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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Clinical, echocardiographic, and pacing parameters affecting atrial fibrillation burden in patients with tachycardia-bradycardia syndrome

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Abstract

Background: The influence of various factors on atrial fibrillation (AF) development in the population of tachycardia-bradycardia syndrome (TBS) patients remains unclear. There are no data on the impact of different right ventricular pacing percentage (RVp%) profiles.

Aim: The purpose of the study was to evaluate the relationship between the AF burden (AFB) and various clinical, echocardiographic, and pacing parameters in TBS patients.

Methods: We performed a prospective, one-year registry of TBS patients with documented AF referred for dual-chamber pacemaker (DDD) implantation.

Results: The data of 65 patients were analysed. The median 12-month RVp% and AFB was 9.4% and 1.0%, respectively. During the follow-up 14% of patients had no AF ($p = 0.003$), and the withdrawal of AF symptoms was observed in 49% of patients ($p < 0.0001$). The AFB was related to the left atrium diameter ($r = 0.31$, $p = 0.02$), especially in the subjects with left ventricular ejection fraction < 60% ($r = 0.44$, $p = 0.04$). Based on the relative change of RVp%, three groups of various RVp% profile were established: stable, decreasing, and increasing RVp%. In the stable RVp% group ($n = 21$) there was a quadratic correlation between the 12-month RVp% and AFB ($r = 0.71$, $p = 0.0003$). In the stable RVp% > 20% subgroup there was a significant increase of AFB in comparison to the RVp% ≤ 20% subgroup (ΔAFB 1.8% vs. 0.0%, $p = 0.03$, respectively). In the increasing RVp% group ($n = 28$) the AFB increased whereas in the decreasing RVp% ($n = 16$) it remained stable (ΔAFB 0.67% vs. 0.0%, $p = 0.034$, respectively).

Conclusions: DDD implantation in TBS patients is related to a significant reduction in AF symptoms, and left atrial diameter correlates with cumulative AFB in the mid-term observation. Stable RVp% > 20% is associated with AF progression whereas lower stable RVp% may stabilise AF development. Increasing RVp% may be associated with the AFB increase in comparison to the decreasing RVp% subgroup in which AFB remains stable.

Key words: tachycardia-bradycardia syndrome, right ventricular pacing percentage, atrial fibrillation burden, dual chamber pacemaker, left ventricular ejection fraction

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INTRODUCTION

The influence of multiple clinical, echocardiographic and pacing factors, including the right ventricular pacing percentage (RVp%), on the development of atrial fibrillation (AF) and heart failure progression has been examined for decades. However, the population of patients suffering from tachycardia-bradycardia syndrome (TBS), i.e. a specific form of sinus node disease coexisting with supraventricular tachycardias, is often neglected, underscored, or not distinguished in those studies, which were predominantly performed in the times of different pacing paradigms [1, 2].

Moreover, the methods of AF progression assessment used in previous studies, especially by counting the number of symptomatic AF episodes, seems questionable in light of cur-

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rent medical knowledge because it has been proven that they do not reflect properly the real AF advancement compared with the continuous methods of rhythm assessment [3–5].

As a result, it still remains unclear what factors are associated with AF occurrence in patients with TBS and implanted DDD pacemakers characterised by a low percentage of right ventricular paced beats.

The aim of this study was to examine prospectively the influence of dual-chamber pacemaker implantation on the occurrence of AF, the correlations between the AF progression measured continuously as an AF burden (AFB) and different echocardiographic and pacing parameters with the special inclusion of RVp% in a group of patients with TBS.

METHODS

The study was conducted according to the declaration of Helsinki, and its protocol was approved by a local institutional Ethics Committee. Before entering the study, all patients provided informed consent.

We performed a prospective registry of 82 consecutive patients with symptomatic TBS, who had been qualified for dual chamber pacemaker implantation in our Department. We included patients if they were 35–80 years old, could provide written informed consent, and had at least two symptomatic paroxysms of AF in the 12-month period prior to the pacemaker implantation. At least one of the paroxysms had to be documented in medical records. Patients were not included if their clinical status was unstable or they had concomitant diseases that could adversely affect their prognosis or the progression of the arrhythmia. The inclusion and exclusion criteria are listed in Table 1.

Table 1. The study inclusion and exclusion criteria

Inclusion criteria
Tachycardia-bradycardia syndrome
Indication for dual chamber pacemaker
Age: 35–80 years
At least two symptomatic atrial fibrillation paroxysms during the 12 months preceding inclusion (with at least one documented)
Written informed consent
Exclusion criteria
Less than six months since myocardial infarction/acute coronary syndrome
Heart failure — New York Heart Association III or IV
Valvular heart disease after surgical treatment
Thyroid dysfunction
Chronic obstructive pulmonary disease
Other inflammatory diseases
Cancer
Chronic use of steroids
Less than three months since major surgery
Pulmonary vein isolation in anamnesis
Simultaneous participation in another clinical trial

Qualification for device implantation

Qualifications for device implantation were performed collectively by a team of experienced electrophysiologists based on the previous medical history and documentation of each patient, according to current guidelines on pacemaker device implantation. The preferred site of right ventricular electrode was mid-low interventricular septum or apical if the septal position was difficult to achieve.

