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Association between routine biomarkers and atrial fibrillation in patients undergoing implantation of a dual-chamber pacemaker

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Abstract

Background: Elderly patients having a permanent pacemaker frequently have atrial remodeling. We examined the association between routine biomarkers and atrial fibrillation (AF) in patients receiving a dual-chamber pacemaker for sinus node disease (SND) or second-/third-degree atrioventricular block.

Methods: We recorded clinical, laboratory, and electrocardiographic parameters as well as pacemaker lead parameters at implantation. The final analysis included 217 patients with SND and 393 patients with atrioventricular block. Notably, 102/217 (47%) of the SND patients (median age: 77 years, 54% men) and 54/393 (14%) of the atrioventricular block patients (median age: 79 years, 54% men) had AF history (paroxysmal or persistent).

Results: Multivariable analysis showed that red blood cell distribution width (RDW) (OR: 1.17; 95% CI: 1.05-1.36; $P = .05$) and serum γ-glutamyl transferase (γGT) levels (OR: 1.15; 95% CI: 1.03-1.28; $P = .04$) were independently associated with AF history in patients with SND. In ROC curve analysis, the area under the curve (AUC) was 0.648; $P < .01$ for RDW, and 0.753; $P < .01$ for γGT. A RDW cut-off point of 14 was associated with AF with a sensitivity of 67% and a specificity of 68%, while a γGT cut-off point of 21 was associated with AF with a sensitivity of 80% and a specificity of 65%. In patients with second-/third-degree atrioventricular block, there were no significant independent correlations between AF and the parameters studied.

Conclusions: In elderly patients with SND, RDW and γGT have an independent association with AF history. Our study failed to show any corresponding associations in patients with advanced disorders of atrioventricular conduction.

KEYWORDS
atrial fibrillation, atrioventricular block, biomarkers, dual-chamber pacemaker, electrocardiogram, implantation parameters, RDW, sick sinus syndrome, γ-glutamyl transferase

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia and its prevalence has been continuously increasing during the last few decades mainly owing to aging of the population and improved survival of patients with other cardiovascular diseases.[1] AF is associated with increased risk of stroke and cardiovascular morbidity and mortality, thus representing a significant worldwide health problem.[1,2] It is a complicated and heterogeneous arrhythmia occurring in diverse clinical settings.[1,2] Of note, AF is prevalent in the elderly especially in the presence of comorbidities and is particularly common among patients with sinus node disease (SND).[3,4] In fact, tachy-brady syndrome is a very frequent manifestation of SND. On the other hand, the evidence linking second- or third-degree atrioventricular block with AF is less robust,[5] while atrial high-rate episodes (AHRE) and AF observed after the implantation of a pacemaker in these patients may be associated with new-onset heart failure/pacing-induced cardiomyopathy.[6,7] The pathophysiology of atrial remodeling is very complex, and the molecular pathways implicated in the initiation and perpetuation of AF show a high diversity and variability across different underlying substrates.[1,2,8] Inflammation and oxidative stress seem to play a significant pathophysiologic role in AF development and perpetuation.[9,10] Several biomarkers associated with these processes have been studied in patients with AF.[9-14]

Recently, much attention has been paid on the role of routine biomarkers of inflammation and oxidative stress, such as uric acid, RDW, and γGT, in AF.[13,15-22] RDW is a marker of anisocytosis of erythrocytes and is related to inflammatory and oxidative stress.[13,17] Interestingly, a relation of RDW with inflammatory and oxidative markers in an experimental model of atrial tachy-pacing has been demonstrated.[18] We have also previously published data indicating an association between baseline RDW levels and postoperative AF after cardiac operations.[19] Of note, recent systematic reviews and meta-analyses indicate that RDW is an independent predictor of AF in several clinical settings as well as a predictor of adverse outcomes and complications in AF patients.[13,17] On the other hand, increased activity of γGT is associated with increased oxidative stress and increased cardiovascular risk and mortality.[20] An increasing body of evidence indicates a significant association between increased γGT levels, within normal limits, and AF.[21,22]

