

Predictive factors of atrioventricular conduction disorders

Carmen Marina Deutsch¹, Elisabeta Badila^{1,2}, Adriana Iliesiu^{2,3}

¹Department of Cardiology, Colentina Clinical Hospital, Bucharest, Romania

²"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

³Department of Cardiology, "Prof. Dr. Theodor Burghel" Clinical Hospital, Bucharest, Romania

ABSTRACT

Atrioventricular conduction disorders represent an alteration in the normal function of the heart's electrical conduction system, a system that connects the atria and ventricles through the atrio-ventricular node and the His-Purkinje system. Consequently, bradycardia can develop and lead to the occurrence of symptoms (dizziness, loss of consciousness, tachyarrhythmias, heart failure phenomena). Identifying patients at risk of developing atrioventricular conduction disorders will allow early interventions on risk factors and improvements in prognosis. This narrative review explores the risk factors that determine the development and progression of atrioventricular conduction disorders. We will discuss traditional risk factors (age, sex, arterial hypertension, ischemic cardiac disease, diabetes, chronic kidney disease), but also risk factors that are currently being researched (genetic predisposition and inflammatory markers). Finally, we will discuss the limitations and challenges of predicting risk factors for atrioventricular conduction disorders.

Keywords: atrioventricular conduction disorders, predictive factors, atrioventricular block, genetics, inflammation

Abbreviations (in alphabetical order):

AVN	– atrioventricular node	IL-6	– interleukin-6
AVB	– atrioventricular block	LV	– left ventricle
CKD	– chronic kidney disease	PBMC	– peripheral blood mononuclear cells
ECG	– electrocardiogram	PCCD	– progressive cardiac conduction disease
HDL cholesterol	– high density lipoprotein cholesterol		
hs-CRP	– high sensitivity C reactive protein		

INTRODUCTION

Atrioventricular conduction disorders are a common pathology in the general population. In the United States of America, the prevalence of third-degree atrioventricular block (AVB) is 0.02%, while globally, the prevalence is 0.04% [1]. The incidence in apparently healthy and supposedly asymptomatic individuals is 0.001% [2]. Bifascicular blocks are a disorder of the conduction system, with a prevalence of 1-1.5%, and their progression to a complete atrioventricular block has a yearly incidence between 2-6% [3,4].

Atrioventricular blocks most frequently develop in the absence of a structural heart disease, with the

cause being idiopathic fibrosis of the conduction system [5]. Most of the bradyarrhythmias with indication of permanent cardiac stimulation are seen in the elderly, with 80% of cardiac pacemakers being implanted in patients aged >65 years old.

Globally, the number of patients who require permanent cardiac stimulation has progressively risen, reaching 1 million cardiac devices implanted yearly.

Less severe conduction disorders, such as prolonged PR interval, right bundle branch block, or left bundle branch block, are known to be associated with advanced forms of AVB [6,7].

Corresponding author:

Carmen Marina Deutsch

E-mail: carmenmarinailie@gmail.com

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Although cardiac pacemakers are an appropriate treatment for atrioventricular block symptoms, there are no preventative or curative methods for AVB. The implantation procedures for cardiac devices have a

low risk of periprocedural complications; however, some complications can be severe (pneumothorax, tamponade, death) [8]. Moreover, reinterventions for replacing cardiac devices have a relatively high risk of infections [9,10].

A good understanding of the conditions associated with atrioventricular conduction disorders allows the development of preventative strategies, ideally avoiding the complications associated with implanting cardiac pacemakers and the related costs.

The purpose of this narrative review is to describe the risk factors associated with AVB. Identifying those factors is essential for stratifying risk, for picking the optimal time for interventional treatment and for improving prognosis.

Thus, we will discuss two types of risk factors. On one hand, there are traditional risk factors, which have been studied more frequently: age, sex, arterial hypertension, coronary disease, diabetes, chronic kidney disease and physical activity. Secondly, we discuss risk factors that are currently being researched: genetic predisposition and inflammatory markers.

In the last years, a few clinical studies have been conducted on the predictive factors of atrioventricular conduction diseases. There have been both prospective and retrospective studies. The conduction disease investigated in these studies include both second- and third-degree atrioventricular block, as well as first-degree AVB.

MATERIALS AND METHODS

We search three relevant medical databases PubMed, MEDLINE and Cochrane Library and used the following keywords and search terms: [atrioventricular conduction disorders], [predictive factors], [atrioventricular block], [genetics], [inflammation].