Control visits and follow-up

The patients' follow-up lasted one year and consisted of four visits performed a day, eight weeks, six months, and 12 months after the implantation. On each visit, a regular control of the device parameters was performed and the data concerning RVp%, percentage of atrial paced beats (Ap%), and AFB were taken. The mentioned parameters were expressed as cumulative values, i.e. total RVp%, Ap%, and AFB beginning from the pacemaker implantation to the follow-up day.

According to current guidelines, the devices were programmed in such a way so as to minimise right ventricular pacing by atrio-ventricular (AV) prolongation, avoidance of rate response function, and introduction of the manufacturer's specific algorithms to minimise RVp% — if relevant. The basic mode of programming was a DDD mode with a base rate of 50 bpm and AV delay of 250 ms. The rate response function (DDDR mode) was omitted. On each visit the patient was questioned about the number of symptomatic paroxysms of AF and current pharmacotherapy. Moreover, each participant underwent echocardiographic examination performed on the day following the device implantation and on the 12-month visit. During echocardiographic examination an assessment of the left atrium diameter (LAd), left ventricular end-systolic, and end-diastolic diameter (LVESd and LVEDd) measured from a parasternal long-axis view as well as the left ventricular ejection fraction (LVEF) was performed using the Simpson method.

Atrial fibrillation burden

Atrial fibrillation burden was defined as a percentage of follow-up time spent in atrial tachyarrhythmia (atrial fibrillation/atrial flutter/atrial tachycardia) with a P-wave rate of 200 bpm or faster, which gave an adequate pacemaker response, i.e. resulting in mode-switching of a device to DDI stimulation pattern. If the default settings of AF diagnosis in the implanted pacemakers had been different to the one assumed in our study, the devices were reprogrammed so as to meet the study AF recognition criteria. Similarly to the basic DDD mode, we omitted rate response function during the "mode switch" DDI mode.

Due to the possibility of overestimation of AFB by improper mode switching of the devices, we carefully revised

all of the intracardiac electrocardiograms that were available during the follow-up and refused "false" recordings.

During follow-up we analysed a change in AFB (delta AFB, ΔAFB) based on the results of cumulative AFB on the eight-week and 12-month visits. We recognised AFB as increasing or decreasing if the absolute change in AFB exceeded 1% or –1%, respectively. AFB was termed stable if the absolute difference between the values obtained on the eight-week and 12-month visit was less than 1%.

Statistical analysis

Descriptive statistics for qualitative variables were reported as frequencies and percentages and compared using the χ^2 test or Fisher's exact test.

Quantitative data were expressed as mean ± standard deviation if normally distributed or median and interquartile range if not normally distributed. Continuous variables were tested for normal distribution with the use of the Kolmogorow-Smirnow test. Means (median) between the two categories were compared by unpaired Student's t-test or the Mann-Whitney U test, as appropriate. Differences between the three groups were assessed by a one-way analysis of variance (with the Tukey's multiple range post-hoc tests) or the Kruskall-Wallis analysis of variance (ANOVA). The correlation analyses were done by the Pearson or the Spearman's test. Univariate regression analysis was performed to assess squared relationships between variables.

All analyses were performed using SAS software version 9.2 (SAS, Cary, NC, USA). Two-sided p values < 0.05 were considered to be statistically significant.

RESULTS

Study population

The analysed registry consisted of 82 consecutive patients (65% females) with TBS, who met the inclusion and exclusion criteria and had been qualified for dual-chamber pacemaker implantation in our Department from February 2010 to January 2013. The mean patients' age was 72 ± 6.8 years. The mean follow-up time was 368 ± 63 days. The patients received pacemakers from various manufacturers, including: Victory XL (St Jude Medical, Sylmar, CA, USA), Talos DR (Biotronik, Berlin, Germany), and E60A and G70 (Vitatron, Maastricht, Netherlands). The choice for the pacemaker was restricted to current availability of the products and was made at the implanting physician's discretion. The analysed group was characterised by a low median RVp% of 9.4% (Q1–Q3: 2.2–38.5) and low AFB (median: 1.0% [0.0–5.1]). The cumulative Ap% was 36.8 ± 27.6%.

The final analysis was performed on a group of 65 patients, having excluded those with incomplete data necessary for the analysis (seven patients), patients with serious AV conduction abnormalities resulting in cumulative RVp% exceeding 90% (seven patients), and patients with persistent AF that lasted throughout the whole follow-up period (three patients). The baseline characteristics of the studied population are shown in Table 2.

