IEGM only (–4.1 ms). On the grounds of the above data, it can be assumed that BiA pacing improves synchrony of atrial activation (Fig. 3, 4), which corresponds to the clinical observations on its antiarrhythmic effects in patients with interatrial conduction disturbances.

The occurrence of atrial late potential (ALP) criteria during SR and BiA pacing in conventional and intraatrial SA ECG/IEGM is presented in Table 4.

Biatrial pacing reduced ALP occurrence in external SA-ECG (79 *vs*. 8%) and in SA-IEGM from the right (96 *vs*. 46%) and left (86 *vs*. 12%) atria. Of utmost importance, ALP criteria in the right atrium are still present in virtually every second patient during BiA pacing (Fig. 5).

Table 4. Presence of atrial late potentials (ALP) criteria during sinus rhythm (SR) and biatrial pacing (BiA) in conventional and intraatrial SA ECG/IEGM.

Rhythm	ALP	Leads		
		Ext.	Int. RA	Int. LA
SR	Yes	19/24 79.2%	23/24 95.8%	19/22 86.4%
	No	5/24 20.8	1/24 4.2%	3/22 14.6%
	Lack*	0/24 0%	0/24 0%	2/24 8.3%
BiA	Yes	2/24 8.3%	11/24 45.8%	3/24 12.5%
	No	22/24 91.7%	13/24 54.2%	21/24 87.5%
	Lack*	0/24 0%	0/24 0%	0/24 0%

*Impossible for evaluation (terminal part of A wave cancelled out in V wave)

The presence of ALP criteria during BiA pacing in conventional and intraatrial SA ECG/IEGM in dependence severity of arrhythmia and antiarrhythmic medication is presented in Table 5.

The data presented in Table 5 confirm that there is no clear relationship between the arrhythmic burden or AA treatment and the presence of ALP criteria during BiA pacing, which suggests that in the study group, those two factors did not have a significant influence on the electrophysiological aspects of BiA pacing assessed with the described methods.

Last year we described the feasibility of recording signal-averaged intracardiac electrograms (SA-IEGM) separately from the right and left atria with the use of standard signal-averaging equipment designed to perform external SA-ECG analysis [18, 19, 22]. The described technique allowed us to record an additional 20 ms of atrial activation, omitted in external SA-ECG, proving its value as a diagnostic and scientific tool. Therefore, the next step was to compare the SA-ECG/IEGM parameters from external and intraatrial leads during BiA pacing. The comparison of biatrially paced atrial potential (P and A wave) duration and its RMS20 and LAS5 in recordings obtained from external and intraatrial leads is presented in Table 6.

The duration of the biatrially paced A wave was 16 ms longer in right atrium (RA) SA-IEGM in comparison to the SA-ECG P wave. The duration of atrial activation was also significantly different in SA-IEGM from the right and left atria, which seems

