Myringosclerosis as a predictor of the requirement for a permanent pacemaker in patients with drug-related atrioventricular block

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Aims. Drug-related atrioventricular block (DR-AVB) may develop in patients with underlying latent degenerative conduction disorders, especially with antiarrhythmics and antihypertensives. Although, according to the current guidelines, reversal is achieved with cessation of the inducing agent, this is not the case for nearly half of the patients. The pathophysiological processes of DR-AVB and myringosclerosis include systemic inflammation and degeneration. This study investigated the role of myringosclerosis in predicting irreversible high-grade DR-AVB despite drug cessation.
Methods. This observational, non-randomized, prospective study involved 152 patients with high-grade DR-AVB, 72 of whom had reversible DR-AVB and 80 had irreversible DR-AVB and required permanent pacemakers. The patients' demographic, clinical, echocardiographic, and laboratory characteristics were recorded. Otoscopic tympanic membrane examinations for myringosclerosis were performed.
Results. There were no major differences in demographic, echocardiographic or laboratory characteristics between the two groups or previous medications. The median monitoring time with a temporary pacemaker was significantly longer in the irreversible than in the reversible group (5 [4–7] days vs. 2 [1–5] days; $P<0.001$). The incidence of myringosclerosis was significantly higher in the irreversible than in the reversible group (61.3% vs. 22.2%; $P=0.001$). Multivariate logistic regression analysis showed that myringosclerosis was an independent predictor of irreversible DR-AVB (odds ratio: 1.703, 95% confidence interval: 1.194–3.058; $P=0.01$).
Conclusion. Myringosclerosis is a readily available, inexpensive, and non-invasive assessment and is a marker of inflammation and degeneration that can predict irreversible DR-AVB.

Key words: atrioventricular block, myringosclerosis, pacemaker, tympanosclerosis

Received: February 15, 2022; Revised: June 6, 2022; Accepted: June 15, 2022; Available online: June 21, 2022
https://doi.org/10.5507/bp.2022.030

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INTRODUCTION

The effects of various drugs widely used to treat cardiovascular diseases, especially antiarrhythmics, on the heart's conduction system are well known[1]. In rare cases, drug-related conduction defects can occur even at therapeutic doses. Discontinuation or dose reduction of the inducing agent is usually sufficient. However, in patients with underlying latent atrioventricular conduction disorders, high-grade atrioventricular block (AVB) may develop[2], which may cause hemodynamic instability and require immediate medical attention with a temporary pacemaker[3]. Permanent pacemaker implantation is not recommended according to the current guidelines for drug-related AVB (DR-AVB), as the condition is assumed to be reversible[4,5]. Although the inducing agent is appropriately discontinued, this is not the case for almost half of the patients due to the persistence or recurrence of high-grade AVB (ref.[6,7]). It is not clear whether DR-AVB reversal will be achieved in a given patient and how long to wait before deciding permanent pacemaker implantation[8]. These uncertainties may result in prolonged patient standby with a temporary pacemaker or unneeded permanent pacemaker implantation.

Myringosclerosis is generally the first stage of tympanosclerosis and does not require treatment unless hearing loss[9,10]. This condition is characterized by hyaline degeneration of the tympanic membrane and is easily diagnosed during an otoscopic examination[11,12]. If it is accompanied by involvement of the middle ear and mastoid cavity, it is called tympanosclerosis[13,14]. Atherosclerotic plaques and sclerotic aortic valve lesions are similar to myringosclerosis in terms of pathological calcification[15–18]. Inflammation and degeneration secondary to autoimmunity, infection, and trauma have been suggested as possible etiological factors[19,20]. Moreover, its frequent occurrence in atherosclerotic patients suggests a genetic predisposition to sclerotic degeneration[21].

