ORIGINAL ARTICLE

The need for permanent pacemaker after restoration of conduction following atrioventricular block: a retrospective cohort study

Atriyoventriküler bloğu takiben iletimin restorasyonu sonrası kalıcı kalp pili gereksinmesi: Geriye dönük bir kohort çalışması

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ABSTRACT

Objective: A permanent pacemaker (PPM) is necessary for patients with a symptomatic third-degree or advanced second-degree atrioventricular (AV) block. An AV block due to medication use can often be reversed; however, subsequent relapse can occur and necessitate subsequent PPM implantation. The aim of this study was to explore the course and prognosis of patients with an AV block.

Methods: This historical cohort study was conducted between January 2013 and June 2018. A total of 1900 patient records were analyzed and 1123 subjects with an AV block on admission were enrolled. The patients were categorized into 2 groups: Group 1 comprised patients with an AV block due to medication use (n=316, 28%) and Group 2 included patients with an AV block caused by other etiologies (n=807, 72%). Data of the cause of AV block, recurrence, and PPM implantation were analyzed. Patients in both groups who did not require a PPM during the index admission were followed up regarding subsequent implantation of a PPM.

Results: AV conduction was recovered in 38 (12%) patients in Group 1 and 48 (6%) patients in Group 2 during the index hospitalization. However, recurrence of the AV block was observed in 18% of Group 1 patients and 40% of Group 2 patients. Only 25 patients in each group (4.5% of the whole study population) remained PPM-free during a median 3-year follow-up period.

Conclusion: The study findings suggest that drug-induced AV blocks may not be as benign as previously thought. The high relapse rate indicates that watchful follow-up may be required despite discontinuation of the responsible medication and that consideration of earlier PPM implantation in cases of early recurrence may be warranted.

ÖZET

Amaç: Semptomlu üçüncü derece veya ileri evre ikinci derece atriyoventriküler (AV) bloğu olan hastalar için kalıcı bir kalp pili (PPM) gereklidir. İlaç kullanımı nedeniyle gelişen AV bloğu sıklıkla tersine çevrilebilirse de daha sonra nüksler ortaya çıkabilir ve PPM implantasyonunu gerektirebilir. Bu çalışmanın amacı AV bloklu hastalarda hastalığın seyrini ve prognozunu araştırmaktı.

Yöntemler: Bu kohort çalışması Ocak 2013 ile Haziran 2018 arasında yapıldı. Toplam 1900 hastanın kaydı incelendi, başvuruda AV bloklu 1123 kişi çalışmaya alındı. Hastalar iki gruba ayrıldı: Grup 1, ilaç kullanımına bağlı AV bloğu olan hastaları (n=316, %28) ve Grup 2, diğer etiyolojilerin neden olduğu AV bloğu olan hastaları (n=807, %72) içermekteydi. AV bloğun nedeni, nüksü ve PPM implantasyonuna ilişkin veriler incelendi. Her iki gruptaki indeks olgu başvuruları sırasında PPM gerektirmeyen hastalar, sonradan uygulanan PPM implantasyonu açısından izlendi.

Bulgular: İndeks hastane yatışı sırasında Grup 1'de 38 (%12), Grup 2'de 48 (%6) hastada AV iletimi iyileşti. Ancak, Grup 1'deki hastaların %18'i ve Grup 2'deki hastaların %40'ında AV blok nüksü gözlendi. Her bir grupta sadece 25 hastaya (tüm çalışma popülasyonunun %4.5'i) ortalama üç yıllık takip süresince kalp pili takılmadı.

Sonuç: Çalışma bulguları ilaca bağlı AV bloklarının daha önce düşünüldüğü kadar iyi huylu olmadığını göstermektedir. Yüksek nüks oranı, sorumlu ilacın kesilmesine rağmen dikkatli izlemin gerekebileceğini ve erken nüks durumunda erken PPM implantasyonunun gerekli olabileceğini göstermektedir.