Of note, there are very limited data in elderly patients subjected to implantation of a pacemaker regarding biomarkers and electrocardiographic parameters in relation to AF. In a previous pilot study, we studied the association between red blood cell distribution width (RDW) and AF in patients with symptomatic SND undergoing pacemaker implantation.[15] In the present study, we aimed to examine the associations between a wide range of routine laboratory parameters with AF in patients who underwent implantation of a dual-chamber pacemaker owing to SND or owing to second- or third-degree atrioventricular block. Also, we examined the potential association of AF with clinical parameters, simple electrocardiographic indexes as well as with lead parameters during the implantation procedure.

2 | METHODS

2.1 | Study population

Consecutive patients >18 years old with symptomatic SND or second-/third-degree atrioventricular block who were planned for a dual-chamber pacemaker implantation by an experienced electrophysiologist (PK) in the University Hospital of Ioannina, Greece were screened (January 2016 - December 2018). We analyzed separately the two groups of patients (according to the pacing indication) and we divided each group into two subgroups according to the history of AF (electrocardiographically documented paroxysmal or persistent AF that had been cardioverted). All patients were in sinus rhythm before pacemaker implantation.

The exclusion criteria included permanent AF, presence of bifascicular or trifascicular block in SND patients, chronic rheumatic and inflammatory conditions, thyroid dysfunction (including subclinical hyperthyroidism or hypothyroidism), hepatic dysfunction/liver diseases, alcohol overuse, severe renal dysfunction (eGFR < 30 mL/min/1.73 m^2), electrolyte disturbances, intake of anti-inflammatory drugs or antioxidant supplements, malignancies and hematologic dyscrasias, anemia, recent infection, acute or recent (<3 months) acute coronary syndrome, and antiarrhythmic drug use, including β-blockers. Patients with left atrial (LA) diameter >50 mm, systolic heart failure with LVEF <45%, or NYHA class >II were also excluded.

2.2 | Study protocol

Demographic, clinical, laboratory, echocardiographic, and electrocardiographic parameters were meticulously recorded. Specifically, routine biomarkers including complete blood count and biochemical investigations were assessed in the morning hours at the fasting state prior to the procedure. The hematologic parameters, including RDW, were determined using a Coulter counter. Conventional inflammatory indexes, such as white blood cell (WBC) count and C-reactive protein (CRP), were also assessed. CRP levels were assessed using a high-sensitivity immunonephelometric assay (Beckman Coulter/Immage Immunochemistry Systems, Behring Diagnostics Inc, Somerville, New Jersey, USA). Biochemical tests, including γ-glutamyl transferase (γGT) assessment, were performed using standard analytical methods. The eGFR was estimated by the Cockcroft-Gault formula. All measurements were performed blindly to the patients' characteristics and treatment.

A transthoracic echocardiographic examination was performed in each patient using a GE Vivid 7 machine. The left ventricular ejection fraction (LVEF) was calculated by the Simpson's method. LA diameter was determined from the parasternal long-axis view at end-systole. A 12-lead electrocardiogram (ECG) was also performed before the operation. Baseline electrocardiographic parameters were blindly measured by an experienced arrhythmia specialist (PK). In specific, all ECGs were scanned and measured using a specific computer program (Cardio Calipers, Iconico.com). Given that

Bazett's formula is not reliable for rates <60/min or >100/min, the Hodges formula was used to calculate the QTc interval. We also recorded atrial and ventricular lead parameters during the implantation procedure. Comparisons according to the presence or not of AF history were performed. All patients provided written informed consent and the Hospital's Ethics Committee approved the study protocol.

