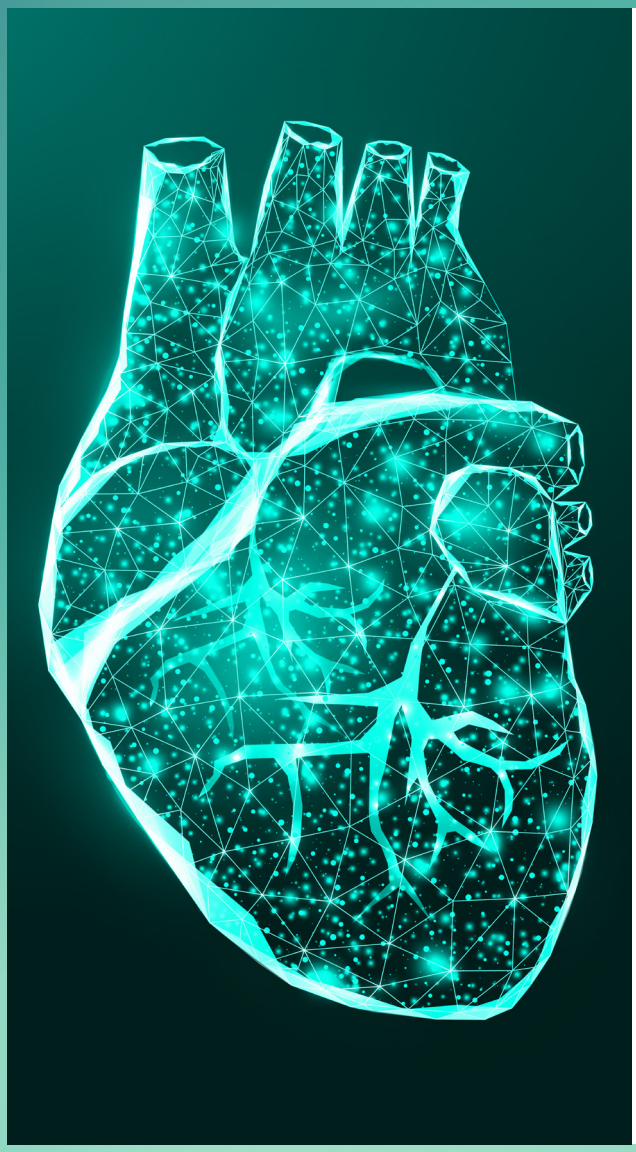
E-ISSN: 2405-819X

CARDIOVASCULAR ACADEMY SOCIETY

INTERNATIONAL JOURNAL OF THE CARDIOVASCULAR ACADEMY

OFFICIAL PUBLICATION OF THE CARDIOVASCULAR ACADEMY SOCIETY

VOLUME: 10 ISSUE: 2 JUNE 2024



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Web: www.galenos.com.tr
Publisher Certificate Number: 14521
Publication Date: June 2024
ISSN: 2405-8181 **E-ISSN:** 2405-819X
International scientific journal published quarterly.

INTERNATIONAL JOURNAL OF THE CARDIOVASCULAR ACADEMY

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The journal is published online.

Owner: Ömer Kozan on behalf of the Cardiovascular Academy Society

Responsible Manager: Mehdi Zoghi

VOLUME: **10**
ISSUE: **2**
JUNE **2024**

INTERNATIONAL JOURNAL OF THE CARDIOVASCULAR ACADEMY

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REVIEW

DOI: 10.4274/ijca.2024.85057
Int J Cardiovasc Acad 2024;10(2):22-30

Antiarrhythmic Properties of Beta Blockers: Focus on Nebivolol

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Abstract

Beta-blockers are commonly used medications for cardiovascular diseases. Beta-blockers are effective antiarrhythmic agents, and they are class 2 agents in the Vaughan-Williams classification. In this review, we first attempt to mention the physiology of beta-adrenergic activation in the myocardium and the role of excessive beta-adrenergic activation in arrythmiagenesis. Then, we will summarize the pharmacological properties of beta blockers and their use in specific arrhythmias. Special emphasis will be given to nebivolol, a new generation cardioselective beta-blocker with vasodilator activity, given the limited data regarding its use in arrhythmias.