We excluded studies on non-adult populations.

RESULTS

The following table summarizes the main results of clinical trials:

TABLE 1. Main results of clinical trials

Reference	Number of patients	Outcomes	Results
Tuomas Kerola et al [11]	6146	Demographic and anthropometric data Comorbidities (hypertension, diabetes, ischemic cardiac disease, heart failure) Lifestyle: smoking, alcohol Laboratory measurements: glucose, lipid profile ECG analysis	Hypertension and increased baseline glucose levels were associated with AVB
Ruiqi Shan et al [6]	15181402	Demographic and anthropometric data Comorbidities (hypertension, diabetes) Laboratory measurements: glucose, lipid profile ECG Analysis	Old age, male sex, obesity, hypertension and diabetes are risk factors associated with AVB. Low levels of HDL-cholesterol were associated with higher risk of AVB.
Julio Martí-Almor et al [12]	263 patients with bifascicular block 263 pacienti cu bloc bifascicular	Comorbidities (hypertension, dyslipidemia, diabetes, heart failure, presence of structural cardiac disease and chronic kidney disease RFG<60ml/min/1,73m ²) Lifestyle: smoking	Patients with bifascicular block have a higher risk of conduction disease progression in the presence of syncope/presyncope, an HV interval >64ms, renal failure RFG<60ml/min/1,73m ² , or QRS width >140 ms
Emilie K. Frimodt-Møller et al [13]	5201	Demographic and anthropometric data Comorbidities: hypertension, diabetes, coronary disease Lifestyle: smoking, alcohol consumption, physical activity Laboratory measurements ECG analysis	Patients with regular physical activity are associated with a lower risk of cardiac conduction disease
Lazzerini et al [14]	46	PR interval in patients with inflammatory disease and correlation with inflammatory markers Correlation between connexin43 from cardiac tissue and PBMC Acute effects of IL-6 on atrioventricular conduction <i>in vivo</i> and connexin 43 <i>in vitro</i>	Systemic inflammation can acutely worsen atrioventricular conduction
Emilie K. Frimodt-Møller [15]	4314	hs-CRP	High levels of hs-CRP were associated with increased risk of cardiac conduction disease

AVB: atrioventricular block; ECG: electrocardiogram; HDL cholesterol: high-density lipoprotein cholesterol hs-PCR (high-sensitivity C reactive protein); IL-6: interleukin-6; PBMC: peripheral blood mononuclear cells

Traditional risk factors associated with atrioventricular diseases

Age and sex

One of the most important factors predictive of atrioventricular conduction disease is age. Consistently, studies have shown an increase in the prevalence of conduction diseases with age, highlighting its importance as an independent risk factor [11]. Moreover, differences regarding sex have been observed, with studies suggesting a higher prevalence of cardiac conduction disease in males.

Retrospective and prospective analyses have shown that women have a higher incidence of sinus node disease, while men have a higher incidence of atrioventricular block [6,11,16].

Arterial hypertension

High blood pressure values lead to the development of myocardial hypertrophy, which in advanced stages leads to loss of cardiomyocytes and fibrotic remodeling [17]. Consequently, in the presence of extended fibrosis, disturbances in electrical impulse conduction might develop. The presence of hypertrophy leads to failures in the process of angiogenesis, leading to myocardial ischemia, which, in turn, can lead to fibrosis. Postmortem studies of individuals with atrioventricular block without other associated cardiovascular diseases have shown fibrosis at the level of the conduction tissue. This fibrosis, also known as Lev disease, is known to be associated with old age, otherwise it is considered idiopathic [18,19].

Diabetes mellitus

Diabetes is a known risk factor for coronary disease and myocardial infarction, the latter leading directly or indirectly to the development of conduction diseases. Consistently elevated glucose levels can lead to microvascular disease, which can also be present at the level of the atrioventricular node (AVN) microcirculation. Moreover, diabetes can cause multiple changes in cardiomyocyte metabolism, including dysregulated fatty acids utilization and an increase in lipotoxic effect, increased production of reactive oxygen species, both mechanisms leading to cell death accompanied by inflammation and fibrosis [20,21]. These processes can predispose the development of cardiac conduction disease. Another mechanism could be diabetic neuropathy, which can affect electrical impulse transmission, including at the AVN level.

Coronary disease

Although it does not directly affect conduction tissue, it can indirectly increase the risk of AVB through different mechanisms.