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Permanent pacemaker (PPM) insertion is recommended for patients with a symptomatic third-degree or advanced second-degree atrioventricular (AV) block. The current opinion is that an AV block induced by medication may be reversible and not require PPM implantation. Discontinuation of the culprit drug is usually the first step in management. [1] However, there is lack of data about subsequent steps and there are some concerns about the natural course and prognosis of patients with drug-induced AV blocks. Recurrence of an AV block in some patients after drug discontinuation raises the question of underlying concomitant AV conduction disease. [2,3] It may be that the relationship between drugs and AV block is not necessarily a cause-and-effect issue. [4] The aim of this study was to investigate the clinical course and prognosis of patients who had an AV block, with or without a culprit drug.

METHODS

All hospital records of patients who were admitted to the Tehran Heart Center with an AV block were retrospectively reviewed. This historical cohort study was conducted between January 2013 and June 2018. The Ethics Committee of Tehran University of Medical Sciences approved the study protocol (IR.TUMS.MEDICINE.REC.1396.4121).

All patients admitted with the diagnosis of a second-degree or greater AV block were included. The exclusion criteria were a lack of documented electrocardiogram (ECG) demonstrating AV block, atrial fibrillation (AF) with advanced AV pause of <5 seconds, acute myocardial infarction (MI), sick sinus syndrome, severe electrolyte imbalance, vagal reaction and periprocedural AV block (due to surgery or radiofrequency ablation). The study patients were categorized into 2 groups:

Group 1) Drug-related AV block (DR-AVB) comprised patients who were using antiarrhythmic agents (Class II, IV, and/or digoxin), irrespective of the duration of use of the responsible drug. After discontinuation of the medication for at least 5 half-lives, the patients were divided into 2 subgroups based on the need for a PPM.

a) PPM necessary: This group was made up of subjects with a persistent AV block after drug discontinuation (at least 5 half-lives) or early recurrence during the index admission who underwent PPM implantation.

b) PPM unnecessary: Patients in this group had restoration of AV conduction after drug discontinuation and PPM implantation at that time was not considered necessary.

Abbreviations:

AF	*Atrial fibrillation*
AV	*Atrioventricular*
BB	*Beta blocker*
CCB	*Calcium channel blocker*
DR-AVB	*Drug-related AV block*
ECG	*Electrocardiogram*
MI	*Myocardial infarction*
PPM	*Permanent pacemaker*

Group 2) Non-drug-related AV block (non-DR-AVB): The AV block of these patients was unrelated to any medication.

a) PPM necessary: Subjects in this group had a persistent AV block or early recurrence during the index admission and underwent PPM implantation.

b) PPM unnecessary: This group demonstrated early recovery of AV conduction during the index admission based on continuous ECG monitoring and the resolution of symptoms. These patients were followed up closely once a week for 1 month, once a month for 6 months, and then annually, according to the protocol of the medical center.

All of the patients were monitored closely and a PPM was implanted in patients with a recurrence or persistence of the AV block. PPM-free patients (in both groups) were followed up to determine any subsequent implantation of a PPM. Hospital records of re-admission were collected, and patients were called to provide a detailed history when the data were incomplete. All of the ECG results were read by an experienced electrophysiologist.

Statistical analysis

Continuous variables were presented as mean and SD for data with a normal distribution, or median and 25th and 75th percentiles for data with a skewed distribution. Normal distribution of the variables was evaluated according to the abovementioned central tendency and dispersion measures as well as histogram charts. Normality of the variables in subgroups with a small sample size was assessed using the Kolmogorov-Smirnov test. The Student's t-test or the Mann-Whitney U test was used to compare continuous variables between groups. Categorical variables were expressed as absolute frequency and percentage and were compared between groups applying a chi-square or Fisher's exact test, as appropriate. All statistical analyses were

conducted using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). A p value ≤0.05 was considered statistically significant.

RESULTS

Based on the inclusion and exclusion criteria, 1123 of 1900 patients were enrolled in the analyses. A total of 316 (28%) patients were included in Group 1 and 807 (72%) patients were included in Group 2 (Fig. 1).