2.3 | Statistical methods

Continuous variables were expressed as mean ± SD or as median [interquartile range] if their values were not normally distributed. Normality was assessed using the Kolmogorov-Smirnov test. Comparisons of the continuous variables were performed using the unpaired Student's *t* test or the nonparametric Mann-Whitney *U* test, as appropriate. The categorical variables were presented as frequencies and compared using the Fisher's exact test. A two-tailed $P < .05$ was considered significant. Multivariable logistic regression analysis was performed in order to examine the association between the candidate parameters and AF. Variables showing a $P < .10$ in the univariate analysis were incorporated into the model. Moreover, ROC curve analysis was performed in order to identify cut-off values and corresponding sensitivities and specificities of the parameters that exhibited independent associations. All analyses were performed using the SPSS software (version 21.0; SPSS Inc, Chicago, IL, USA).

3 | RESULTS

Initially, 668 patients were screened but 58 patients were excluded according to the prespecified criteria. Thus, the final analysis included 217 patients with SND (median age: 77 [71-82] years; 54% men) and 393 patients with second- or third-degree atrioventricular block (median age: 79 [74-84] years; 54% men; 54% with complete heart block). Specifically, 102/217 (47%) of the SND had AF history and 54/393 (14%) of the atrioventricular block patients had a history of this specific arrhythmia.

In patients with SND, the baseline characteristics of the two subgroups are presented in Table 1. Patients with SND and AF had an increased heart rate and P wave duration (Table 1). Regarding laboratory parameters, RDW and γGT values were significantly increased in AF patients (Table 2), whereas no differences were evident in pacemaker lead measurements at implantation (Table 3). Multivariable analysis indicated that RDW (OR: 1.17; 95% CI: 1.05-1.36; $P = .05$) and serum levels of γGT (OR: 1.15; 95% CI: 1.03-1.28; $P = .04$) were independently associated with AF history in patients with SND. ROC curve analysis showed that the area under the curve (AUC) was 0.648; $P < .01$ for RDW (Figure 1) and 0.753; $P < .01$ for γGT (Figure 2). A RDW cut-off point of 14 was associated with AF with a sensitivity of 67% and a specificity of 68%, while a γGT cut-off point of 21 was associated with AF with a sensitivity of 80% and a specificity of 65%.

TABLE 1 Baseline demographic, clinical, and electrocardiographic characteristics in patients with sinus node disease

	No AF (n = 115)	AF (n = 102)	P-value
Age (years)	76 [72-82]	78 [73-82]	0.36
Sex, men (%)	50	54	0.58
BMI (kg/m^2)	26.6 [23.9-29.8]	27.4 [24.5-31.5]	0.18
Syncope (%)	40	48	0.32
Diabetes mellitus (%)	23	32	0.16
Hypertension (%)	79	87	0.16
CAD (%)	10	19	0.12
CHA$_2$DS$_2$VASc score	3 [2.5-3.4]	3.2 [2.6-3.4]	0.56
Heart rate (beats/min)	44 [37-59]	53 [42-67]	0.002
LVEF (%)	57 ± 13	56 ± 9	0.83
LA diameter (mm)	40 [38-43]	42 [39-45]	0.57
P wave duration (ms)	100 [85-120]	120 [95-130]	0.10
PR interval (ms)	190 [160-240]	200 [158-265]	0.64
QRS interval (ms)	100 [85-120]	105 [80-122]	0.92
QTc (ms)	425 [385-451]	410 [377-447]	0.44

Note: AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; LA, left atrial; LVEF, Left ventricular ejection fraction.

Regarding patients with second- or third-degree atrioventricular block, those who had a history of AF had a significantly greater prevalence of coronary artery disease (Table 4). Also, increased age, increased QRS duration, and greater prevalence of hypertension were noted in AF patients, but these differences did not reach statistical significance (Table 4). Of note, no difference in laboratory parameters between AF and no AF groups was evident in these patients (Table 5). The same was true for pacemaker lead measurements at implantation (Table 6). Multivariable analysis did not show any independent associations between studied parameters and AF in patients with second- or third-degree atrioventricular block.