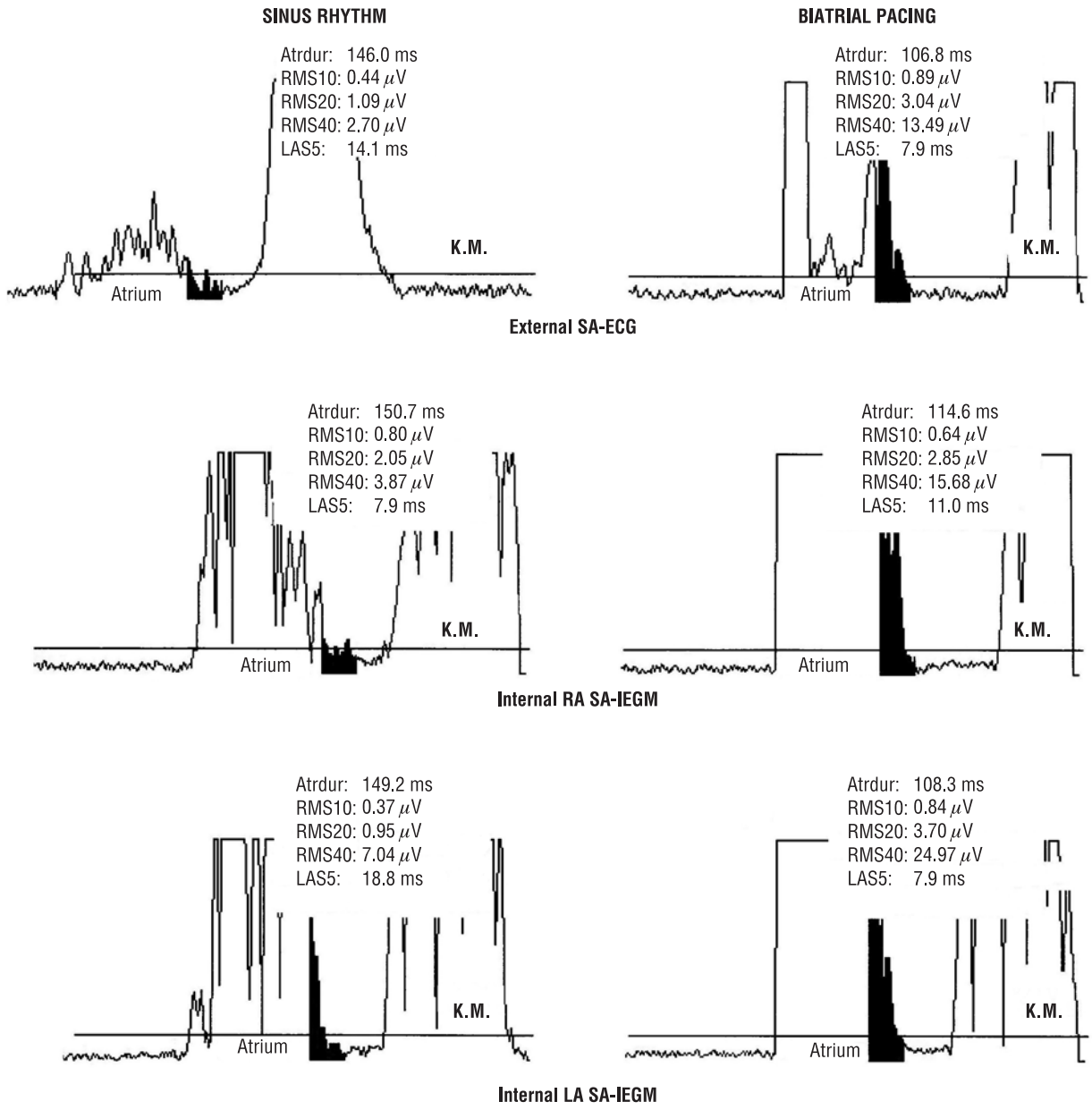

Figure 3. Signal-averaged electrogram obtained from external and intraatrial leads in the same patient during sinus rhythm and biatrial pacing reveals its beneficial effect on atrial activation synchrony.

to be a specific effect of BiA pacing (the activation of left atrium spreads from the distal CS towards posterior and anterior wall of left atrium, whereas simultaneous depolarization starting from RAA needs more time to activate the right atrium completely). On the other hand, it can also be a reflection of atrial size. The RMS20 value was significantly higher in the left atrium compared to the right atrium. This confirms less homogenous activation of RA despite the BiA pacing; moreover, it reflects the limited value of body-surface SA-ECG for atrial activation appraisal. The LAS5 values were significantly higher in the right atrium in comparison to the external P wave and to the left atrium. The described data suggests that during simultaneous pacing from RAA and CS, right atrial potential is prolonged and less homogenous than in the left atrium, which may imply that RAA is not an optimal choice for right-atrial pacing.

The assessment of mutual correlations between atrial potential (P and A wave) duration and its RMS20 and LAS5 values in recordings obtained from external and intraatrial leads during BiA pacing is presented in Table 7.