Studies examining the relationship between cardiovascular diseases and tympanosclerosis have reported rates of tympanosclerosis in healthy adults ranging between 4.9% and 13%. These studies have reported a higher incidence

of myringosclerosis in patients with various cardiovascular diseases than in the general population[10,21–23]. Although the heart and ear are different organs, tissue degeneration due to a systemic inflammatory response is similar in both conditions, suggesting a common etiopathogenesis. However, the possible relationship between DR-AVB and myringosclerosis has not been previously examined. Therefore, this study aimed to examine the potential role of myringosclerosis, which is an indicator of systemic inflammation and sclerosis, in predicting irreversible high-grade DR-AVB despite drug cessation.

MATERIALS AND METHODS

Study population

This observational, non-randomized, prospective study was undertaken between March 2020 and January 2022. A total of 204 patients undergoing temporary pacemaker insertion were reviewed. High-grade AVB patients with symptomatic or severe bradycardia were evaluated for eligibility (n=198). Patients with AVB that was not drug-related, as well as those who used drugs in suicidal attempts or greater than prescribed amounts, were excluded from the study. In patients receiving digoxin, plasma digoxin levels were examined. Patients whose clinical findings or laboratory results were consistent with digoxin intoxication were excluded from the study. Patients with previous otologic diseases, otosurgical procedures, such as ventilation tube insertion, clinically significant ear trauma, active systemic infection (e.g., Lyme disease), chronic inflammatory disorders including systemic rheumatologic diseases, anti-inflammatory drug use, psychiatric disorders, uncontrolled endocrinological-especially hypothyreosis-disorders, chronic renal failure, malignancies, and significant electrolyte disturbances were also excluded. Likewise, patients who died for any reason before it was determined whether they required a permanent pacemaker were excluded. Finally, patients with hemodynamically significant lesions (>75% or >50% in case of left main coronary artery) were also excluded from the study, even if they were using rate-blocking drugs. A total of 155 patients were found to be eligible for enrollment based on these criteria. Three patients declined to participate. Thus, 152 patients were enrolled. Fig. 1 depicts the patient enrollment flowchart. Ethical approval was obtained from the local ethics committee before the study. Signed informed consent was obtained from all participants.

Data collection

The participants' demographic and clinical characteristics, including age, gender, smoking status, symptoms, previous diseases, previous medications, AVB type, temporary pacemaker monitoring time, and New York Heart Association (NYHA) functional class, were recorded. A cardiologist performed echocardiographic examinations to evaluate the left ventricular ejection fraction (LVEF) using an X5-1 (1–5 MHz) transducer and a Philips Epiq 7C device (Koninklijke Philips Electronics N.V., Amsterdam, Netherlands). Routine laboratory parameters, including complete blood counts (i.e., hemoglobin, white blood cell and platelet counts) and fasting blood glucose, creatinine, and low-density lipoprotein levels, were analyzed and recorded. Coronary angiography was performed to exclude an ischemic etiology in patients requiring a permanent pacemaker before the procedure. On the day of admis-