The incidence of AF and its symptoms during the follow-up period

During the 12-month follow-up period nine (13.8%) patients remained free from AF paroxysms, which was defined as no AFB at all (i.e. no time spent in the auto mode switch). There was a significant reduction of the AF incidence in comparison to the time before the pacemaker implantation (86.2% vs. 100%; $p = 0.003$). The reduction of the symptomatic AF paroxysm was greater, i.e. 30 (49.2%) patients had no symptoms at all during the follow-up ($p < 0.0001$).

Echocardiographic indices and AFB

In the entire group there was a linear correlation between the AFB and LAd both measured at a 12-month visit ($r = 0.31$, $p = 0.02$; Fig. 1). Moreover, in patients who had AF paroxysms during the whole follow-up period the LAd increased significantly more often than in those who did not have any paroxysms of AF at the beginning of observation (AFB at the eight-week follow-up was 0) and remained practically free from AF during the whole follow-up (AFB at the 12-month follow-up < 1%), i.e. 35% vs. 8.7%, ($p = 0.03$). In patients with reduced LVEF (that is LVEF < 60%) the correlation became stronger ($r = 0.44$, $p = 0.04$; Fig. 1).

These correlations between the AFB and LAd were not related to the RVp%. Both in the whole group and in patients with reduced LVEF we found no correlations between the RVp% and the LAd measured at the 12-month follow up ($r = 0.01$, $p = 0.92$ and $r = –0.04$, $p = 0.84$, respectively). Similarly, there were no correlations of the AFB or LAd with the left ventricular diameter (i.e.: LVESd and LVEDd) and LVEF.

Right ventricular pacing, its profiles, and AFB

Overall. In the entire group we found no linear correlations of cumulative AFB with either RVp% or Ap% (Fig. 2). However, while examining the subgroups of patients according to RVp% change in time, the influence of RVp% and its profile became significant.

Different profiles of the right ventricular pacing percentage

Based on a relative difference in RVp% between the eight-week visit and 12-month visit, the examined population was divided into three categories with different RVp% profiles:

- if the RVp% increased more than 25% of the value measured at the eight-week visit, the patient was assigned to the group of **increasing RVp% (I-RVp%)**;
- the group of **decreasing RVp% (D-RVp%)** consisted of patients in whom RVp% decreased more than 25% from the eight-week to 12-month follow-up visit;

Table 2. Baseline characteristics of the studied population and its right ventricular pacing percentage profile subgroups

Parameter	Overall (n = 65)	D-RVp% group (n = 16)	S-RVp% group (n = 21)	I-RVp% group (n = 28)	P
Age [years]	71.5 ± 6.8	72.5 ± 5.8	69.8 ± 6.1	72.4 ± 7.8	0.4
Females	44/65 (67.7%)	9/16 (56.2%)	17/21 (80.9%)	18/28 (64.3%)	0.3
BMI [kg/m^2]	28.4 ± 4.0	26.8±2.7	27.9 ± 4.4	30.1 ± 4.0	0.2
CHA_2DS_2-VASc score	3.21 ± 1.14	3.31 ± 1.14	3.32 ± 1.44	3.86 ± 1.35	0.3
Comorbidities:					
CAD	19 (29.3%)	3 (18.7%)	10 (47.6%)	6 (21.4%)	0.08
Myocardial infarction	9 (13.9%)	0 (0%)	7 (33.3%)	2 (7.1%)	0.007*
Previous PTCA	7 (11.0%)	0 (0%)	4 (19.1%)	3 (10.7%)	0.2
Previous CABG	1 (1.5%)	0 (0%)	1 (4.8%)	0 (0%)	0.6
Arterial hypertension	57 (87.7%)	13 (81.2%)	20 (95.2%)	24 (85.7%)	0.3
Diabetes mellitus	12 (18.5%)	2 (12.5%)	4 (19.0%)	6 (21.4%)	0.9
Smoking	11/41 (26.8%)	2/13 (15.4%)	5/13 (38.5%)	4/14 (26.7%)	0.6
Hyperlipidaemia	38/64 (59.4%)	7 (46.7%)	15 (71.4%)	16 (57.1%)	0.3
Previous stroke	3 (4.6%)	1 (6.2%)	0 (0%)	2 (7.1%)	0.6
Arteriosclerosis obliterans	3 (4.8%)	0 (0%)	2 (9.5%)	1 (3.8%)	0.6
IVCD	8 (12.5%)	3 (18.8%)	3 (14.3%)	2 (7.4%)	0.5
Pharmacological treatment:					
Beta-blockers	46/56 (82.1%)	8/12 (66.7%)	16/20 (80%)	22/24 (91.7%)	0.2
Calcium blockers	21/57 (36.8%)	5/12 (41.7%)	8/20 (40.0%)	8/25 (32%)	0.8
Digitalis	1/57 (1.7%)	0/12 (0%)	1/20 (5%)	0/25 (0%)	0.6
Antiarrhythmics	25/57 (43.9%)	7/12 (58.3%)	8/20 (40%)	10/25 (40%)	0.5
Statins	31/57 (54.4%)	4/12 (33.3%)	13/20 (65%)	14/25 (56%)	0.2
Fibrates	4/56 (7.1%)	1/12 (8.3%)	2/20 (10%)	1/24 (4.2%)	0.8
Diuretics	26/57 (45.6%)	5/12 (41.7%)	9/20 (45%)	12/25 (48%)	0.9
Aldosterone antagonists	9/57 (15.8%)	3/12 (25.0%)	3/20 (15%)	3/25 (12%)	0.6
ACE-I	29/57 (50.9%)	7/12 (21.1%)	11/20 (55%)	11/25 (44%)	0.6
Anticoagulants	36/57 (63.2%)	7/12 (58.3%)	14/20 (70%)	15/25 (58.8%)	0.9
Acetylsalicylic acid	17/57 (29.8%)	1/12 (8.3%)	7/20 (35%)	9/25 (36.0%)	0.2
Clopidogrel	3/57 (5.3%)	0/12 (0.0%)	1/20 (5%)	2/25 (8.0%)	1.0
Anti-diabetics	8/57 (14.0%)	1/12 (8.3%)	2/20 (10%)	5/25 (20.0%)	0.7