There was a strong correlation (r = 0.6–0.7) between SA-ECG P wave and SA-IEGM A wave

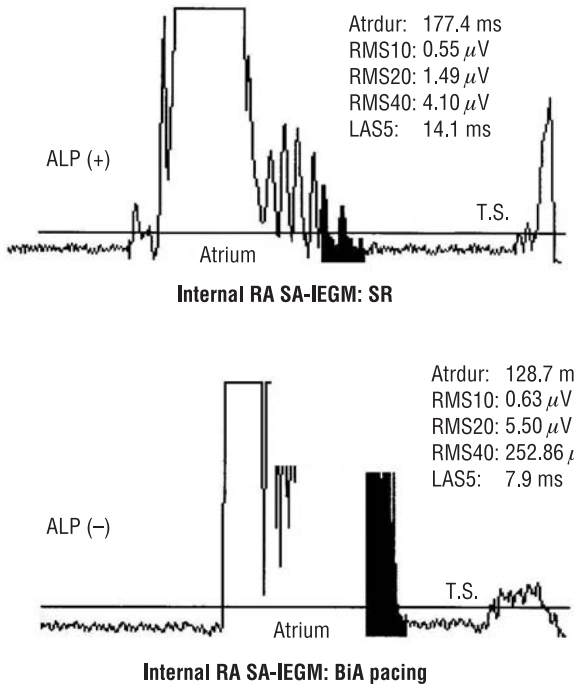

Figure 4. In this patient (T.S.), biatrial pacing results in complete extinction of atrial late potential (ALP) criteria in right-atrial leads.

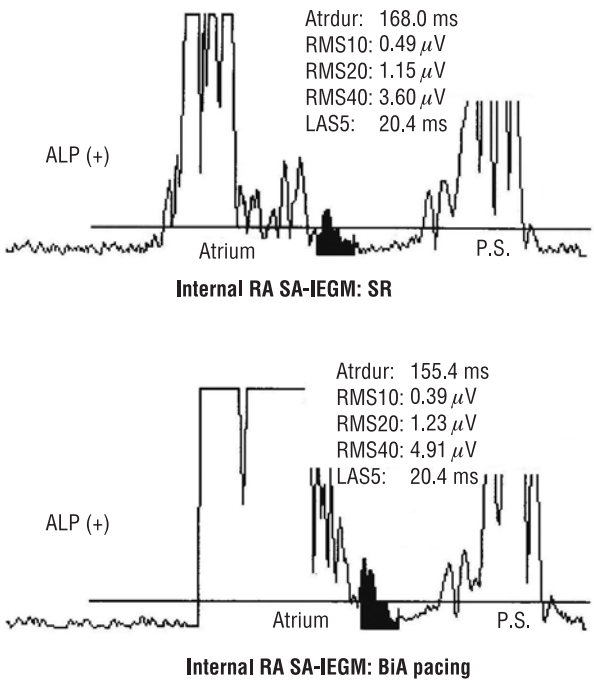

Figure 5. Persisted atrial late potential (ALP) criteria in right-atrial leads despite effective biatrial pacing.

duration in the right and left atria during BiA pacing. The strongest correlation was observed between SA-IEGM A wave duration in the right and left atria (r = 0.76). There was no correlation between the RMS20 values (except for a weak correlation between its values in the right and left atria) or the LAS5 values in external and intraatrial leads. This may suggest that the substrate responsible for atrial late potentials in unevenly distributed in both atria.

During the study we observed that BiA pacing failed to achieve its resynchronizing effect in almost 50% of patients, particularly as assessed by analysis of right-atrial SA-IEGM, disclosing regions with delayed depolarization. To assess the significance of this phenomenon, we subsequently analysed its

Table 5. Presence of atrial late potentials (ALP) criteria during biatrial pacing (BiA) in conventional and intraatrial SA ECG/IEGM in dependence severity of arrhythmia and antiarrhythmic drug utility.

Atrial fibrillation severity and ALP during BiA				**Antiarrhythmic therapy and ALP during BiA**			
Atrial fibrillation severity	**Appearance of ALP**			**No. of drugs**	**Appearance of ALP**		
	External leads	**Int. RA leads**	**Int. LA leads**		**External leads**	**Int. RA leads**	**Int. LA leads**
Sporadic (monthly)	1/7 14.3%	4/7 57.1%	1/7 14.3%	0	0/11 0%	4/11 36.6%	1/11 9.1%
Recurrent (weekly)	0/8 0.0%	3/8 37.5%	1/8 12.5%	1	01/5 20.0%	2/5 40.0%	1/5 20.0%
Frequent (daily)	1/9 11.1%	4/9 44.4%	1/9 11.1%	2	1/8 12.5%	5/8 62.5%	1/8 12.5%
All	2/24	11/24	3/24	All	2/24	11/24	3/24
χ^2	1.142	0.591	0.036	χ^2	2.072	1.360	0.374
Pearson's (p)	0.56472	0.744	0.982	Pearson's (p)	0.354	0.506	0.829

Table 6. The comparison of biatrial (BiA) paced atrial potential (P&A wave) duration and its RMS20 and LAS5 in recordings obtained from external (Frank's) and intraatrial leads.