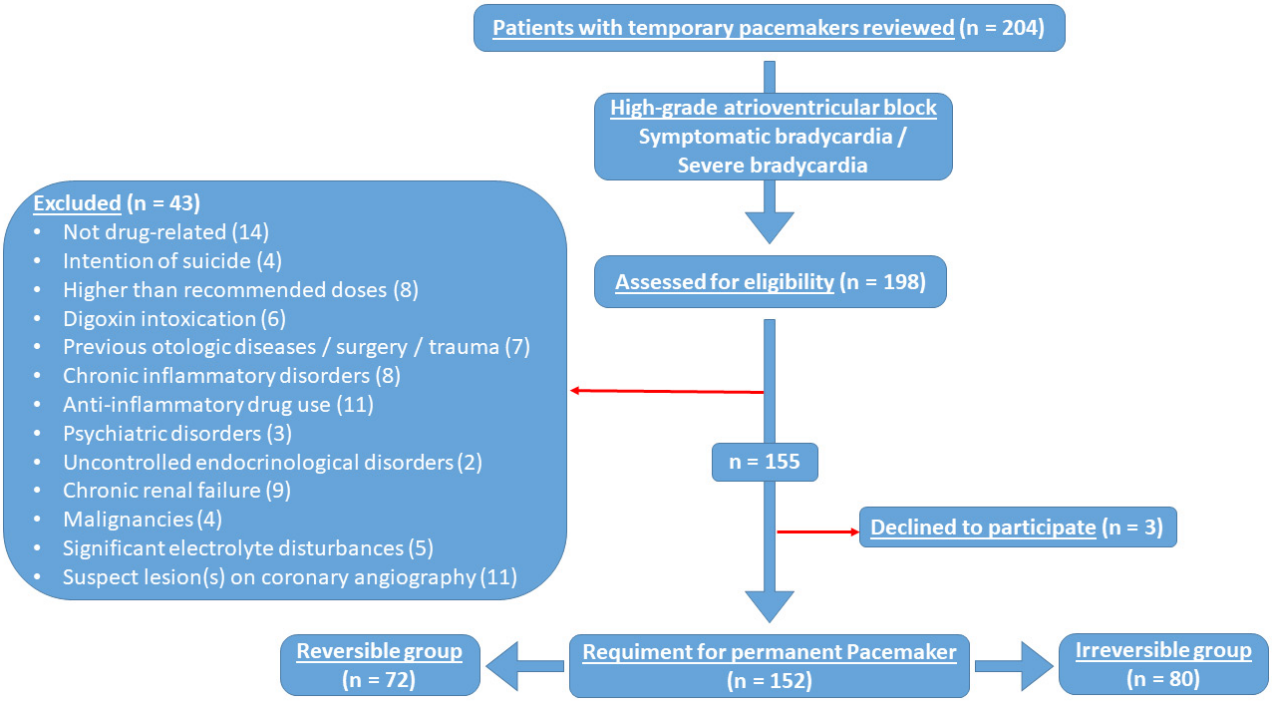

Fig. 1. Study flowchart.

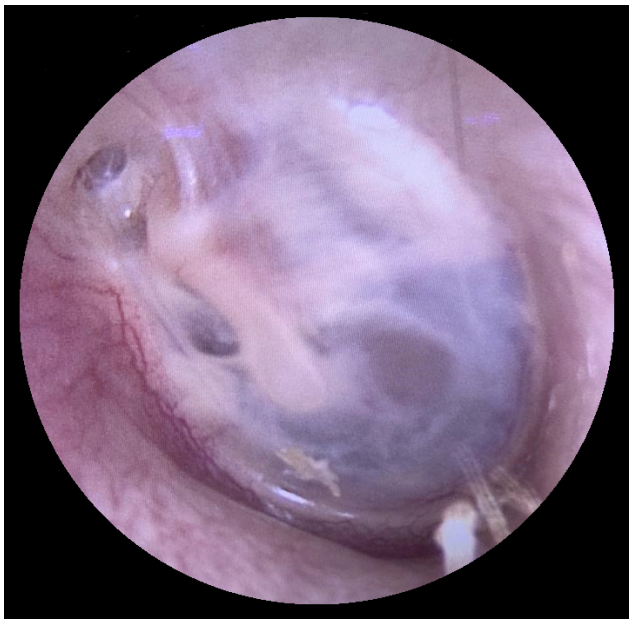

Fig. 2. Diffuse hyaline plaques on the tympanic membrane.

sion, an experienced otorhinolaryngologist blinded to the patients' clinical characteristics examined each patient's tympanic membranes for myringosclerosis using a Riester UNI I Otoscope (Rudolf Riester, Stuttgart, Germany).

Definitions

An electrocardiographic evaluation was performed for rhythm analysis. The presence of advanced second-degree (Mobitz type II, 2:1, and P:QRS ratio of 3:1 or higher-level) or third-degree (complete) AVB was described as high-grade AVB. Symptomatic bradycardia was defined as a heart rate of fewer than 50 beats/min, with effort intolerance, pre-syncope, and syncope symptoms. A heart rate of fewer than 40 beats/min was considered severe bradycardia.