- **AVN ischemia:** in some cases stenosis can develop at the level of the AVN artery, with the development of ischemia at this level and secondary AVB.
- **Post myocardial infarction scar:** a severe consequence of coronary disease is myocardial infarction, after which myocardial necrosis and the development of myocardial tissue scarring can occur. If the infarction area includes the AVN zone, the myocardial scar can extend to the level of conduction tissue, causing AVB.
- **Inflammation:** atherosclerosis is an inflammatory process. Chronic inflammation associated with coronary disease can extend to the level of the AVN.

Chronic kidney disease (CKD)

Both CKD and cardiac conduction disease are widespread conditions, with significant morbidity and mortality. Although traditionally they are considered to be different entities, more and more evidence demonstrates a link between the two.

Electrolytic disturbances, particularly in potassium, magnesium, and calcium, have an essential role in electrical conduction at the cardiac level. Metabolic acidosis can directly impact the function of the AVN. Anemia, frequently present in CKD, can lead to myocardial ischemia with secondary AVN impact. Not least, CKD involves a chronic inflammatory status with increased oxidative stress, which can affect cardiac conduction tissue.

Fibroblastic activation and fibrosis, toxins present in uremia, and endothelial dysfunction are mechanisms present in chronic kidney disease with a potential effect on electrical cardiac tissue.

Although the number of studies is growing, the precise mechanisms through which CKD increases the risk of conduction diseases are not yet completely understood.

Systemic diseases

Can lead to myocardial and cardiac conduction system damage. Patients with AVB aged <60 should be evaluated for systemic diseases. These include infiltrative diseases, rheumatologic, endocrinologic and genetic neuromuscular degenerative diseases. Cardiac amyloidosis, through the deposit of amyloid, and cardiac sarcoidosis, through non-caseating granulomas, can infiltrate the atrioventricular conduction system, leading to conduction diseases at this level. Accelerated atherosclerosis, vasculitis, myocarditis, and intestinal inflammation contribute to the development of AVB in rheumatological diseases. Moreover, Becker, myotonic, and Duchenne neuromuscular dystrophies impact the myocarditis, leading to cardiac conduction disorders.

Physical activity

A recent study suggests that patients with intense physical activity are less predisposed to the development of cardiac conduction disease [13].

The mechanisms underlying the protective effect of physical activity on cardiovascular risk could be explained through a lowering of the atherosclerosis process, including the improvement of endothelial function and systemic inflammation reduction [22].

Novel risk factors

Genetic predisposition

The role of genetics in atrioventricular conduction disorders is a complex and fascinating area of research.

The number of studies that support the role of genetic factors in developing cardiac conduction disorders is on the rise. Familial aggregation of cardiac conduction disorders suggests a hereditary component, with specific mutations identified in some cases. Genetic testing can play an essential role in identifying risk factors, but also in guiding familial screening programs.

Recent research in molecular biology and genetic technology has allowed the discovery of familial forms of progressive cardiac conduction disease (PCCD). The term PCCD refers to a hereditary cardiac disease characterized by a progressive alteration of electrical impulse conduction at the level of the His Purkinje system, leading to right bundle branch block or left bundle branch block, with the potential development of complete AVB, syncope and sometimes even sudden cardiac death. This disease can develop in patients with or without structural cardiac disease [23]. Current knowledge suggests that familial forms of PCCD, in the absence of congenital or structural cardiac diseases, or of a systemic disease, result from mutations in genes that code for cardiac ionic channels involved in the propagation of electrical impulse. On the other hand, PCCD in the context of a structural cardiac disease are often caused by mutations in genes that code for transcriptional factors, enzymes, or structural proteins.

Mutations associated with a higher risk of atrioventricular block have been identified, some of which can lead to isolated cardiac conduction disorders (mutations in SCN5A, SCN1B, SCN4B, SCN10A, DSP, TRPM4, etc. genes), and some of which are associated with structural cardiac disease [23,24]. With regard to mutations associated with structural cardiac disease, we bring up conduction diseases associated with hypertrophic cardiomyopathy (cardiac diseases associated with glycogen accumulation caused by mutations in the PRKAG2 or LAMP2 genes, Fabry disease – lysosomal deposit disease with mutations in the GLA genes), with dilated cardiomyopathy (LMNA

mutation, DES protein mutation, TNNT3K mutation), with left ventricle (LV) non-compaction (mutation in the HCN4 gene).