Examined parameters	N	Leads	Aver.	SE	Analysis of variance	LSD test				
						Groups rison	Compa- diff.	Aver. of diff.	SD	p
SA ECG/IEGM	24	Ext.	120.5	2.83	F = 1648.4	1	1 *vs*. 2	–16.3	2.88	0.000
P&A wave duration	24	Int. RA	136.8	4.03	p = 0.000	2	1 *vs*. 3	–7.3	2.88	0.014
	24	Int. LA	127.8	3.75		3	2 *vs*. 3	9.0	2.88	0.003
SA ECG/IEGM	23	Ext.	2.95	0.18	F = 274.5	1	1 *vs*. 2	0.22	0.27	0.419
P&A RMS20	23	Int. RA	2.72	0.28	p = 0.000	2	1 *vs*. 3	–0.48	0.27	0.088
	23	Int. LA	3.43	0.26		3	2 *vs*. 3	–0.71	0.27	0.014
SA ECG/IEGM	23	Ext.	5.39	0.62	F = 83.6	1	1 *vs*. 2	–4.43	1.28	0.001
P&A LAS5	23	Int. RA	9.83	1.56	p = 0.000	2	1 *vs*. 3	–0.82	1.28	0.527
	23	Int. LA	6.21	0.79		3	2 *vs*. 3	3.62	1.28	0.007

association with the clinical outcome of BiA pacing in six-month follow up. After the completion of follow up, the patients were divided into two groups: with and without AF episodes during follow-up period. The comparison of external SA-ECG and intraatrial SA-IEGM parameters between both groups assessed during pacemaker implantation procedure is presented in Table 8.

There were no significant differences in SA-ECG/IEGM parameters between the two groups at sinus rhythm. On the contrary, during BiA pacing in the AF group, A wave duration in the right atrial SA-IEGM was significantly longer (148 *vs*. 128 ms) than in the arrhythmia-free group; also, the RMS20 value was significantly lower (2.0 *vs*. 3.4 μV) and the LAS5 duration was significantly longer (13.3 *vs*. 6.5 ms) in the group with subsequent arrhythmic episodes during follow up. This phenomenon proves the relationship between electrophysiological and clinical effects of BiA pacing.

Table 7. Examination of mutual correlations between high gain, SA P duration obtained from external (conventional) leads and A duration measured from RA and LA intraatrial recordings during biatrial pacing (BiA).

Parameters	N	Aver.	SD	r (X,Y)	t/p
Ext. Pdur BiA	24	120.5	13.9	0.64	3.906/0.000
Int. RA Adur BiA		136.8	19.8		
Ext. Pdur BiA	24	120.5	13.9	0.65	4.045/0.000
Int. LA Adur BiA		127.8	18.4		
Int. RA Adur BiA	24	136.8	19.8	0.76	5.581/0.000
Int. LA Adur BiA		127.8	18.4		
Ext. RMS20 BiA	23	2.947	0.878	0.29	1.368/0.185
Int. RA RMS20 BiA		2.721	1.331		
Ext. RMS20 BiA	23	2.947	0.878	0.23	1.106/0.281
Int. LA RMS20 BiA		3.429	1.237		
Int. RA RMS20 BiA	23	2.722	1.331	0.51	2.730/0.012
Int. LA RMS20 BiA		3.429	1.237		
Ext. LAS5 BiA	23	5.39	2.99	0.34	1.664/0.110
Int. RA LAS5 BiA		9.83	7.52		
Ext. LAS5 BiA	23	5.39	2.99	0.35	1.699/0.104
Int. LA LAS5 BiA		6.21	3.81		
Int. RA LAS5 BiA	23	9.83	7.52	0.40	2.005/0.058
Int. LA LAS5 BiA		6.21	3.81		

Table 8. Appearance of atrial late potentials (ALP) in SA recordings obtained from external and internal LA leads during biatrial pacing (BiA). Analysis of accordance.