4 | DISCUSSION

The present study indicated that RDW and γGT were independently associated with AF history in SND patients who were implanted a dual-chamber pacemaker. On the other hand, in patients with advanced conduction abnormalities (second- or third-degree atrioventricular block), AF did not correlate independently with any of the studied parameters.

AF is a complex and heterogeneous arrhythmia associated with different conditions and substrates. Besides local triggers, atrial electrophysiological and structural abnormalities that constitute atrial remodeling seem to play an important role in AF development and persistence.[1,8] Remarkably, the role of pathophysiologic pathways that involve oxidative and inflammatory processes in AF is under meticulous investigation.[9,10] Several inflammatory indexes and oxidative stress markers have been associated with AF in different clinical settings.[9-14] These include CRP, interleukin (IL)-6, tumor

	No AF (n = 115)	AF (n = 102)	P-value
Hb (gr/dL)	13.2 [11.7-14.5]	13.4 [12.4-14.3]	0.67
RDW%	13.4 [13.1-13.7]	14.3 [13.6-15.3]	0.03
WBC (×10³/μL)	7.23 [5.86-8.44]	6.63 [6.11-8.73]	0.95
NEU (%)	63.5 [55.9-67.75]	61.1 [57.9-69.1]	0.49
Pt (×10³/μL)	223.5 [189.2-253.2]	208 [178-236.5]	0.31
MPV	10.8 [10.4-11.7]	10.8 [10.2-11.8]	0.90
eGFR (mL/min/1.73 m²)	58.3 [42.3-80.2]	57.9 [46.8-80.4]	0.38
Na⁺ (mEq/L)	138 [134-142]	139 [133-144]	0.27
K⁺ (mEq/L)	4.3 [3.9-4.7]	4.3 [3.8-4.9]	0.58
AST (IU/L)	20 [19-27]	21 [17-25]	0.382
ALT (IU/L)	22 [19-29]	18 [15-23]	0.18
γGT (IU/L)	18 [14-26]	27 [16-52]	0.02
CRP (mg/dL)	1.2 [0.8-2.1]	1.5 [0.9-2.8]	0.70
Uric acid (mg/dL)	8.4 [5.6-13]	7.2 [5.9-12.2]	0.61

Note: AF, atrial fibrillation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; γGT, gamma-glutamyl transferase; RDW, red blood cell distribution width; WBC, white blood cell count.

	No AF (n = 115)	AF (n = 102)	P-value
P wave (mV)	3 [2.2-4]	2.9 [2-4.3]	0.77
RA threshold (V)	0.45 [0.3-0.7]	0.5 [0.4-0.7]	0.68
RA impedance (Ω)	580 [457-792]	518 [456-652]	0.29
R wave (mV)	11.8 [8.3-17.7]	12.5 [9.8-16.8]	0.53
RV threshold (V)	0.4 [0.3-0.42]	0.4 [0.3-0.52]	0.52
RV impedance (Ω)	864 [[670-1300]	854 [717-1087]	0.74

Note: RA, right atrial; RV, right ventricular.

necrosis factor (TNF), myeloperoxidase, galectin-3, nitrotyrosine, F2 isoprostanes, and others.[9-14]

SND is associated with atrial fibrosis, atrial myopathy, and structural remodeling, creating a substrate that facilitates AF development and perpetuation.[3,4] Furthermore, bradycardia per se, ion-channel remodeling, abnormal calcium handling, electrophysiological alterations, and autonomic abnormalities contribute to the atrial arrhythmogenesis.[3,4] Indeed, up to 70% of patients implanted a dual chamber for SND may suffer AF, while in 40%–70% of SND patients atrial arrhythmias are evident at the time of diagnosis.[3,4] On the other hand, SND affects up to one in five patients with AF and it has been suggested that the structural and electrophysiological abnormalities associated with AF may provoke or aggravate sinus node dysfunction.[23] In support to these notions, it seems that pulmonary vein isolation, apart from reducing AF burden and tachy-brady episodes, ameliorates sinus pauses and related symptoms as well.[23] In the present study, which included a greater number of patients than our previous pilot investigation,[15] we showed an independent association of RDW with AF in patients with SND. In addition, we demonstrated, for the first time, a significant association between γGT and AF in these patients, independently from RDW.