*A p value of < 0.05 is considered statistically significant. Data are presented as mean ± standard deviation or median (95% confidence interval) or number/number of observations (percentage) — as appropriate; ACE-I — angiotensin converting enzyme inhibitors; BMI — body mass index; CABG — coronary artery by-pass grafting; CAD — coronary artery disease; D-RVp% — decreasing right ventricular pacing percentage; I-RVp% — increasing right ventricular pacing percentage; IVCD — interventricular conduction delay (defined as a native QRS complex duration > 120 ms); PTCA — percutaneous transluminal coronary angioplasty; S-RVp% — stable right ventricular pacing percentage

— if a relative change in RVp% during follow-up did not exceed 25% the RVp% profile was recognised as **stable (S-RVp% group)**.

Based on the value of RVp% on the 12-month visit, the S-RVp% was divided into two subgroups:

1 the patients with **stable high RVp%** if RVp% exceeded 20% **(S-RVp% > 20%)**;
2 the patients with **stable low RVp%** if RVp% was ≤ 20% **(S-RVp% ≤ 20%)**.

There were no differences in the baseline characteristics between the analysed groups except for the history of previous myocardial infarction, which was most prevalent in the stable RVp% group. However, there were statistically significant differences in the baseline (i.e. the eight-week) RVp% between the increasing RVp% and the decreasing RVp% groups (14.7% vs. 1.9%, p = 0.007). The groups did not differ as to the pharmacological treatment, including the use of the typical antiarrhythmic drugs, beta-blockers, or anticoagulants (Table 2). We did not observe any differences in the prevalence of interventricular conduction disturbances between the analysed groups, which generally was a rare finding.

