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The Predictors of the Reversibility Among Patients With a High-Grade Atrioventricular Block

Yüksek Dereceli Atriyoventriküler Bloğu Olan Hastalarda Geri Dönüşlülüğün Öngördürücüleri

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Öz

Amaç: Klinik uygulamada atriyoventriküler bloğun geri dönüşlü olabildiği görülmektedir. Atriyoventriküler blok (AVB) geri dönüşlülüğü ile ilişkili belirleyicileri tespit etmek, gereksiz kalıcı kalp pili (KKP) implantasyonlarını ve ilgili komplikasyonları önlemek açısından önemlidir. Bu çalışmada AVB'nin geri dönüşlülüğünün olası nedenlerini belirlemeyi amaçladık.

Yöntemler: Demografik ve klinik veriler, hastane elektronik bilgi sistemi 2012-2020 yılları arasında geriye dönük taranarak toplandı. Yüksek dereceli AVB nedeniyle ilk kez hastaneye yatırılan hastalar çalışmaya dahil edildi.

Bulgular: Geri dönüşümsüz AVB 165 hastada, geri dönüşümlü AVB ise 78 hastada gözlendi. AVB düzelmesi olmayan hastalar daha yaşlıydı (77 yaş - 74,5 yaş; p=0,026) ve bu hastalarda koroner arter hastalığı (KAH) öyküsü daha sıktı (%29,4 - %13,9; p=0,004). Geri dönüşümlü bloğu olan hastalarda akut koroner sendrom (AKS) ile başvuru daha sıktı (%15,3 - %2,4; p<0,001). Beta-bloker kullanımı (%38,4 - %15,1; p<0,001) ve non-dihidropiridin kalsiyum kanal blokerleri (NKKB) kullanımı (%7,7 - %1,8; p=0,033) geri dönüşümlü AVB'li hastalarda daha yaygındı. Çok değişkenli analizde başvuru sırasında AKS (OR 0,103; %95 GA: 0,030-0,350; p<0,001), beta bloker kullanımı (OR 0,235; 95% GA: 0,116-0,476; p<0,001) ve NKKB kullanımının (OR 0.13, %95 GA: 0.030-0.563; p=0.006) AVB'nin geri dönüşlülüğünü öngördüğü görüldü. Ancak yaş ve anlamlı kronik KAH öyküsü AVB'nin geri dönüşlülüğünün belirleyicisi değildi (sırasıyla p=0,07 ve p=0,178).

Sonuç: AKS veya beta-bloker/NKKB kullanımıyla başvuran hastalarda AVB geri dönüşümlü olabilir ve KKP implantasyonundan önce dikkatle sorgulanıp tedavi edilmelidir. Geri dönebilirliğin göstergesi olmayan önemli KAH öyküsü, kalp pili implantasyonundan önce tedaviyi beklemeyi gerektirmeyebilir.

Anahtar Kelimeler: Atriyoventriküler blok, kalp pili implantasyonu, geri dönüşümlü atriyoventriküler blok

Abstract

Aim: Reversibility of atrioventricular block (AVB) is evident in clinical practice. Identifying predictors associated with AVB reversibility is important to prevent unnecessary permanent pacemaker (PPM) implantations and related complications. We aimed to identify possible causes of AVB reversibility.

Methods: Demographic and clinical data were collected by retrospectively scanning the hospital electronic information system between 2012 and 2020. Patients hospitalized for the first time with high-degree AV block were included.

Results: Irreversible AVB was observed in 165 patients while reversible AVB was observed in 78 patients. Patients without AVB recovery was older (77 years vs 74.5 years, p=0.026) and had more frequent previous history of coronary artery disease (CAD) (29.4% vs 13.9%, p=0.004). Presentation with acute coronary syndrome (ACS) was more frequent in patients with reversible block (15.3% vs 2.4%, p<0.001). Beta-blockers use (38.4% vs 15.1%, p<0.001) and non-dihydropyridine calcium channel blockers (NCCB) use (7.7% vs 1.8%, p=0.033) were more common in patients with reversible AVB. The multivariate analysis displayed that ACS on admission (OR 0.103, 95% CI 0.030-0.350, p<0.001), beta-blockers use (OR 0.235, 95% CI 0.116-0.476, p<0.001) and NCCBs use (OR 0.13, 95% CI 0.030-0.563, p=0.006) predicted the reversibility of AVB; however, age and significant chronic CAD history was not a determinant of the reversibility of AVB (p=0.07 and p=0.178, respectively).