Keywords: Beta-blockers, arrhythmias, anti-arrhythmic medications, nebivolol

INTRODUCTION

Cardiac arrhythmia is a common problem in clinical practice. Although the annual incidence of ischemic stroke and myocardial infarction is reported to be similar, the frequency is higher in the elderly, those with chronic kidney disease, and those with heart failure.[1] The fact that the sympathetic nervous system (SNS) plays an important role in the neurohormonal activation of cardiovascular diseases makes beta-blockers indispensable in the treatment of coronary artery disease, heart failure, and arrhythmias. Antiarrhythmic medications are typically categorized according to the Vaughan-Williams (VW) classification system. Beta-blockers constitute class 2 agents in the VW classification.[2] Nebivolol is a cardio-selective beta-blocker with additional endothelium-dependent vasodilating activity that stimulates nitric oxide (NO) synthesis, resulting in NO-mediated vasodilation. Considering its positive effects on cardiac pathologies, nebivolol can be involved in both direct and indirect treatment of rhythm disorders.[3]

In this article, the role of autonomic nerve activity in arrhythmias, the molecular mechanisms of action, and the pharmacological properties of Beta-Adrenergic Blockers, as

To cite this article: Görenek B, Çalık AN, Kepez A, Öz A, Özmen Ç, Sinan ÜY, Yontar OC, Yıldırım Ç. Antiarrhythmic Properties of Beta Blockers: Focus on Nebivolol. Int J Cardiovasc Acad. 2024;10(2):22-30

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Received: 31.03.2024
Revised: 23.06.2024
Accepted: 27.06.2024
Published Online: 02.07.2024

well as the evidence-based potential effects of Nebivolol as an anti-arrhythmic drug in different cardiac pathologies, are discussed.

1. Overview: Role of β-adrenergic Activation in Heart

The SNS is responsible for organisms' "fight or flight" response to constant changes in the surrounding environment. It is crucial for maintaining life in a stable position. Activation of the SNS triggers a series of physiological and metabolic events that ultimately result in an interaction between catecholamines and adrenoreceptor. In brief, catecholamines increase heart's rate and contractility, at the same time regulate blood pressure, airway reactivity, and metabolism.[4,5]

Normal heart function depends on the organized and coherent working of two types of cells: conduction system cells and cardiomyocytes. These two types of cells work together, and only if they are in harmony would cardiac muscles work as desired. The relationship between these two cells' functions is complex and nave; however, it is crucial to maintain coherence otherwise rhythm problems may occur. The heart contains pacemaker cells throughout the conduction system, whereas pacemaker cells in the sinoatrial node function as primary pacemakers in sinus rhythm. Any dysfunction in these pacemaker cells may result in the activation of other pacemaker cells that are localized in other parts of the conduction system, such as the atrioventricular node and bundle of His, thus generating escape beats. Rhythm disturbances have many reasons, primarily problems with signal production and vicious cycles in signal propagation (reentry). It is possible to suggest that the overexcitation of the SNS is responsible for most of these phenomena.[4]

There are five adrenoreceptor, namely α1, α2, β1, β2 and β3. We will focus on β1, β2 and β3 due to their cardiac effects.

β1 adrenoreceptor constitute nearly 80% of all β receptors in the human heart. β1 stimulation generally starts with bonding between norepinephrine and G-stimulator protein and continues with activation of adenylyl-cyclase, which transforms adenosine triphosphate to cyclic adenosine monophosphate (cAMP). Increased cAMP levels activate protein kinase A (PKA), which phosphorylates several proteins involved in cardiac function, such as L-type calcium channels, phospholamban, troponin I, and ryanodine receptors. Calcium transition into cytoplasm and increase in contractility take place. In specialized conduction cells (pacemaker cells), PKA phosphorylates ion channels in the cell membrane, leading to calcium inflow and increased signal frequency. Moreover, the conduction velocity of atrioventricular node cells increases.[6] All these modulations lead to increased heart rate (chronotropy), contraction force (inotropy), relaxation speed (lusitropy), and conduction (dromotropy).