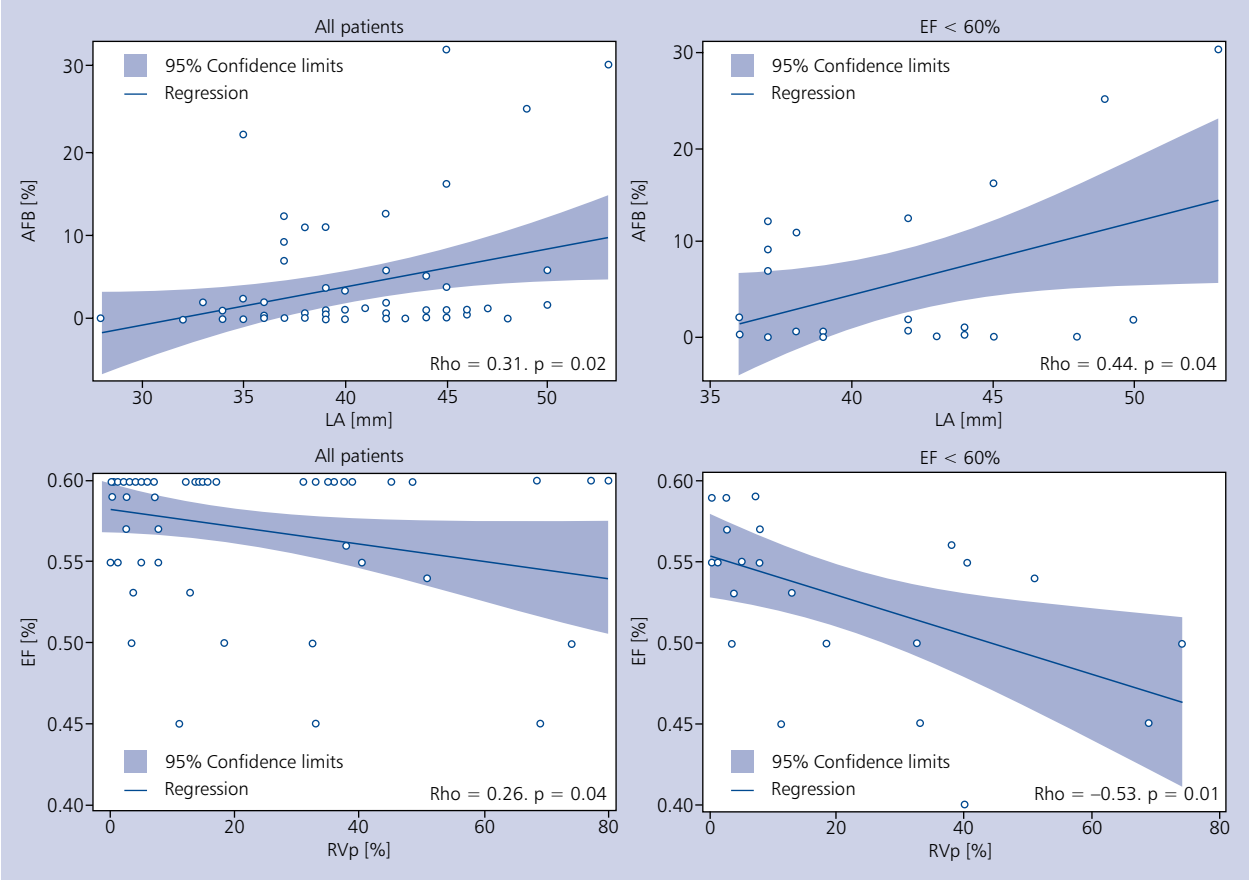


Figure 1. Plots showing correlations between the left atrium diameter (LA) and the atrial fibrillation burden (AFB; **top**) and between the right ventricular paced beats percentage (RVp%) and the ejection fraction (EF; **bottom**) measured at12 months. The **left side** shows correlations in the whole group and the **right side** — in patients with EF less than 60%; p — probability

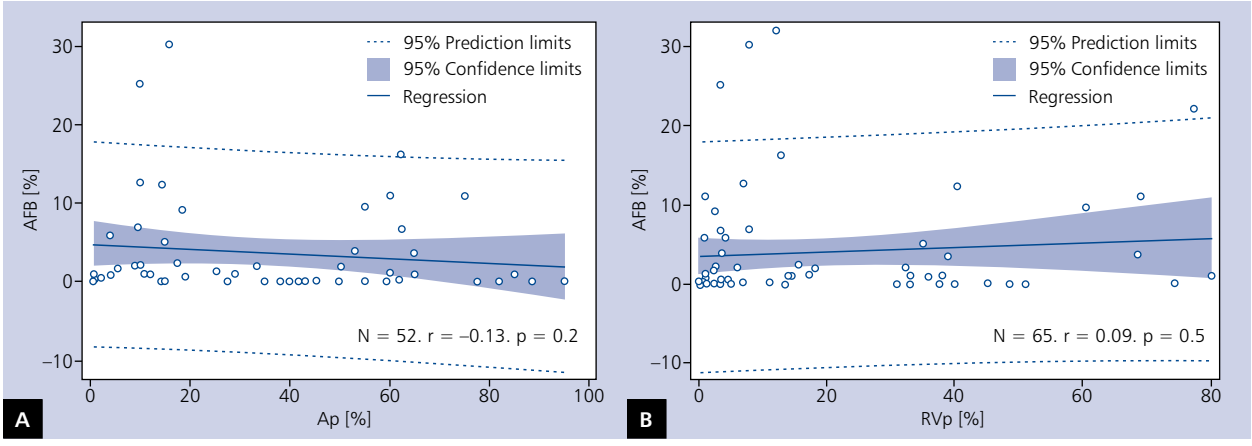


Figure 2. Plots showing lack of significant correlations between cumulative 12-month atrial fibrillation burden (AFB) and cumulative 12-month atrial paced beats percentage (Ap%, **A**) and cumulative 12-month right ventricular paced beats percentage (RVp%; **B**); N — number of observations; p — probability; r — "rho" correlation coefficient

The groups with various RVp% profiles did not differ between each other on other echocardiographic measurements except for a statistically significant difference in the LVEF at 12 months. Surprisingly, during the follow-up the LVEF decreased slightly but statistically significantly in the D-RVp% ($\Delta EF = -2 \pm 4$, $p = 0.03$), whereas in the remaining I-RVp%

and S-RVp% it was stable, which led to that difference between the LVEF at the 12-month time point.