Baseline demographic and clinical features of the study groups are summarized in Table 1. The mean age and the frequency of hypertension, diabetes mellitus, dyslipidemia, and chronic renal failure were higher in the DR-AVB group compared with the non-DR-AVB group. There were no significant differences between the 2 groups in terms of sex; presence of chronic heart failure, coronary artery disease, lung, or thyroid disease; stroke; smoking; or the type and level of AV block.

Group 1) Drug-related-AV block (DR-AVB)

The prevalence of the culprit drugs was analyzed: Beta blockers (BBs) were the medication used by 274 (86.7%) patients, 16 (5.1%) used diltiazem, 3 (0.9%) used verapamil, 41 (13%) used digoxin, a combination of a BB and digoxin was used by 41 (13%), a combination of a BB and a calcium channel blocker (CCB) was used by 32 (10.1%), and a combination of a CCB and digoxin was used in 1 (0.3%) case. Among 316 patients with DR-AVB, 278 (88%) underwent PPM implantation during the index admission. In 38 (12%) subjects, the AV block was resolved during the index hospitalization after discontinuation of the use of responsible drug for at least 5 half-lives and the patients were discharged uneventfully. During a median of 3 years of follow-up, a PPM was implanted in 7 of 38 (18.4%) patients due to recurrence of AV block. No follow-up data could be collected for 4 patients, and 2 deaths had occurred due to noncardiac causes (1 due to end-stage malignancy and 1 due to end-stage renal disease). In all, a total of 25 (7.9%) patients in Group 1 were PPM-free at the time of writing this manuscript (Fig. 1).

Group 2) Non-drug-related AV block (non-DR-AVB)

Among 807 patients in Group 2, a total of 759 (94.1%) patients underwent PPM implantation during the index admission. AV conduction was recovered and symptoms resolved in 48 (5.9%) subjects and the patients were discharged uneventfully. During the median 3-year follow-up period, a PPM was implanted in 19 of 48 (40%) patients due to recurrence of AV block. A total of 25 (3.1%) subjects in Group 2 remained PPM-free at the time of writing this manuscript, and there were 4 deaths due to causes other than the AV block (2 due to malignancies, 1 due to acute MI, and 1 due to a massive pulmonary thromboembolism).

PPM-free patients in both groups

At a median 3-year follow-up point, PPM implantation had been required in a total of 7 (2.2%) and 19

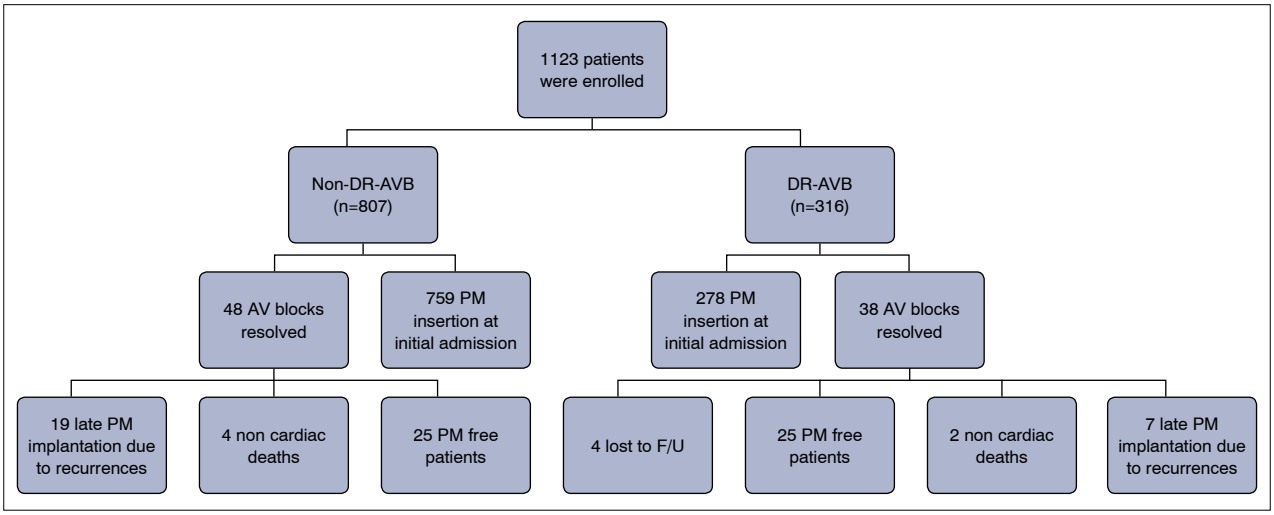

Figure 1. Flow diagram of the study (DR-AVB: Drug-related AV block; F/U: Follow–up; Non-DR-AVB: Non-drug-related AV block; PPM: Permanent pacemaker).