ALP in ext. leads	ALP in RA int. leads			ALP in ext. leads	ALP in LA int. leads			ALP in RA int. leads	ALP in LA int. leads		
	Yes	No	All		Yes	No	All		Yes	No	All
Yes	2 8.3%	0 0%	2 8.3%	Yes	2 8.3%	0 0%	2 8.3%	Yes	3 12.5%	8 33.3%	11 45.8%
No	9 37.5%	13 54.2%	22 91.7%	No	1 4.2%	21 87.5%	22 91.7%	No	0 0%	13 54.2%	13 54.2%
All	11 45.8%	13 54.2%	24 100%	All	3 12.5%	21 87.5%	24 100%	All	3 12.5%	21 87.5%	24 100%
χ^2		2.578		χ^2		15.273		χ^2		4.051	
p		0.108		p		0.000		p		0.044	

Table 9. High gain, SA IEGM right atrial A wave time domain parameters and appearance of atrial fibrillation (AF) during 6-month follow up.

Parameters		Sinus rhythm				Biatrial pacing			
		Adur	RMS20	LAS5	ALP	Adur	RMS20	LAS5	ALP
All patients		174.77	1.77	12.91	23/24 (96%)	136.83	2.72	9.83	11/24 (46%)
Recurrence of AF during follow-up	No	172.26	1.59	13.65	12/23 (52%)	128.14	3.36	6.54	4/11 (36%)
	Yes	177.73	2.00	11.95	11/23 (48%)	147.10	2.02	13.42	7/11 (64%)
Statistic	t	–0.56	–1.34	0.52	0.88	–2.528	2.774	–2.364	2.59
	p	0.6	0.2	0.6	0.9	0.02	0.01	0.03	0.6

In the subsequent analysis of right-atrial SA-IEGM parameters, the patients were divides into two groups: with and without positive ALP criteria during BiA pacing. Eleven out of 24 patients fulfilled ALP criteria (SA-IEGM A wave > 125 ms and RMS20 < 2,40 μV). The analysis confirmed a possible relationship between the occurrence of ALP in RA during BiA pacing and the arrhythmia incidence in the six-month follow up since, in 85% of patients without ALP criteria, BiA pacing virtually eliminated arrhythmic episodes. In the group with positive ALP criteria this effect was less apparent (by 22%).

The incidence of ALP in RA IEGM during BiA pacing and the appearance of AF during six-month follow up is presented in Table 9. The severity of arrhythmia during the follow-up period was assessed by time to the first episode, number of hospitalizations due to AF, and frequency of recurrence according to Kingma et al. [20].

The time to the first AF recurrence after implantation was shorter (by 1/3) and the Kingma's class higher (2.1 *vs*. 1.5) in the subgroup with persisted ALP criteria in RA despite BiA pacing. The number of hospital admissions did not differ between the two subgroups, which can be explained by spontaneous pharmacological termination of arrhythmia at home (*pill in the pocket* strategy) in both subgroups. The clinical effectiveness of BiA pacing was higher in the subgroup without ALP criteria (2.2 *vs*. 1.5). The statistical tests, however, did not have enough power to reach significant levels in the studied group (Table 10).

Discussion

The literature confirms that BiA pacing leads to reduction or even elimination of arrhythmic episodes in most patients with recurrent, drug-resistant AF [1, 6–8, 10–12]. The mechanism of BiA pacing is explained by the restoration of the natural synchrony of atrial excitation during sinus rhythm, BiA pacing and premature beats of both right and left atrial origin. In the spotlight of contemporary electrophysiological knowledge concerning the effects of CS pacing [13–27, 23–28], as well as the crucial role of

Table 10. Presence of atrial late potentials (ALP) in SA RA IEGM during biatrial pacing (BiA) and appearance of atrial fibrillation (AF) during 6-month of follow up.