The presence of hyaline plaques occupying at least 1/5 of the tympanic membrane was accepted as myringosclerosis (Fig. 2). Naturally diffuse opacification, which can be seen in elderly patients, was not considered clinically significant.

Statistical analysis

Categorical variables are reported as numbers (n) and percentages (%), and the relationship was analyzed using Pearson's chi-square and Fisher's exact test. The one-sample Kolmogorov–Smirnov test was used to assess the distribution of continuous variables. Normally distributed variables are reported as means ± standard deviations, whereas variables that were not normally distributed are reported as medians and ranges. For normally distributed continuous variables, the Student's *t*-test was employed, and for skewed variables, the Mann-Whitney *U* test was utilized. To identify the independent predictors of irreversible high-grade DR-AVB, parameters with *P*-value <0.1 in the univariate logistic regression analysis were evaluated using multivariate logistic regression analysis and reported as odds ratios (OR) with 95% confidence intervals (CI). The statistical significance level was set at $P<0.05$. IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA) was used to conduct all of the analyses.

RESULTS

The patients' demographic, clinical, echocardiographic, and laboratory characteristics are presented in Table 1. The mean age of the patients was 76 ± 11 years, and 38.8% (n=59) were male. After discontinuation of the inducing drug, DR-AVB was reversed in 72 (47.4%) of the 152 patients (reversible group), whereas it was not reversed in 80 (52.6%) patients, who required a permanent pacemaker (irreversible group). There were no statistically significant differences between the two groups in terms of age, gender, smoking status, symptoms, previous diseases (including hypothyroidism), or previous medications (including antiarrhythmics). Effort intolerance was the most observed presentation (n=98, 64.5%), and beta-blockers were the most common AVB-inducing drugs (n=88, 57.9%). Combined drug use induced AVB in 20 patients (13.2%), with the most common combination being a beta-blocker with a non-dihydropyridine calcium channel blocker (NDH–CCB) (n=12, 7.9%). AVB-inducing drugs were generally used chronically (n=138, 90.8%), whereas newly initiated treatments induced AVB less frequently (n=14, 9.2%). Ninety-two (60.5%) patients had complete AVB, whereas 60 (39.5%) had Mobitz type II AVB. There was no statistically significant difference between the reversible and irreversible groups in terms of AVB grade. The median monitoring time with a temporary pacemaker was significantly longer in the irreversible group than in the reversible group (5 [4–7] days vs. 2 [1–5] days; $P=0.01$). In the reversible group, DR-AVB was resolved within two days of AVB-inducing drug discontinuation in 48 (66.7%) patients and after the second day in 24 patients (33.4%). There were no statistically significant differences between the two groups in terms of NYHA functional class or LVEF. Likewise, no significant differences were found in terms of routine hematological or biochemical parameters. The incidence of myringosclerosis was significantly higher in the irreversible group than in the reversible group (61.3% vs. 22.2%; $P<0.001$). Multivariate logistic regression analysis showed that myringosclerosis was an independent predictor of irreversible high-grade DR-AVB (OR: 1.703, 95% CI: 1.194–3.058; $P=0.01$; Table 2).

DISCUSSION

In this study, cessation of the inducing agent did not reverse high-grade DR-AVB in more than half of the patients. The presence of myringosclerosis was related to the requirement for permanent pacemaker implantation. The results also suggest that the monitoring period with a temporary pacemaker in patients with reversible high-grade DR-AVB may be longer than expected.

Table 1. Comparison of demographic, clinical, echocardiographic, and laboratory characteristics between groups.