Abnormal atrioventricular conduction might be associated with AF and other adverse outcomes. In fact, first-degree atrioventricular block, namely prolonged PR interval, has been linked to AF, atrial fibrosis, as well as to increased pro-inflammatory and pro-fibrotic biomarkers.[24] However, it has been argued that only when there is an increased P wave, which reflects more accurately atrial remodeling, the prolonged PR interval is associated with AF.[25] Regarding the association of second- or third-degree atrioventricular block and AF, the data are sparse. Recently, in a retrospective analysis, Zhao et al showed that all three main types of atrioventricular block are associated with AF.[5] Moreover, in a small study of 81 patients over 70 years old, with no AF history, who were implanted a pacemaker owing to complete heart block, 65% developed AHRE with duration >5 min after 18 months of follow-up.[6] Nevertheless, it should be stressed that the identification of AHRE detected by devices diagnostics with clinical AF, and their correlation with adverse events such as stroke is often problematic.[26] The same group of investigators studied 308 patients who implanted a dual-chamber pacemaker owing to second- or third-degree atrioventricular block without AF history.[7] After a 3 year follow-up, 34 (11%) patients developed persistent AF associated with increased cardiovascular mortality as
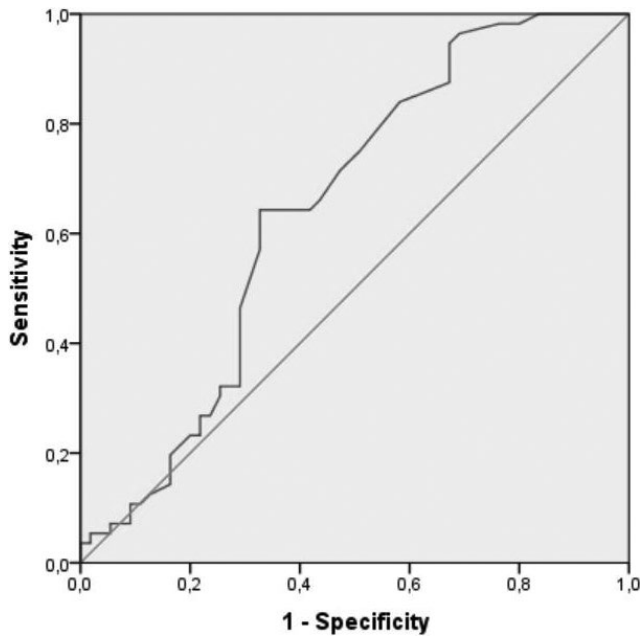
FIGURE 1 Receiver operating characteristic curve analysis demonstrating the predictive value of RDW for atrial fibrillation in sinus node disease
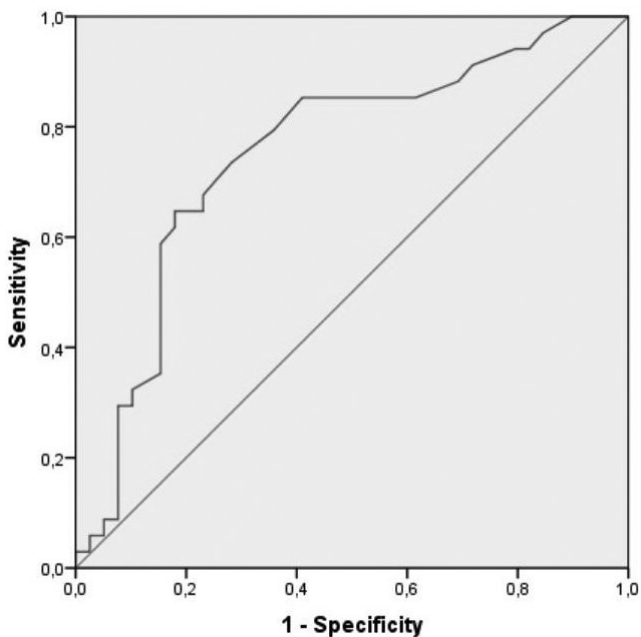