AF severity during 6 months of BiA		Time to first recurrence of AF (days)*	Number of hospital admissions due to AF*	Frequency of recurrence (Kingma's class)**	Clinical effectiveness of BiA**
ALP in RAA during BiA	No	48.75	0.92	1.54	1.54
	Yes	31.29	0.82	2.09	2.18
Statistic	t/Z	–0.459	–0.139	0.25	1.08
	p	0.67	0.89	0.80	0.28
All patients	Mean	37.64	0.875	1.79	1.83

*Student's *t* test, **Mann-Whitney's *U* test; modes of evaluation were presented in Table 1

local conduction disturbances in the triangle of Koch region for initiation and perpetuation of atrial arrhythmias [14, 23–29], the described explanation of BiA pacing mechanism is rather an oversimplification.

In 1996 Papageorgiou et al. [14, 23] demonstrated that CS pacing prevents AF induction by HRA extrastimuli; the presence of preferential conduction pathways between the atria leads to earlier activation of the triangle of Koch by CS pacing, compared to pacing from HRA [27]. That is how the unfavourable consequences of anisotropic conduction from HRA to (and within) the triangle of Koch can be eliminated. At the same time, the group of Saksena demonstrated similar electrophysiological effects of CS ostium pacing; they described 56% efficacy of dual-site RA pacing in abolishing induction of AF by HRA extrastimuli, while during HRA pacing alone the same extrastimuli induced AF inconsistently [16, 17]. As mentioned before, Yu et al. [13] proved that premature extrastimuli from HRA produced a markedly prolonged atrial potential recorded from the infero-posterior interatrial septum during HRA pacing. Simultaneous pacing from HRA and distal CS reduced the potential duration, preventing AF initiation in a high number of patients; Yu emphasizes that the antiarrhythmic effect of BiA pacing is based on the elimination of delayed conduction in the infero-posterior interatrial septum, caused commonly by atrial extrasystolic beats [13]. Wood et al. [24] demonstrated (on isolated rabbit hearts) that left atrial and BiA pacing decrease the dispersion of atrial repolarization. However, Giligan et al. [26] did not confirmed this observation in humans; interestingly, in his material, the refractory period was shorter in the left atrium in the control group, whereas in patients with recurrent atrial arrhythmias the opposite tendency was observed. He believes, however, that BiA pacing does not influence atrial repolarization time, but that it considerably shortens global atrial depolarisation [26]. The remarkable results published by Ogawa et al. [15] confirmed the facilitated induction by RAA premature extrastimulus during RAA pacing (12/20) in comparison to BiA (7/20) and CS (7/20) pacing. The effective atrial refractory period was longer in the right atrium. By adding the conduction time with the effective refractory period, the authors assessed a parameter called atrial recovery time (ART). The difference between ART measured in both atria was lower during CS pacing and BiA pacing and increased during RAA pacing. Biatrial and left atrial pacing, due to permanent preexcitation of the infero-posterior region, delayed conduction of RAA originated extrasystolic beats to this area (including the His bundle region), thus prolonging the coupling interval [15]. The study, however, was conducted on patients without organic heart disease or conduction disturbances within the atria, and the premature stimuli were delivered from RAA only, even though pulmonary veins are one of the most common locations of autonomic foci [30]. In 1999 Orr et al. [31] applied the signal-averaged ECG technique to the assessment of electrophysiological effects of atrial resynchronization. In ten patients with BiA pacing system, they demonstrated that BiA pacing shortens P wave duration in SA-ECG with no effect on its energy (P30: 25 *vs.* 22; P60: 3.8 *vs.* 3.3 $\mu V^2/s$). Moreover, BiA pacing reduced paroxysmal atrial fibrillation (PAF) episodes (151 *vs.* 28) in three-months follow up. There was no correlation ($r = 0.25$) between the reduction of P wave duration and arrhythmia suppression. Yu considers there is no connection between the antiarrhythmic effect and the reduction of conduction disturbances within the atrial, suggesting another mechanism [31]. The P wave signal-averaged time domain parameters during different atrial pacing modes (including BiA pacing) in patients with atrial arrhythmias was also assessed by the authors [21]; we demonstrated the significant influence of pacing mode upon

SA-ECG P wave duration. The changes in parameters reflecting homogeneity of extinction of atrial potential (RMS20 and LAS5), although noticeable, were not significant [21].