Table 1. Patient characteristics at initial admission

	Non-drug-related AV block (n=807)	Drug-related AV block (n=316)	*p*
Age (years)	68.6±15.01	72.2±10.86	<0.001
Sex			
Male	391 (48.5)	146 (46.2)	0.700
Female	416 (51.5)	170 (53.8)	
Hypertension	431 (53.4)	234 (74.1)	<0.001
Diabetes mellitus	198 (24.5)	106 (33.5)	0.020
Hyperlipidemia	188 (23.3)	102 (32.3)	0.004
Chronic renal failure	32 (4)	25 (7.9)	0.004
Chronic heart failure	30 (3.7)	18 (5.7)	0.190
Coronary artery disease	1 (0.1)	1 (0.3)	0.470
Cerebrovascular event	27 (3.3)	19 (6)	0.060
Thyroid disease	30 (3.7)	21 (6.6)	0.320
Smoking	66 (8.2)	22 (7)	0.600
Block_type*			0.150
Atrioventricular block 2:1	121 (15)	63 (20)	
Wenckebach	15 (1.9)	8 (2.5)	
Mobitz II	24 (3)	12 (3.7)	
Third-degree	647 (80.1)	233 (73.8)	

* Block types were recorded based on electrocardiogram findings; age is presented as mean±SD and other variables as number (proportion).
AV: Atrioventricular.

(2.4%) patients in the DR-AVB and Non-DR-AVB groups, respectively. In all, 25 patients in each group (4.5% of the whole study group) remained PPM-free. The mean age and the frequency of hypertension and diabetes were greater in the PPM-free patients in Group 1; however, the ECG parameters and the level of AV block were not statistically different (Table 2).

DISCUSSION

In the present study, nearly one-third of the patients admitted to the hospital due to an AV block were on AV-blocking agents. BBs, verapamil, and diltiazem were among the most commonly used medications causing AV block in our study group. Despite discontinuation of the responsible drug and resolution of the AV block in 7.7% (n=86) of the patients during the index hospitalization, a total of 30.2% (26/86) of these patients underwent a subsequent PPM implantation in the follow-up period. The majority of patients with the diagnosis of drug-induced AV block at the index hospitalization underwent PPM implantation (278 patients during index hospitalization and 7 patients during follow-up, a total of 285/316 patients). Most of the patients with non-DR-AVB needed PPM implantation during the index admission or after discharge (759 patients during the index hospitalization and 19 patients during the follow-up period). A high rate of AV block relapse in this patient group was confirmed in our study. In all, 3.1% (25/807) of the patients remained asymptomatic without PPM implantation.

As a referral hospital, patients from all over the country and even private centers in the city are referred to our center for pacemaker implantation. This fact likely contributed to a higher rate of pacemaker implantation during the first hospitalization than that seen in other studies.

Although the percentage of patients with DR-AVB who underwent PPM implantation during the index admission or after discharge was less than that of the non-DR-AVB group, discontinuation of the responsible medications did not always obviate the necessity of PPM implantation. According to our findings, the risk of recurrence is not negligible (18.4% for Group 1 and 40% for Group 2) and a significant number of