These mutations can impact different components of the conduction system, including genes responsible for ionic channels function, gap junctions and extracellular matrix components.

Although it is an area of ongoing research, the role of genetics in atrioventricular blocks remains a challenge. The complex interactions between genes and environmental factors such as age and preexisting medical conditions make it difficult to determine genetic contributions in each patient.

Inflammatory biomarkers

Chronic inflammation plays an important role in the development and progression of different diseases. Recent studies have demonstrated that higher levels of inflammatory markers such as C-reactive protein and interleukin-6 are associated with a higher risk of cardiac conduction diseases.

Some studies suggest that systemic inflammation can negatively impact conduction tissue, regardless of the presence of acute cardiac lesions [14,26].

Physiologically, the electrical coupling between two adjacent cardiomyocytes is achieved through intercellular channels called gap junctions, which are in turn formed by 6 transmembrane ionic channels or connexins. Of the connexins present at the level of the cardiac tissue, all of them characterized by fast cellular turnover, connexin-43 is the most abundant and is present in atria, ventricles, conduction tissue, including the lower portion of the AVN. Gap junctions that contain connexin 43 also electrically couple cardiomyocytes with non-cardiomyocyte cells, playing a modulatory role in cardiac electrophysiology. Hulsmans et al. demonstrated that cardiac macrophages, which are present in a higher density in the distal AVN portion, facilitate electrical conduction at this level, coupling cardiomyocytes with connexin 43. This mechanism is very relevant from an electrophysiological standpoint because both conditional deletion of connexin 43 in macrophages and congenital absence of macrophages can cause delayed electrical impulse conduction [26]. A study conducted by Lazerrini et al. demonstrated that:

- (1) in patients with elevated CRP levels regardless of basal inflammatory condition, ECG markers of atrioventricular conduction are elevated and are rapidly normalized following a decrease in inflammatory markers, especially IL-6;
- (2) in those subjects, connexin 43 expression in mononuclear peripheral blood cells, which are correlated to those measured in cardiac tissue, are inversely correlated with IL-6 changes;
- (3) administering IL-6 in guinea pigs leads to a worsening of cardiac conduction disorders;

(4) in *in vitro* experiments, incubating IL-6 significantly reduced the expression of connexin 43 in both cardiomyocyte and macrophage cultures [14].

It is important to always evaluate the impact of inflammatory status on atrioventricular conduction, especially when the conduction disease is severe and present in older people with a history of cardiac disease and a history of medications that negatively impact the AVN. In patients with AVB that develops or progresses in the presence of systemic inflammation, prompt and specific therapies targeting the inflammatory process are important, ideally with therapeutic effects at the level of the cardiac conduction tissue. Anti-cytokine therapies, especially those targeting IL-6, can be an innovative and short-term anti-arrhythmic treatment for those patients, giving the possibility of delaying the implantation of a cardiac pacemaker or even making its implantation not necessary.

Limitations and challenges

- The development of clear predictive models requires large clinical trials, with a well-established design
- Current research is based on a limited category of risk factors
- Balancing precise predictions with unnecessary interventions is essential, but difficult to achieve
- Cardiac conduction disorders develop progressively. Although research evaluates long-term risk, some cases might be omitted
- The exact cause of AVB remains unclear in some cases, making it difficult to identify reliable predictive factors
- The implementation of new, cost-effective predictive strategies can be a challenge. The potential benefit of early detection might require high costs due to necessary investigations.

- Although there is progress in identifying atrioventricular conduction disorder predictors, the contribution of risk factors displays inter-individual variability.

CONCLUSIONS

Cardiac conduction disorders are a multifaceted condition. Understanding predictive factors is essential for fast detection and targeted interventions aimed at preventing and treating cardiac conduction disorders.

After identifying individuals at high risk of developing AVB, preventative measures and targeted monitoring can be implemented depending on each case. We can discuss a personalized patient approach, which can lead to results improvement and decrease the need for implanting cardiac pacemakers.

Although current research is based on a limited number of risk factors, the future seems promising, with the involvement of new biomarkers such as genetic variation and inflammatory markers, for improving the prediction of cardiac conduction disorders.

Clearly identifying predictive factors for AVB remains a challenge. Overcoming the limitations previously described is essential for the development of reliable methods to identify individuals at risk. This will involve ongoing research, collaborations between medical specialties, and efficiently integrating new technologies.

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