Variables	Reversible group (n=72)	Irreversible group (n=80)	*P*
Age, years (mean ± SD)	74 ± 9	78 ± 13	0.312
Male gender, n (%)	26 (36.1)	33 (41.3)	0.516
Smoking status, n (%)	5 (6.9)	7 (8.8)	0.68
Presentation, n (%)			0.979
Effort intolerance	47 (65.3)	51 (63.8)	
Presyncope – syncope	20 (27.8)	23 (28.7)	
None	5 (6.9)	6 (7.5)	
Previous diseases, n (%)			
Hypertension	50 (69.4)	61 (76.3)	0.345
Coronary artery disease	31 (43.1)	38 (47.5)	0.583
Diabetes mellitus	24 (33.3)	31 (38.8)	0.488
Hyperlipidemia	26 (36.1)	24 (30)	0.423
Heart failure	16 (22.2)	22 (27.5)	0.453
Hypothyroidism	8 (11.1)	5 (6.3)	0.285
Previous medications, n (%)			0.085
Beta-blockers	37 (51.4)	51 (63.7)	
NDH-CCBs*	26 (36.1)	16 (20)	
Combination# with beta-blockers	9 (12.5)	13 (16.3)	
Drug initiation time, n (%)			0.723
More than 15 days	66 (91.7)	72 (90)	
Less than 3 days	6 (8.3)	8 (10)	
Atrioventricular block type, n (%)			0.092
Complete	39 (54.2)	54 (67.5)	
Mobitz type II	33 (45.8)	26 (32.5)	
TP& monitoring time, day (median [range])	2 [1–5]	5 [4–7]	0.01
New York Heart Association functional class, n (%)			0.473
I–II	60 (83.3)	63 (78.7)	
III–IV	12 (16.7)	17 (21.3)	
Left ventricular ejection fraction, %	55 ± 10	51 ± 11	0.164
Laboratory characteristics (mean ± SD)			
Hemoglobin, g/dL	11.7 ± 1.7	12.1 ± 1.3	0.434
White blood cell, $\times 10^9$/L	8.6 ± 3.7	9.3 ± 3.1	0.432
Platelet, $\times 10^9$/L	212 ± 62	238 ± 71	0.329
Fasting blood glucose, mg/dL	128 ± 33	134 ± 41	0.529
Creatinine, mg/dL	1.1 ± 0.3	1.2 ± 0.3	0.211
Low-density lipoprotein, mg/dL	148 ± 41	156 ± 48	0.12
Myringosclerosis, n (%)	16 (22.2)	49 (61.3)	< 0.001

*Non-dihydropyridine calcium channel blockers; #Combination: Non-dihydropyridine calcium channel blockers; 12, digoxin; 5, amiodarone; &Temporary pacemaker

Table 2. Logistic regression analysis to assess predictors of irreversible high-grade atrioventricular block development.

Variables	Univariate analysis		Multivariate analysis	
	OR* (95% CI#)	*P*	OR* (95% CI#)	*P*
Age	1.207 (0.786–5.804)	0.384		
Hypertension	1.462 (0.192–1.214)	0.396		
Hypothyroidism	0.484 (0.118–1.884)	0.318		
Inducer agent (beta-blockers)	1.812 (0.892–3.996)	0.093	1.786 (0.878–3.953)	0.218
Atrioventricular block grade (complete)	2.214 (0.914–4.218)	0.097	2.142 (0.870–4.148)	0.918
TP& monitoring time	1.611 (1.014–2.512)	0.04	1.569 (0.987–2.481)	0.108
Left ventricular ejection fraction	0.612 (0.319–1.321)	0.282		
Creatinine	1.352 (0.912–1.856)	0.316		
Low-density lipoprotein	1.840 (0.988–2.776)	0.208		
Myringosclerosis	1.814 (1.244–3.216)	0.007	1.703 (1.194–3.058)	0.01

*Odds ratio; #Confidence interval; &Temporary pacemaker

Identical inflammation-related risk factors have been identified for tympanosclerosis and various cardiovascular – especially atherosclerotic – diseases[24]. Inflammation causes fibrosis and degeneration in the long-term, leading to blockage of atrioventricular conduction[25]. It is the main trigger of both myringosclerosis and AVB developing for various reasons. However, the relationship between myringosclerosis and the development of AVB has not been previously investigated.