FIGURE 2 Receiver operating characteristic curve analysis demonstrating the predictive value of γGT for atrial fibrillation in sinus node disease

well as congestive heart failure.[7] However, the development of AF could be related to pacing-induced cardiomyopathy. Interestingly, Lin et al studied patients without heart failure admitted for pacemaker implantation and they showed that those with second- or third-degree atrioventricular block had greater left and right atrial dimensions compared to age- and sex-matched patients with SND.[27] The authors attributed this finding to the atrioventricular

TABLE 4 Baseline demographic, clinical, and electrocardiographic characteristics in patients with second- or third-degree atrioventricular block

	No AF (n = 339)	AF (n = 54)	P-value
Age (years)	79 [74-84]	82 [76-86]	0.07
Sex, men (%)	54	58	0.68
BMI (kg/m^2)	27.2 [24.7-31.2]	26.5 [24.4-28.4]	0.36
Complete heart block (%)	53	55	0.47
Syncope (%)	36	40	0.50
Diabetes Mellitus (%)	29	29	0.99
Hypertension (%)	79	88	0.09
CAD (%)	12	24	0.03
CHA$_2$DS$_2$VASc score	2.8 [2.3-3.3]	3 [2.6-3.4]	0.36
Heart Rate (beats/min)	38 [32-44]	41 [35-44]	0.22
LVEF (%)	56.5 ± 9.8	53.9 ± 15.4	0.46
LA diameter (mm)	38 [36-41]	42 [37-45]	0.35
P wave duration (ms)	85 [80-94]	95 [82-102]	0.48
QRS interval (ms)	120 [89-130]	125 [100-160]	0.08
QTc (ms)	445 [410-464]	450 [402-475]	0.39

Note: AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; LA, left atrial; LVEF, Left ventricular ejection fraction.

dyssynchrony but they did not report any data regarding AF history in each group.[27] The present study provides evidence that none of the markers associated with atrial remodeling is independently associated with AF history in patients with remarkable atrioventricular conduction abnormalities. Presumably, the advanced conduction disturbances, although most commonly are owing to degenerative fibrosis and calcinosis (Lenegre-Lev disease), are not associated with such an extensive atrial remodeling as in SND. By extension, the underling inflammatory and oxidative processes are less robust. However, increased values of CRP and uric acid in the patients with advanced atrioventricular block (compared to SND patients) may mask the effects of AF on other parameters in this group.

Of note, the RDW values in non-AF patients of the atrioventricular conduction block group were greater than RDW values in the non-AF patients of the SND group. The most plausible explanation is that patients in the SND group were younger, although both groups had similar prevalence of comorbidities. Indeed, it has been demonstrated that RDW values increase with age.[28]

In this study, we also recorded the pacemaker lead parameters during the implantation procedure. It had been shown that relatively increased right ventricular stimulation thresholds at implantation of defibrillators, indicating extensive ventricular fibrosis and remodeling, are predictive for ventricular arrhythmias and appropriate therapies.[29] Therefore, we hypothesized that increased atrial thresholds at implantation reflecting atrial fibrosis and remodeling could be associated with AF. However, no association between AF and pacemaker lead parameters was evident in either group of patients.