β2 adrenoreceptor are mostly found in the smooth muscle cells of bronchioles. In the human heart, β2 adrenoreceptor are nearly 20% of whole β receptors and they are mostly capable of bonding with epinephrine. Just like β1 adrenoreceptor, they act over the adenylyl cyclase-cAMP-PKA axis. However, in this scenario, increased intracellular cAMP inhibits the release of stored calcium, which facilitates muscle relaxation. In addition, this process increases contractility and heart rate. Distinctively from β1 effect, β2 stimulation augments coronary vasodilatation during stressful events.[7] Although both β1 and β2 receptors use the adenylate cyclase pathway β1 receptors express higher functional effects in cardiomyocytes.

The cardiac effect of β3 adrenoreceptor are supposed to be a mechanism by which its NO increases in situations of overstimulation in β1 and β2 receptors.[8] As a result of NO generation, β3 adrenoreceptor pathway in the ventricular myocardium is accompanied by decreased contractility.[8] Catecholamines directly stimulate β adrenergic receptors, and chronic catecholamine exposure leads to desensitization and downregulation of β1 and β2 receptors via G-protein coupled kinases (GRK). β3 adrenoreceptor differ from β1 and β2 receptors by not having GRK recognition sites, so their levels remain unchanged or upregulated and act as a protective mechanism against chronic catecholamine exposure.[9]

2. Role of the Autonomic Nervous System in Arrhythmia

The autonomic nervous system (ANS), which consists of the sympathetic (SNS) and parasympathetic nervous systems (PNS), plays a major role in the regulation of cardiac electrophysiological activity and triggers cardiac arrhythmia. Sympathetic efferent fibers reach the heart through the paravertebral stellate ganglion (inferior - middle cervical).[10] Vagal preganglionic fibers reach the heart via the superior cervical, inferior cervical, and thoracic rami, which anastomose cardiac sympathetic nerves to form the cardiac plexus. Cardiac ganglia are distributed along the plexus and become more abundant near the heart, particularly subepicardially.[11] Both SNS and PNS can act as pro- and anti-arrhythmic.[12] The SNS and PNS provide autonomic control by interacting with the intrinsic and extrinsic cardiac nervous systems. This interaction is complex and differs for all specific arrhythmias. For instance, an increase in both sympathetic and PNS activity may be the trigger for AF occurrence.[13] On the other hand, sympathetic activity is proarrhythmic, whereas parasympathetic activation is antiarrhythmic, especially in ventricular arrhythmia associated with myocardial ischemia.[14] Similarly, SNS triggers ventricular arrhythmia and sudden cardiac death (SCD) in some hereditary cardiac channelopathies [long QT syndrome type 1, catecholaminergic polymorphic ventricular tachycardias (VT)]. In Brugada syndrome, SNS activation suppresses arrhythmia, whereas PNS activation may be arrhythmogenic.

Hence, decreased and/or increased vagal tonus can cause arrhythmia through complex electrophysiological mechanisms, similar to sympathetic overactivation. Therefore, an appropriate balance between sympathetic and PNS activity is essential for maintaining normal sinus rhythm.[12,14]

SNS activation and increased catecholamine release are important triggers of arrhythmias via various effects on electrophysiological system. Sympathetic overactivation is associated with atrial fibrillation (AF) and ventricular arrhythmias [ventricular premature complex, VT and ventricular fibrillation (VF)]. Catecholamines activate cardiac beta receptors via the cAMP/protein kinase cascade. Exposure of cardiomyocytes to endogenous and exogenous catecholamines causes autonomic tachyarrhythmias by increasing the rate of spontaneous depolarization. In addition, since sympathetic nerve endings are not uniformly distributed in the heart, a shortening of the refractory period occurs at varying degrees in different parts of the heart during increased sympathetic activation. This process may end with re-entry circuits. The presence of coexisting facilitating factors as ischemia and/or electrolyte imbalance might increase the susceptibility of myocardium to arrythmia generation in a hyperadrenergic state. Sympathetic activation may also increase ventricular arrhythmia generation by inducing ischemia. Norepinephrine secreted locally by the ischemic region accelerates ischemic cell damage, which might end in VF. Therefore, beta blockers that prevent sympathetic activation and, in resistant cases, sympathetic denervation are effective treatment methods for the prevention and treatment of various arrhythmias.[15] Physical and emotional stress, sleep disorders, metabolic disorders, and medical conditions, surgery, and drugs might trigger arrhythmia by increasing SNS activity. Moderate exercise is beneficial in both healthy individuals and patients with CVD; intense and strenuous exercise can trigger arrhythmia via sympathetic hyperactivation in patients with CVD. Physical and emotional stress can cause cardiac arrhythmia in patients with CVD. An optimal sleep pattern (average of 7 hours a day) is necessary to maintain the ANS. Short sleep duration, ineffective sleep, insomnia, and sleep breathing disorders have pro-arrhythmic effects. Sleep disorders cause both AF and ventricular arrhythmias.