Conclusion: In patients those admitting with ACS and beta-blockers or NCCBs use, AV block might be reversible that should be carefully questioned and treated before a PPM implantation. Significant CAD history is not an indicator of the reversibility which might not be needed to wait for treatment to avoid PPM implantation.

Keywords: Atrioventricular block, pacemaker implantation, reversible atrioventricular block

Introduction

Atrioventricular (AV) block is a relatively rare arrhythmia with a rising prevalence due to the increasing aging population. In most cases, the underlying cause is the dissociation of atrial and ventricular activity due to lack of conduction through the AV node or His-Purkinje system (1). Various pathological conditions that cause infiltration, fibrosis, or loss of connectivity in some areas of the healthy conduction system can lead to acquired AV block. Medications that may affect the conduction system, valve surgery, percutaneous interventions, myocardial infarction, septal alcohol ablation, or electrophysiological ablation of the slow or fast pathway of the AV node may also cause AV block. Treatment of AV block requires implantation of a device that stimulates or imitates the conduction system; hence, a medical treatment with the same feature is not yet available (2, 3). A permanent pacemaker (PPM) can save lives, but its implantation is expensive and might cause complications such as infection, bleeding or hematoma, hemothorax, lead dislodgment, and rupture of the cardiac chambers (4, 5). In addition, pacemaker leads can break, fracture, or require recall over time. In these cases, lead extraction—a potentially dangerous procedure—might be necessary (6).

In some occasions, AV block may be reversible. Thyroid disorders, metabolic abnormalities, infections, chemotherapeutic or negative chronotropic agents, and even herbal medications might cause temporary AV block (7, 8). It is crucial to identify those with reversible AV block to avoid unnecessary device implantations.

In this study, we aimed to identify predictors associated with improvement of AV block in order to prevent unnecessary PPM implantations and related complications.

Material and methods

The study was approved by the institutional ethics committee and was conducted in accordance with the principles stated in the Declaration of Helsinki.

Retrospective screening was performed by retrospectively collecting demographic (age and gender) and clinical data using the hospital electronic information system between 2012 and 2020. A standard 12-lead ECG was performed on all participants. Patients hospitalized for the first time with high-degree AV block were included. A search of the database included International Classification of Diseases, Tenth Revision (ICD-10) codes I44.1 (second-degree AV block) or I44.2 (third-degree AV block).

Cardiovascular Comorbidities

Hypertension was defined as systolic blood pressure over 140 mmHg and diastolic blood pressure over 90 mmHg measured on two different days in patients not using blood pressure-lowering medications. Patients using blood pressure-lowering treatment and patients with antihypertensive medication use in the database were defined as patients with a history of hypertension (9).

Diabetes mellitus was defined as patients with at least 200 mg/dL in a single measurement or at least 126 mg/dL in a fasting state in 2 separate measurements and using anti-diabetic medications (10).

Advanced, high-grade or high-degree atrioventricular block was described presence of ≥2 consecutive P waves at a constant physiologic rate that do not conduct to the ventricles with evidence for some AV conduction or no evidence of AV conduction (11).

In patients with recent changes in clinical symptoms or signs, the diagnosis of acute coronary syndrome (ACS) was made using universal criteria, with or without changes in the 12-lead electrocardiogram (ECG) and with or without an acute increase in cardiac troponin (cTn) and creatine kinase –myocardial band (CK-MB) concentrations (12).