The current guidelines are that DR-AVB is reversible, and there is no need for a permanent pacemaker[4]. However, recent studies have shown that the block continues or recurs in almost half of the patients despite cessation of the inducing drug[26,27]. In line with these studies, the block persisted in more than half of the patients in the presented study despite discontinuation of the inducing agent. An electrophysiological study (EPS) to detect the level of infranodal blocks in AVB and predict the requirement for a permanent pacemaker is the most appropriate approach. However, it is an invasive and costly procedure and is not available in all centers. For this reason, a recent study using a method similar to that of our study reported that the systemic immune-inflammation index (SII), which is a readily available and inexpensive inflammatory biomarker, can be used to predict irreversible high-grade DR-AVB (ref.[8]).

A possible genetic relationship between tympanosclerosis and cardiovascular diseases was first demonstrated by Koç et al.[21], who found that the frequency of tympanosclerosis in patients with atherosclerosis was significantly higher than in patients without atherosclerosis. The significance remained in a subgroup of patients with a history of otitis media, the most important risk factor for tympanosclerosis. Two other studies conducted in the same year and with the same population showed that patients with carotid artery stenosis had tympanosclerosis three times more frequently than those without cardiovascular diseases[22,23]. In another study, the frequency of tympanosclerosis was significantly higher in patients with hypercholesterolemia than in healthy subjects, and the rate was even higher in patients with plaques in the carotid or vertebrobasilar arteries[10]. Thus, with few exceptions[28,29], most studies' findings support a relationship between tympanosclerosis and cardiovascular diseases.

Another important finding of our study concerns the temporary pacemaker monitoring time in reversible high-grade DR-AVB. Reversible DR-AVB is defined as AVB resolved within two days of drug cessation[7]. However, due to differences in drugs' half-lives and patients' metabolism, there is no consensus on how long patients with high-grade DR-AVB should be monitored with temporary pacemakers. Prolonged patient standby with a temporary pacemaker is associated with in-hospital adverse events, such as infection, malignant ventricular arrhythmia, and asystole[30]. It is therefore crucial to identify patients with irreversible AVB early to prevent such complications, which may result in death. At the same time, it should be ensured that patients with reversible AVB do not undergo unnecessary permanent pacemaker implantation. In our study, DR-AVB was resolved in approximately one-third of the patients in the reversible group after two days. This suggests that a decision should not be made based only on temporary pacemaker monitoring or the inducing agent's half-life but should be supported with additional markers, such as myringosclerosis and SII.

Study Limitations

The most serious limitation of this study is that the indications for combined drugs were not always available. However, the rate of the unusual concomitant of beta-blockers and NDH-CCBs was relatively low. Another limitation is that no specific evaluations for rare accumulation diseases such as amyloidosis and Fabry were performed. Nevertheless, physical examination and echocardiography did not reveal any findings to suggest these conditions. In addition, these diseases were not probable given the patient age.

CONCLUSIONS

Cessation of the inducing agent did not reverse high-grade DR-AVB in more than half of the patients. Myringosclerosis is a readily available, inexpensive, and non-invasive assessment and is a marker of inflammation and degeneration that can predict irreversible DR-AVB.

ABBREVIATIONS

AVB, Atrioventricular block; CI, Confidence interval; DR-AVB, Drug-related atrioventricular block; EPS, Electrophysiological study; LVEF, left ventricular ejection fraction; MHz, Megahertz; NDH-CCB, Non-dihydropyridine calcium channel blocker; NYHA, New York Heart Association; OR, Odds ratio; SII, Systemic immune-inflammation index.

Author contributions: MSC, HH; concept/design; MSC, MRK, UK, IS: data collection / Statistics; MSC, HD, RC: data analysis/interpretation; MSC, HH, HD, RC: Drafting article; MSC, UK: Critical revision of article; MSC, HH, HD, RC, MRK, UK, IS: Approval of article.
Conflict of interest statement: The authors state that there are no conflicts of interest regarding the publication of this article.

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