The increasing versus the decreasing right ventricular pacing groups (I-RVp% vs. D-RVp%)

In the D-RVp% group (n = 16) there was a tendency for stabilisation of AFB during the follow-up period compared with patients in whom RVp% increased (n = 28). In the D-RVp% group the AFB increased in as few as two (12.5%) patients and remained stable or decreased in the remaining 87.5%, whereas in the I-RVp% the AFB increased in 11 (39%) subjects and decreased in a single patient (7%) (Fig. 3). These differences were not significant. However, the ΔAFB between the D-RVp% and I-RVp% groups differed significantly (0.0% vs. 0.67%, p < 0.04, respectively).

The stable right ventricular pacing group (S-RVp%)

In the S-RVp% group (n = 21) we found a strong correlation between the cumulative RVp% and AFB, both measured in the 12-month observation (r = 0.71, p = 0.0003). The correlation was quadratic. The plot resembled a J curve with the turning point close to RVp% = 20%: when RVp% increased and its value exceeded 20% the AFB increased as well; when the RVp% was less than 20% the AFB increased with the decrease of RVp% (Fig. 4).

In the subgroup with stable-low RVp% (S-RVp% ≤ 20%), AFB tended to remain unaltered during the follow-up period in the majority of patients (85%) whereas in the stable-high subgroup (S-RVp% > 20%) it was stable in only 37.5% and in the remaining 62.5% AFB increased (p = 0.01; Fig. 5). The overall change in AFB during the follow-up (ΔAFB) differed significantly between the stable-low RVp% and the stable-high RVp% groups (ΔAFB 0.0 vs. +1.8%, p < 0.03, respectively).

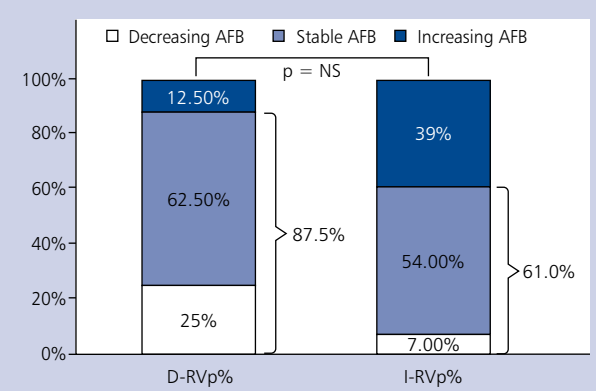
Right ventricular pacing and the LVEF

Cumulative 12-month RVp% correlated negatively with LVEF measured at the last follow-up visit (r = –0.26, p = 0.04) and in patients with reduced LVEF (i.e. LVEF < 60%) the correlation became stronger (r = –0.53, p = 0.01 for RVp%; Fig. 1).

DISCUSSION

The incidence of AF and its symptoms during the follow-up period

The withdrawal of symptoms in a significant number of patients is an expected finding. Implantation of a pacemaker enables us to uptitrate chrono- and dromotropic drugs to slow down the rhythm of the ventricles during the AF paroxysm and diminishes the symptoms reported by the patients. Surprisingly there have been no papers to support this concept and the previously published data is contradictory [6]. The withdrawal of AF, defined as no AFB at all, observed in our study is a novel finding. It may also be related with higher



	Increasing AFB	Stable or decreasing AFB	AFB [95% CI]	Delta AFB
D-RVp%	2 (12.5%)	14 (87.5%)	0.38 [0.01–4.44]	0.0 [–1.05; –0.02]
I-RVp%	11 (39%)	17 (61%)	1.0 [0.12–5.50]	+0.67 [–0.11; 2.17]
p	0.09		0.5	0.036*

Figure 3. Bar chart and table showing differences in atrial fibrillation burden (AFB) change during 12-month follow-up in decreasing right ventricular paced beats percentage (D-RVp%) and increasing right ventricular paced beats percentage (I-RVp%) subgroups; *A p value < 0.05 is considered statistically significant; delta AFB — absolute AFB change between the eight-week and the 12-month time point; p — probability

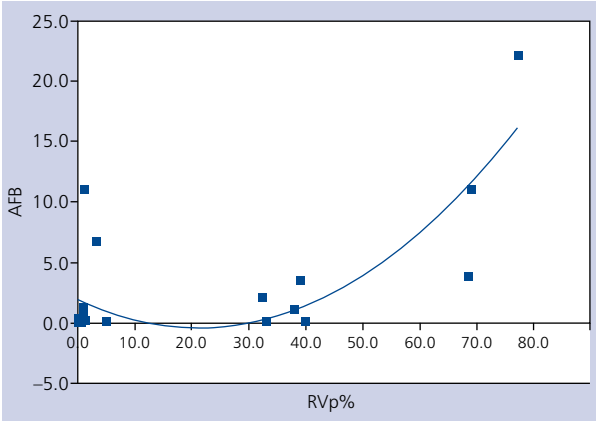
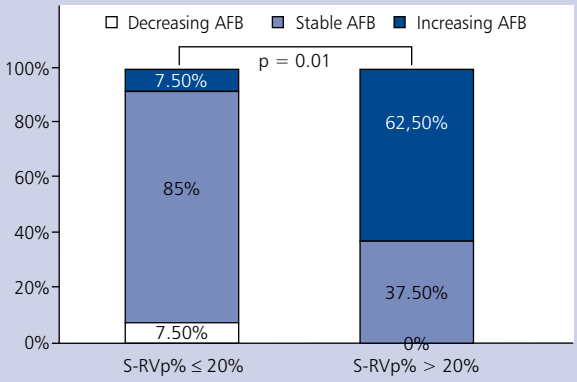