Significant coronary artery disease (CAD) was defined as >50% stenosis in the left main stem,>70% stenosis in at least one of the major coronary vessels, or 30% to 70% stenosis with fractional flow reserve ≤ 0.8 in coronary angiography (13). Previous diagnoses of cerebrovascular disease, chronic obstructive pulmonary disease, previous significant CAD, and current smoking were queried from the patient's history and electronic database.

Laboratory measurements

Serum creatinine level at admission and before discharge, white blood cells count, hemoglobin, platelet, serum calcium, and serum potassium at admission were all recorded.

Medication history

Use of medications that affect rhythm (beta blocker, calcium channel blocker, digoxin, amiodarone, propafenone or ivabradine) was noted

Table-1: Baseline characteristics of the study population

Variables	Irreversible AV block (IB group) n=165	Reversible AV block (RB group) n=78	P value
Demographic and clinic features			
Age (years)	77 (33-99)	74.5 (37-97)	**0.026**
Gender, male (%)	79 (47.8)	35 (44.8)	0.661
Current smoker (%)	33 (20)	24 (30.7)	0.064
Diabetes mellitus (%)	51 (30.9)	28 (35.8)	0.438
Hypertension (%)	107 (64.8)	60 (76.9)	0.058
Cerebrovascular disease (%)	29 (17.5)	11 (14.1)	0.495
Chronic obstructive pulmonary disease (%)	33 (20)	18 (23)	0.582
Prior significant CAD (%)	23 (13.9)	23 (29.4)	**0.004**
Presentation with ACS (%)	4 (2.4)	12 (15.3)	<**0.001**
Requirement of TPM (%)	125 (75.7)	50 (64.1)	0.059
Medication use affecting rhythm (%)	32 (19.3)	40 (51.2)	<**0.001**
Laboratory tests			
Hemoglobin (g/L)	8.8 (2.5-18.5)	9.3 (3.3-17.2)	0.281
White blood cells (cell/µl)	12.1±2.0	12.2±2.1	0.709
Platelet (cell/µl)	226 (34-807)	232 (92-453)	0.499
Calcium (mg/dL)	8.8 (7.2-11)	8.8 (8.2-10.5)	0.297
Potassium (mmol/L)	4.4 (3-6.7)	4.6 (2.9-6.8)	0.289
First admission creatinine (mg/dL)	1.09 (0.51-12)	1.2 (0.63-8.6)	0.068
Discharge creatinine (mg/dL)	0.94 (0.52-7.65)	0.97 (0.63-8.8)	0.601
Medications			
Beta blockers (%)	25 (15.1)	30 (38.4)	<**0.001**
Calcium channel blockers (%)	3 (1.8)	6 (7.7)	**0.033**
Digoxin (%)	3 (1.8)	4 (5.1)	0.215
Amiodarone (%)	0 (0)	2 (2,6)	0.102
Propafenone (%)	1 (0.6)	3 (3.8)	0.099
Ivabradine (%)	0 (0)	1 (1.3)	0.321

Abbreviations: CAD, coronary artery disease; ACS, acute coronary syndrome; TPM, temporary pacemaker
Values are presented as mean ± SD, median (IQR:Q1-Q3), or n (%).

Irreversible AV block was observed in 165 patients (IB group), while reversible AV block was observed in 78 patients (RB group). Patients without AV block recovery was older (77 years vs 74.5 years, p=0.026) and had more frequent previous history of significant CAD (29.4% vs 13.9%, p=0.004). Presentation with ACS was more frequent in patients with reversible AV block (15.3% vs 2.4%, p<0.001). A total of 175 patients had a temporary pacemaker implantation procedure; 125 patients (75.7%) from IB group and 50 patients (64.7%) from RB group (p=0.059). Two groups had similar baseline laboratory parameters (Table 1). Among the medications that have an impact on the conduction system, beta-blockers use (38.4% vs 15.1%, p<0.001) and non-dihydropyridine calcium channel blockers use (7.7% vs 1.8%, p=0.033) were more common in patients with reversible AV block.