The presented literature illustrates the relatively complex, ambiguous influence of resynchronizing pacing on the inducibility and perpetuation of atrial arrhythmias. The quoted authors focused on the electrophysiological effects of supplementary pacing from CS [13–15, 23–28] or its ostium [16, 17], whereas the right atrium was paced from the HRA region in electrophysiological studies [13–15, 23–27] or from RAA during clinical trials [1, 6–8, 10–12, 31]. The optimal location of the pacing lead in the upper right atrium was taken into limited consideration [28, 32]. Three years ago we suggested that the delayed (by 30–40 ms compared to HRA) detection of atrial activation from RAA postpones the left atrial pacing, reducing the efficacy of resynchronisation [33, 34]. In the spotlight of our present study, it appears that the pacing rather than the sensing site plays the key role, which brings the necessity of further investigations.

In the presented study we demonstrated that BiA pacing radically shortens atrial activation, reflected by the reduction of P wave duration in ECG, total atrial activation time, P duration in external SA-ECG and A wave duration in SA-IEGM from the right and left atria. This pacing mode also increases the homogeneity of the extinction of atrial potential, reflected by RMS20 and LAS5 parameters both in external and intraatrial leads. The outcome was the reduction of ALP criteria occurrence (compared to SR) in external (79 *vs*. 8%) and left-atrial (86 *vs*. 12%) leads. The principal observation is the persistence of ALP criteria in RA in almost every second patient (96 *vs*. 46%) during BiA pacing. The detection of less homogenous activation in the right atrium, despite BiA pacing, should have some practical value as it suggests that RAA is not the optimal pacing site in the right atrium.

In the spotlight of the demonstrated data, standard BiA pacing (from RAA and distal CS) does not restore the synchrony of activation in the right atrium where regions of delayed activation can be still present. The discovered phenomenon can explain the lack of antiarrhythmic efficacy of BiA pacing in many patients. This observation corresponds with data published by Yu et al. [13].

In the follow up, it was demonstrated that in patients with recurrences of arrhythmia in the right-atrial SA-IEGM, the duration of the A wave was longer, RSM20 lower and LAS5 higher, despite BiA pacing. In the 85% of patients without ALP criteria, BiA pacing virtually eliminated arrhythmic episodes; in the group with positive ALP criteria this effect was less apparent (by 22%), and the time to the first PAF episode was shorter. The clinical effectiveness of BiA pacing was higher in the subgroup without ALP criteria (2.2 *vs*. 1.5), which verifies the association between the electrophysiological effects of this pacing mode and the clinical outcome; incomplete resynchronisation can explain the ineffectiveness of arrhythmia suppression in some patients. The presented data advocate the search for another site for the right-atrial lead in BiA pacing systems (region of Bachmann's bundle or sinus node?) or potential utility of trifocal pacing (RAA + Koch's triangle + CS), particularly in patients with severe conduction disturbances within the atria, with recurrent, drug-resistant AF, in whom BiA pacing fails to restore the synchrony of atrial activation.

Conclusions

1. Biatrial pacing radically shortens atrial potential, reflected by reduction of P wave duration in ECG, total atrial activation time, P duration in external SA-ECG and A wave duration in SA-IEGM from the right and left atria. BiA pacing also increases the homogeneity of the extinction of atrial potential, reflected by RMS20 and LAS5 parameters both in external and intraatrial leads.
2. Biatrial pacing reduces the occurrence of ALP criteria (compared to SR) in external (79 *vs*. 8%) and left-atrial (86 *vs*. 12%) leads, although fails to eliminate ALP criteria in RA in almost every second patient (96 *vs*. 46%).
3. Less homogenous extinction of activation in the right atrium, despite BiA pacing, suggests that RAA is not the optimal pacing site in the right atrium; it could explain the lack of antiarrhythmic efficacy of this pacing mode in some patients.
4. There is an association between the electrophysiological effects and the clinical outcome of BiA pacing, since the ratio of acceptable antiarrhythmic effects is less (by 20%) in the subgroup of patients with persisted ALP criteria.
5. An alternative site for the right-atrial lead in BiA pacing systems (region of Bachmann's bundle or sinus node?) or potential utility of trifocal pacing (RAA + Koch's triangle + CS) should be considered; particularly in patients with severe conduction disturbances within the atria, with recurrent, drug-resistant AF, in whom BiA pacing fails to restore the synchrony of atrial activation.

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