Figure 4. Correlation of AFB with cumulative RVp% in the group with stable RVp%. Square regression equation: AFB = 0.005*(RVp%)2 – 0.223*RVp%_12m12 + 1.869; R^2 = 0.596. Correlation of AFB with square RVP%: r = 0.71; p = 0.0003; AFB — cumulative 12-month atrial fibrillation burden; RVp% — cumulative 12-month right ventricular pacing percentage

drug doses but it needs further analysis, while the influences between the pharmacological treatment, cardiac pacing, and development of AF is a very complex issue. It encompasses many mechanisms that may influence each other, such us atrial pacing, restoration of proper AV conduction, the influ-



S-RVP%	Decreasing AFB	Increasing AFB	Stable AFB	AFB [95% CI]	Delta AFB
≤ 20%	1 (7.5%)	1 (7.5%)	11 (85%)	0.12 [0.0–1.00]	**0.0 [–0.18–0.00]**
> 20%	0 (0%)	5 (62.5%)	3 (37.5%)	2.71 [0.5–7.35]	**+1.8 [0.0–3.56]**
p	**0.01***			0.1	**0.03***

Figure 5. Bar chart and table showing differences in atrial fibrillation burden (AFB) change during 12-month follow-up in the stable low RVp% (S-RVp% ≤ 20%) and the stable high RVp% (S-RVp% > 20%) subgroups; *A p value of < 0.05 is considered statistically significant; delta AFB — absolute AFB change between the eight-week and the 12-month time point; p — probability; S-RVp% — stable right ventricular paced beats percentage group

ence of changes in the drugs' dosage, let alone the effect of ventricular pacing, which should be further discussed. The explanation of this observation is beyond the scope of the current study.

Echocardiographic indices and AFB

A correlation between the LAd and AFB observed in the present study is in line with previous reports that found that the LA enlargement and its extent are related to the advancement of AF [7, 8]. However, to the best of our knowledge, our study proves for the first time the direct correlation between the LAd and AFB in TBS patients.

It has been hypothesised that LA enlargement could link the detrimental cumulative effect of RVp% with AF progression. As a result of pathological ventricular contraction due to excessive cumulative RVp% the LA would enlarge, and this could lead to AF progression [3, 9]. Our study does not support this view, where we have not found any significant correlation between LA and RVp%. The same holds true for such associations in the whole study population and in any of the RVp% profile subgroups. These findings suggest that the detrimental effect of RVp% on AFB may be related to atrial pressure overload and contractility impairment rather than atrial enlargement itself [8, 10]. Atrial enlargement would be a result rather than a cause of AF progression in this case, which agrees also with available evidence [11].

Right ventricular pacing and AFB

While the harmful effect of high mid- and long-term RVp% seems unquestionable, there was a lack of evidence showing whether the amount of RVp% still affects the progression of AF in patients receiving devices programmed to minimise RVp%. Additionally, the progression of AF was measured mainly by assessing the progression of paroxysmal AF to its persistent form in previous studies, but the data showing a correlation between the RVp% and AFB were inconsistent [3, 12].

Continuous measurement of AFB seems to reflect better the AF advancement, poorly correlates with the risk of persistent AF [3–5], and seems to be more clinically relevant in terms of the risk of stroke in patients with asymptomatic paroxysmal AF. To the best of our knowledge, the presented study proves for the first time that the detrimental effect of RVp on AFB is also noticeable in the population of TBS patients with low cumulative RVp%, where the given amount of stable RVp% has a strong influence on AFB. However, stable RVp% lower than 20% does not seem to play any important role in AF progression.

The presented paper examines for the first time the influence of different RVp% profiles on AFB. Our study suggests that not only the cumulative RVp% itself influences the AF burden but also whether RVp% increases, decreases, or is stable over time.

Although we have not shown that the influence of the RVp% profile on AFB is independent of the cumulative RVp% itself, there exists indirect evidence that supports this thesis. Such a hypothesis neatly explains the fact that there is a lack of correlation between cumulative RVp% and AFB in the whole examined group and, simultaneously, strong correlation between those factors in the stable RVp% group. On the other hand, the lack of strong differences between the I-RVp% and D-RVp% groups in regard to AFB may be explained by the fact that the patients in the D-RVp% group had significantly higher initial RVp%, but at 12 months the cumulative RVp% equalised in those groups.