Digoxin use was similar between two groups (p=0.215). Univariate analysis revealed several significant factors associated with AV block reversibility; male gender {odds ratio (OR) 0.974, 95% confidence interval (CI) 0.952-0.997, p=0.027}, prior significant CAD (OR 2.582, 95% CI 1.339-4.978, p=0.005), ACS on admission (OR 7.318, 95% CI 2.278-23.515, p=0.001), beta blockers use (OR 3.5, 95% CI 1.876-6.531, p<0.001) and calcium-channel blockers use (OR 4.5, 95% CI 1.095-18.495, p=0.037). The results of multivariate analysis showed that only ACS on admission (OR 0.103, 95% CI 0.030-0.350, p<0.001), beta-blockers use (OR 0.235,95% CI 0.116-0.476, p<0.001) and calcium channel blockers use (OR 0.13, 95% CI 0.030-0.563, p=0.006) predicted the reversibility of AV block.

Table-2: Variables associated with reversibility of atrioventricular block

	Univariate Regression Analysis			Multivariate Regression Analysis		
Variables	**OR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Age	0.974	0.952-0.997	**0.027**	0.976	0.951-1002	0.070
Prior significant CAD	2.582	1.339-4.978	**0.005**	0.593	0.278-1.267	0.178
ACS on admission	7.318	2.278-23.515	**0.001**	0.103	0.030-0.350	**<0.001**
Beta-blockers use	3.5	1.876-6.531	**<0.001**	0.235	0.116-0.476	**<0.001**
Calcium-channel blockers use	4.5	1.095-18.495	**0.037**	0.13	0.030-0.563	**0.006**

Abbreviations: CAD, coronary artery disease; ACS, acute coronary syndrome; OR, odds ratio; CI, confidence interval

Discussion

In this study, we found that patients with reversible AV block were more frequently admitted to the hospital with a preliminary diagnosis of ACS. Additionally, the use of medications that impact the conduction system, such as beta-blockers or non-dihydropyridine calcium-channel blockers, and presenting with ACS upon admission were indicators of the reversibility of AV block; however, chronic significant CAD was not related to the reversibility of AV block. Age was not also a determinant of the reversibility of the AV block.

The occurrence of high-grade AV block in ACS has been previously demonstrated. A 3-14% incidence of AV block has been reported in patients with ACS and has been associated with increased in-hospital mortality (14). In a national ACS registry in Portugal, patients with high-degree AV block were older, more often female, and had a higher prevalence of history of stroke compared with those without AV block (15).

The frequency of inferior myocardial infarction (MI) was higher in patients with AV block. The higher incidence of inferior MI was attributed to hypoperfusion of the AV node due to occlusion of the right coronary artery (RCA) and increased parasympathetic tone in the context of ACS. The AV node also has collateral perfusion from septal arteries originating from the anterior descending artery, so anterior MI can cause AV block in addition to inferior MI (16). Perfusion of the occluded artery via percutaneous intervention has often restored the functions of the conduction system in most patients in the setting of ACS (17). In the current study, admission with ACS was found to be associated with the reversibility of AV block. Patients who present with AV block in the setting of an acute MI is advised to undergo a waiting period before determining the need for permanent pacing. However, duration of the waiting period is unclear (11).

The reversibility of AV block after revascularization in non-acute coronary ischemia attacks is controversial. It is mostly attributed to the vagally mediated heart block and ischemia-driven conduction delay in patients with CAD, more pronounced in subjects with RCA lesions. Ischemia-induced mechanical stretch and the release of chemical substances that stimulate receptors on the inferior and posterior walls of the left ventricle are the proposed mechanisms of AV block. These receptors activate unmyelinated C fibers in the vagus nerve, leading to increased vagal tone and bradyarrhythmia known as the Bezold-Jarisch reflex. In a case report involving a non-ST-elevation MI patient with complete heart block due to 90% stenosis of the acute marginal branch of the RCA, resolution of AV block after balloon angioplasty of the lesion was attributed to the Bezold-Jarisch reflex. Since the acute marginal branch AV node has no supply vessel, it was suggested to be triggered by ischemia in the inferior wall (18). The decrease in post-exercise heart rate deterioration after coronary revascularization in patients with RCA lesions also supported the idea that vagal activity decreased after reperfusion in the ischemic inferior and posterior walls. It remains challenging to determine whether reduced cardiac sensitivity to vagal stimuli after revascularization can completely reverse high-grade AV block and prevent its further occurrence. Moreover, if heart block were solely the result of increased vagal tone, intermittent attacks of AV block would be expected to be observed during periods of increased vagal tone, even after revascularization (19). In this study, presentation with ACS was associated with reversibility of AV block, whereas a history of significant CAD was not.