Table 2. Patient characteristics during follow-up

	Drug-related (n=38)		Non-drug-related (n=48)	
	Needed PPM after FU (n=7)	PPM-free (n=25)	Needed PPM after FU (n=19)	PPM-free (n=25)
Age (years †‡	72.9±8.34	72.3±11.52	74.2±8.4	58.8±19.46
QRS_width (ms)†	125.7±27.6	123.2±22.86	132.2±25.4	124.2±27.65
PR interval (ms)†	200 (140, 240)	320 (200, 320)	240 (200, 360)	260 (200, 320)
Escape rate (ms)†	44.1±3.72	40.8±9.48	44.3±9.44	46.7±7.79
Sex				
Male	2 (28.6)	11 (44)	8 (34.8)	16 (64)
Female	5 (71.4)	14 (56)	15 (65.2)	9 (36)
HTN†‡	2 (28.6)	17 (68)	15 (65.2)	7 (28)
DM†‡	1 (14.3)	10 (40)	9 (39.1)	3 (12)
HLP	1 (14.3)	5 (20)	4 (17.4)	1 (4)
CRF	0 (0)	4 (16)	3 (13)	1 (4)
CHF	0 (0)	0 (0)	0 (0)	1 (4)
CVA	0 (0)	1 (4)	2 (8.7)	1 (4)
Thyroid disease	1 (14.3)	0 (0)	1 (4.3)	3 (12)
Smoking	0 (0)	0 (0)	0 (0)	1(4)
Block type*				
AV block 2:1	3 (43)	5 (20)	6 (31.5)	9 (36)
Wenckebach	0 (0)	5 (20)	4 (21)	7 (28)
Mobitz II	0 (0)	0 (0)	0 (0)	0 (0)
Third-degree	4 (57)	15 (60)	9 (47.5)	9 (36)

†Mean±SD; ‡Factors with a statistically significant difference between groups. *Block type was recorded based on electrocardiogram findings.
AV: Atrioventricular; CHF: Chronic heart failure; CRF: Chronic renal failure; CVA: Cerebrovascular event; DM: Diabetes mellitus; DR-AVB: Drug-related AV block; HTN: Hypertension; HLP: Hyperlipidemia; Non-DR-AVB: Non-drug-related AV block; PPM: Permanent pacemaker.

patients experienced a recurrence of AV block during a median 3-year follow-up period. Longer follow-up could reveal an even greater number.

Zeltser et al.[3] found that BBs and/or CCBs were responsible for 15% of AV blocks in their study. It has also been reported that in patients using BBs or CCBs, symptomatic bradycardia can occur unrelated to suspected drugs (innocent bystander), and that these drugs were more likely to be the culprit in sinus bradycardia than high-grade AV block.[5,6] The strategy of drug cessation has been built on the belief that drugs are a reversible or curable cause of AV block. However, recovery of AV conduction may also occur in patients who are not using these drugs (6% in this study),[7] which suggests a drug-independent process. AV conduction improvement after drug discontinuation may be a coincidental finding or a natural course of the underlying disease.[8,9] Duarte et al.[10] observed that a large percentage of patients with potentially reversible bradyarrhythmia experienced relapse or lack of improvement during follow-up, and that patients with AV node disease had a higher risk of recurrence and pacemaker implantation after the first admission. The findings in that study are consistent with ours, but the sample size is much smaller.

It is also noteworthy that the true etiology of the cardiac conduction block in patients with DR-AVB is still not fully understood. It may be that relapse after discontinuation of the culprit drug suggests a baseline conductive disease abnormality aggravated by the AV-blocking agent. Therefore, watchful follow-up of these patients should be considered, and prompt PPM implantation in cases of early recurrence may be recommended.

Limitations

The strengths of this study include the large number of patients and long-term follow-up period; however, our study has a number of limitations. First, this is a single-center, retrospective study conducted at a referral center, which may have rendered it susceptible to biases. Second, an electrophysiology study was not performed before PPM implantation and there was no Holter ECG monitoring during follow-up. Third, due to the retrospective nature of our study, major symptoms at first admission could not be evaluated in some cases.

Conclusion

According to current guidelines, the general consensus is against immediate PPM implantation in cases of DR-AV block. However, the results of our study and similar studies have revealed that discontinuation of responsible medications does not completely eliminate the need for PPM implantation. Drug-induced AV block does not appear to be as benign as previously thought, and an active follow-up plan for after discharge is required even after discontinuation of culprit medications due to the high recurrence rate.

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