Finding a mechanism that would explain the link between the RVp% profile and AFB progression is challenging. Indeed, the progression of AF in patients with pacemakers is a more complex issue than only a simple correlation between the detrimental effect of cumulative RVp% on the AF incidence. It has been shown that in those patients the incidence of AF may have different patterns beginning from non-progressive, chronic progressive or relapsing-remitting paroxysmal AF [13], and the AF pattern has not been related to any of the clinical features examined. Because there are some links between the incidence of AV block and sinus node disease like the elevated risk of AV block in patients with sinus node disease [14, 15] or potentially the same genetic factors [16] and there exist such correlations between the sinus node disease and the AF [17, 18], it is possible that the RVp% changes in the presented study may reflect the advancement

of the disease affecting simultaneously both nodes and atria. Such a hypothesis may explain the correlations between the AV prolongation and AF progression observed in some large studies [12, 19]. Moreover, it neatly explains why more sophisticated algorithms of avoiding right ventricular pacing fail to show the clear benefit of further RVp% reduction in terms of AF development [15, 20, 21]. The benefit of right ventricular pacing avoidance would be compensated in those cases by the detrimental effect of a too long AV delay and greater advancement of the degenerative disease concerning the atria and both nodes in which AV prolongation would be a sign rather than a cause. The results of our study showing a negative correlation between the RVp% and AF in the subpopulation of very small stable RVp% may also be explained by the mentioned thesis.

Right ventricular pacing and the LVEF

Our finding of a linear correlation between the RVp% and LVEF supports the evidence suggesting that there is some detrimental effect of non-physiological RV pacing on the ventricular function [1, 3, 22], which becomes more apparent in subjects with already reduced LVEF. However, until now there have not been sufficient data concerning this correlation in the subgroup of patients characterised by low RVp%. The recent retrospective evidence questions the clinical relevance of such an influence, especially in subjects with preserved LVEF [23], but the assessment of cumulative RVp% in the cited paper could have been substantially different to our study.

It is difficult to explain why the only subpopulation in which the LVEF reduced was the D-RVp% group. Because of the fact that in this group the cumulative RVp% was significantly the highest at the initial eight-week observation and then it became similar to the one observed in the I-RVp% group (7.8 [2.8–15.9] vs. 9.6 [3.1–35.4], $p = 0.3$), one may speculate that, unlike AFB progression, LVEF% seem to be mainly affected by cumulative RVp% itself but not the RVp% profile.

Limitations of the study

One of the limitations of the study is a fairly small group of analysed patients, which hampers the statistical power of the results and hinders more precise, multifactorial analysis.

Additionally, the study lacks the ability to adequately assess the influence of drug usage on the results. One of the reasons is the already mentioned small number of analysed subgroups. Another is the fact that the baseline treatment was assessed on the day of discharge from hospital after the pacemaker implantation, so we have no reliable data concerning the intensification of the treatment immediately after the implantation. However, it must be stressed that during the follow-up we observed no substantial changes in the usage of antiarrhythmic drugs (mainly propafenone and rarely amiodarone). Moreover, the hypothetical protective effect of beta-blockers could have only hindered the influence of the RVp% on the AFB development, while the intensification of treatment with beta-blockers would have only lead to an increase of the RVp%.

The definition of the AF paroxysms used in our work are not the same as the current definition of atrial high-rate episodes (AHREs) [24], but at the time of the development of the protocol for our study the evidence about the clinical relevance and clear definitions of AHRE were not yet available. As we took into consideration the episodes that lasted less than 30 s our mode of assessing AFB was more sensitive. However, we revised all of the accessible intracardiac electrocardiograms and rejected the false positive ones.

Another limitation may be the possible influence of the right ventricular electrode localisation (i.e. the RV apex or RV middle/distal septum) on the study data. However, a recent study of Ng et al. [25] suggests that there are no significant differences in the long-term haemodynamic effect during pacing in those two locations.

During the study we could not discriminate the fusion and the pseudofusion beats from the true paced ones, so the real RVp% might have been overestimated. However, except for the continuous long-term electrocardiogram monitoring methods, which are expensive and affect the quality of life of the patients, there is no good method to overcome this problem, and it was not evaluated in other studies on this subject.

Finally, the analysis of the influence of different RVp% profiles on other parameters was performed *post hoc*. However, it has to be underlined that the data from the registry was collected prospectively.

CONCLUSIONS

The DDD implantation in TBS patients is related to significant reduction of AF symptoms. The LAd in these patients correlates with cumulative AFB in the mid-term observation. AFB is may not only be related to the RVp% value but its change in time. Increasing RVp% may be connected to the AFB increase in comparison to the decreasing RVp% subgroup in which AFB remains stable. The value of stable RVp% correlates strongly with AFB and the correlation is quadratic. Stable RVp% > 20% is associated with AF progression whereas lower stable RVp% may stabilise AF development.

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