In a study of 507 patients requiring a PPM who underwent coronary angiography within 2 months before or after implantation, 42% (n=212) of patients underwent coronary angiography and showed significant narrowing of the coronary arteries (≥ 50% stenosis of coronary arteries with a diameter of ≥ 2.5 mm) was detected in 150 (71%) patients. Merely 19% of the patients received percutaneous coronary intervention treatment, whereas 21% of the patients underwent coronary artery bypass grafting. The distribution of atherosclerotic lesions in the LAD, CX, or RCA coronary arteries was similar, and neither the left nor the right circumflex coronary arteries predominated in the study group. Despite not providing correlation analysis, the study showed no association between the need for a pacemaker and CAD (20). Most studies have suggested that myocardial revascularization does not provide long-term improvement in AV conduction, and patients with severe CAD and severe conduction abnormalities may benefit from receiving a pacemaker in addition to anti-ischemic therapy (1, 21). Similar to other studies we observed no relation with chronic CAD and resolution of AV block. It seems reasonable to schedule patients for PPM implantation in those without finding of an acute MI.

Medications that slow or block AV conduction, such as beta blockers, non-dihydropyridine calcium channel blockers, and class I or III anti-arrhythmic drugs, are commonly used to treat hypertension, arrhythmias, heart failure, and other cardiac diseases. As a result, patients taking these medications may often experience AV block. In addition, these medications are sometimes an essential part of the pharmacological regimen that should not be interrupted. Although AV block can sometimes be reversible with discontinuation of medications, several case series indicate that this is unusual if medications are used in therapeutic doses. Furthermore, even when acute reversal of AV block is observed, subsequent pacemaker implantation may be necessary (22). In our study, cessation of these medications was associated with the reversibility of AV block. Long-term follow-up of these patients should be considered to determine the need for a PPM in the relatively elderly population.

Aging is associated with the development of chronotropic incompetence and a decline in heart rate variability, but the underlying causes are not fully understood. Some studies have previously reported that the prevalence of AV block increases with age (24, 25). The median PR interval has been shown to increase with age in a healthy Chinese population (26). In older people, electrical and structural restructuring occurs due to calcification and fibrosis of the conduction system, which may play an important role in prolonging the PR interval. Electrophysiological studies have also confirmed that increased atrial refractoriness and conduction times accompany aging (27). In our study, age was not a determinant of the reversibility of the AV block.

Limitations

The current study had several limitations that should be addressed. Since this study was observational and non-randomized, there may have been related confounders that affected the results. There is no follow-up of the patients after their medications were stopped, however AV block recovery was observed before the hospital discharge. Therefore, this study does not provide long term results but provides in hospital AV block recovery results.

Conclusion

In patients presenting with AV block, underlying conditions that may cause reversibility should be carefully questioned before PPM treatment. Significant CAD seemed to be not related to the AV block recovery while an ACS on admission was related with reversibility of the AV block. Use of medicine should also be carefully evaluated before a making PPM implantation.