	No AF (n = 339)	AF (n = 54)	P-value
Hb (gr/dL)	13.1 [11.8-14.1]	13.3 [11.5-14.3]	0.87
RDW%	13.9 [13.2-14.6]	14.2 [13.2-15.9]	0.26
WBC (×10³/μL)	7.7 [6.5-9.9]	7.4 [6.7-8.6]	0.73
NEU (%)	66.9 [57.4-75.2]	69.3 [59.8-78.5]	0.15
Pt (×10³/μL)	210 [174-239]	210 [180-236]	0.61
MPV	11.2 [10.3-12]	11.2 [10.5-12.2]	0.69
eGFR (mL/min/1.73 m²)	58.2 [42.5-72]	49.8 [36.2-67.6]	0.28
Na⁺ (mEq/L)	139 [131-141]	138 [133-141]	0.66
K⁺ (mEq/L)	4.5 [4.1-4.8]	4.4 [4.1-5]	0.60
AST	21 [16-28]	25 [17-37]	0.11
ALT	22 [16-32]	23 [16-38]	0.57
γGT	24 [16-37]	22 [18-37]	0.98
CRP (mg/dL)	6 [2.1-7.6]	6.3 [4.5-8.7]	0.37
Uric acid (mg/dL)	12.5 [6.9-25.2]	14.5 [6.6-23.7]	0.84

Note: AF, atrial fibrillation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; γGT, gamma-glutamyl transferase; RDW, red blood cell distribution width; WBC, white blood cell count.

TABLE 6 Atrial and ventricular lead parameters at pacemaker implantation in patients with second- or third-degree atrioventricular block

	No AF (n = 339)	AF (n = 54)	P-value
P wave (mV)	3 [2.1-4]	3.1 [2.9-4]	0.33
RA threshold (V)	0.4 [0.3-0.5]	0.32 [0.3-0.4]	0.28
RA impedance (Ω)	500 [450-600]	510 [452-615]	0.50
R wave (mV)	8.6 [6.9-11]	7.6 [6.1-10]	0.16
RV threshold (V)	0.3 [0.27-0.4]	0.3 [0.2-0.35]	0.95
RV impedance (Ω)	650 [560-800]	588 [533-675]	0.31

Note: RA, right atrial; RV, right ventricular.

4.1 | Study limitations

Some limitations should be acknowledged. *Firstly*, we did not assess the AHRE burden after pacemaker implantation using the device diagnostics. This is a subject of future research. Our principal aim was to investigate baseline parameters that are related to known and well-documented AF in patients with SND and in patients with second- or third-degree atrioventricular block. *Secondly*, we did not report data on patients implanted a dual pacemaker owing to other indications, such as carotid hypersensitivity syndrome, because a subgroup analysis according to the presence of AF was not feasible owing to the small number of patients. *Thirdly*, we did not assess specific markers of oxidative stress and inflammation. In fact, our main intention was to evaluate the predictive value of conventional clinical, electrocardiographic, and laboratory indexes used in everyday clinical practice. *Fourthly*, although we did not include patients with anemia or hematologic dyscrasias, we do not have data on iron and ferritin status that may potentially interfere with RDW *Finally*, it should be noted that this study provides data on associations and not on mechanistic insights.

5 | CONCLUSION

In elderly patients undergoing dual-chamber pacemaker implantation, SND is related to AF, while routine biomarkers that have been linked to inflammation and oxidative stress, such as RDW and γGT, manifest an independent association with AF history in this population. On the other hand, no such associations were observed in patients with advanced disorders of atrioventricular conduction. No clinical, electrocardiographic, and pacemaker parameters at implantation were shown to have a predictive value in this setting. Given that many patients with SND may suffer from asymptomatic AF episodes or may develop AF in the future, the presence of increased RDW (>14%) and γGT (>21 IU/L) may lead to the intensification of AF detection during follow-up. The correlations of specific biomarkers with AF development after pacemaker implantation need further study. Also, the applicability of these markers in the general elderly population, especially in those with palpitations or in subjects with several risk factors for AF development, represents a subject of future research.

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