References

1. Barra SN, Providência R, Paiva L, Nascimento J, Marques AL. A review on advanced atrioventricular block in young or middle-aged adults. Pacing Clin Electrophysiol. 2012 Nov;35(11):1395-405. doi: 10.1111/j.1540-8159.2012.03489. x. Epub 2012 Aug 16. PMID: 22897386.
2. Epstein AE, DiMarco JP, Ellenbogen KA, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices); American Association for Thoracic Surgery; Society of Thoracic Surgeons. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008 May 27;51(21):e1-62. doi: 10.1016/j.jacc.2008.02.032. Erratum in: J Am Coll Cardiol. 2009 Apr 21;53(16):1473. Erratum in: J Am Coll Cardiol. 2009 Jan 6;53(1):147. PMID: 18498951.
3. Brignole M, Auricchio A, Baron-Esquivias G,et al; ESC Committee for Practice Guidelines (CPG); Zamorano JL, Achenbach S, Baumgartner H,et al; Document Reviewers; Kirchhof P, Blomstrom-Lundqvist C, Badano LP et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J. 2013 Aug;34(29):2281-329. doi: 10.1093/eurheartj/eht150. Epub 2013 Jun 24. PMID: 23801822.
4. Castelnuovo E, Stein K, Pitt M, Garside R, Payne E. The effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation. Health Technol Assess. 2005 Nov;9(43): iii, xi-xiii, 1-246. doi: 10.3310/hta9430. PMID: 16266560.
5. Osman F, Krishnamoorthy S, Nadir A, Mullin P, Morley-Davies A, Creamer J. Safety and cost-effectiveness of same day permanent pacemaker implantation. Am J Cardiol. 2010 Aug 1;106(3):383-5. doi: 10.1016/j.amjcard.2010.03.038. PMID: 20643250.
6. Buch E, Boyle NG, Belott PH. Pacemaker and defibrillator lead extraction. Circulation. 2011 Mar 22;123(11): e378-80. doi: 10.1161/CIRCULATIONAHA.110.987354. PMID: 21422393.
7. Singh JB, Starobin OE, Guerrant RL, Manders EK. Reversible atrioventricular block in myxedema. Chest. 1973 Apr;63(4):582-5. doi: 10.1378/chest.63.4.582. PMID: 4695358.
8. Guha S, Dawn B, Dutta G, Chakraborty T, Pain S. Bradycardia, reversible panconduction defect and syncope following self-medication with a homeopathic medicine. Cardiology. 1999;91(4):268-71. doi: 10.1159/000006922. PMID: 10545684.
9. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8) [published correction appears in *JAMA*. 2014;311(17):1809]. *JAMA.* 2014;311(5):507-520
10. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010 Jan;33 Suppl 1(Suppl 1): S62-9. doi: 10.2337/dc10-S062. Erratum in: Diabetes Care. 2010 Apr;33(4): e57. PMID: 20042775; PMCID: PMC2797383.
11. Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients with Bradycardia and Cardiac Conduction Delay: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2019 Aug 20;140(8): e382-e482. doi: 10.1161/CIR.0000000000000628. Epub 2018 Nov 6. Erratum in: Circulation. 2019 Aug 20;140(8): e506-e508. PMID: 30586772.
12. Kumar A, Cannon CP. Acute coronary syndromes: diagnosis and management, part I. Mayo Clin Proc. 2009 Oct;84(10):917-38. doi: 10.4065/84.10.917. PMID: 19797781; PMCID: PMC2755812.
13. Neglia D, Rovai D, Caselli C, et al; EVINCI Study Investigators. Detection of significant coronary artery disease by noninvasive anatomical and functional imaging. Circ Cardiovasc Imaging. 2015 Mar;8(3):e002179. doi: 10.1161/CIRCIMAGING.114.002179. PMID: 25711274.
14. Aguiar Rosa S, Timóteo AT, Ferreira L, et al. Complete atrioventricular block in acute coronary syndrome: prevalence, characterisation and implication on outcome. Eur Heart J Acute Cardiovasc Care. 2018 Apr;7(3):218-223. doi: 10.1177/2048872617716387. Epub 2017 Jun 15. PMID: 28617040.
15. Santos H, Santos M, Almeida I, et al; Portuguese Registry of Acute Coronary Syndromes. High-grade atrioventricular block in acute coronary syndrome: Portuguese experience. J Electrocardiol. 2021 Sep-Oct; 68:130-134. doi: 10.1016/j.jelectrocard.2021.08.002. Epub 2021 Aug 16. PMID: 34419648.
16. Kennel AJ, Titus JL. The vasculature of the human atrioventricular conduction system. Mayo Clin Proc. 1972 Aug;47(8):562-6. PMID: 5049161.
17. Kimura K, Kimura T, Ishihara M, et al; Japanese Circulation Society Joint Working Group. JCS 2018 Guideline on Diagnosis and Treatment of Acute Coronary Syndrome. Circ J. 2019 Apr 25;83(5):1085-1196. doi: 10.1253/circj. CJ-19-0133. Epub 2019 Mar 29. PMID: 30930428.
18. Chiladakis JA, Patsouras N, Manolis AS. The Bezold-Jarisch reflex in acute inferior myocardial infarction: clinical and sympathovagal spectral correlates. Clin Cardiol. 2003 Jul;26(7):323-8. doi: 10.1002/clc.4950260706. PMID: 12862298; PMCID: PMC6654613.
19. Tahara N, Takaki H, Taguchi A,et al. Pronounced HR variability after exercise in inferior ischemia: evidence that the cardioinhibitory vagal reflex is invoked by exercise-induced inferior ischemia. Am J Physiol Heart Circ Physiol. 2005 Mar;288(3):H1179-85. doi: 10.1152/ajpheart.00045.2004. Epub 2004 Oct 21. PMID: 15498830.
20. Brueck M, Bandorski D, Kramer W. Incidence of coronary artery disease and necessity of revascularization in symptomatic patients requiring permanent pacemaker implantation. Med Klin (Munich). 2008 Dec 15;103(12):827-30. doi: 10.1007/s00063-008-1130-z. Epub 2008 Dec 20. PMID: 19099211.
21. Yesil M, Bayata S, Arikan E, Yilmaz R, Postaci N. Should we revascularize before implanting a pacemaker? Clin Cardiol. 2008 Oct;31(10):498-501. doi: 10.1002/clc.20280. PMID: 18855876; PMCID: PMC6653110.
22. Pavone C, Pelargonio G. Reversible Causes of Atrioventricular Block. Cardiol Clin. 2023 Aug;41(3):411-418. doi: 10.1016/j.ccl.2023.03.004. PMID: 37321691.
23. Byrne EA, Fleg JL, Vaitkevicius PV, Wright J, Porges SW. Role of aerobic capacity and body mass index in the age-associated decline in heart rate variability. J Appl Physiol (1985). 1996 Aug;81(2):743-50. doi: 10.1152/jappl.1996.81.2.743. PMID: 8872642.
24. Kerola T, Eranti A, Aro AL, et al. Risk Factors Associated with Atrioventricular Block. JAMA Netw Open. 2019 May 3;2(5): e194176. doi: 10.1001/jamanetworkopen.2019.4176. PMID: 31125096; PMCID: PMC6632153.
25. Shan R, Ning Y, Ma Y, et al. Prevalence and risk factors of atrioventricular block among 15 million Chinese health examination participants in 2018: a nation-wide cross-sectional study. BMC Cardiovasc Disord. 2021 Jun 11;21(1):289. doi: 10.1186/s12872-021-02105-3. PMID: 34116630; PMCID: PMC8194203.
26. Wu J, Kors JA, Rijnbeek PR, van Herpen G, Lu Z, Xu C. Normal limits of the electrocardiogram in Chinese subjects. Int J Cardiol. 2003 Jan;87(1):37-51. doi: 10.1016/s0167-5273(02)00248-6. PMID: 12468053.
27. Kistler PM, Sanders P, Fynn SP, et al. Electrophysiologic and electroanatomic changes in the human atrium associated with age. J Am Coll Cardiol. 2004 Jul 7;44(1):109-16. doi: 10.1016/j.jacc.2004.03.044. PMID: 15234418.