Overactivation of PNS is also responsible for maladaptive change and arrhythmia occurrence. It has long been established that vagal stimulation is associated with AF.[15] The underlying mechanism is a shortened atrial refractory period. However, vagal stimulation decreases the risk of VT/VF occurrence under ischemic conditions. Increased PNS activity compared with SNS activity is referred to as vagotonia. Vagotonia is pro-arrhythmic in Brugada syndrome. Disturbances of rapid inactivation at slow cardiac rates induce a persistent sodium current that lengthens repolarization. Variable action potential durations due to repolarization differences were proposed to cause reentry.[16] Vagal activation and increased inflammatory response secondary to atrial stretch are responsible for AF in elite athletes.

2a. Supraventricular Tachyarrhythmias

There are different types of SVTs that occur with abnormal automaticity or triggered activity due to increased SNS activity. On the other hand, SVTs due to reentry may also be induced by increased sympathetic activity. In patients with atrioventricular nodal re-entering tachycardia (AVNRT), the tachycardia circuit may be sensitive to catecholamines. Increased SNS activity can trigger potential malignant arrhythmias in Wolf-Parkinson-White syndrome. Increased sympathetic activity might accelerate AV conduction in the accessory pathway, resulting in the conversion of atrial tachyarrhythmias (AF, atrial flutter) to VF and SCD in these patients. Atrial tachycardia may develop due to imbalance between SNS and PNS. Adrenergic sensitivity characterizes atrial tachycardia associated with increased automaticity and/or triggered activity rather than re-entry. Inappropriate sinus tachycardia is used to describe sinus tachycardia with a heart rate >100 bpm in sinus rhythm without an underlying primary cause. It has been suggested that an increased sympathetic tone is the main cause of this arrhythmia.

There is evidence that abnormal ANS activation is closely related to AF development. The atria are the innermost chambers of the heart. They are innervated with fibers originating from both intra-cardiac and extra-cardiac autonomic nerves and ganglia. Autonomic imbalance not only acts as a trigger for AF occurrence but also may create a substrate for arrythmia development. AF itself might also induce autonomic imbalance. The imbalance between SNS and PNS activation has been suggested to be the main contributing factor to the development and maintenance of AF. Although PNS is the main mechanism underlying spontaneous AF, adrenergic stimulation is also a co-regulatory mechanism in the initiation and maintenance of cholinergic-mediated AF.[12] Strenuous exercise can create an appropriate arrhythmogenic atrial substrate by affecting autonomic tone in elite athletes.[17]

2b. Ventricular Tachyarrhythmias

The ANS is the main contributor to VT/VF occurrence. In the presence of facilitating factors, such as channelopathy, ARVC, acquired structural heart disease, MI, and heart failure, sympathetic and parasympathetic imbalance can trigger ventricular arrhythmia and SCD. Sympathetic system activation can act as both a trigger (increased automaticity/triggered activity and extrasystole) and a substrate (shortened action potential duration, heterogeneity in repolarization). Sympathetic system activation has also been suggested to be involved in the

pathogenesis of idiopathic VTs, especially those originating from the outflow tracts. The intense sympathetic innervation of the right ventricular outflow tract (RVOT) might increase the susceptibility of RVOT to VT development in the presence of increased sympathetic activation.

3. Pharmacological Properties of Beta-adrenergic Blockers

Beta-blockers are antagonists of β-adrenergic receptors that play a significant role in controlling physiological processes, such as blood pressure, heart rate, airway reactivity, and the central nervous system. They bind to β-adrenergic receptors, blocking the binding of norepinephrine and epinephrine to these receptors and exerting sympatholytic effects.[18-21] β1 adrenergic receptors are dominant in the heart, while β2 adrenergic receptors are dominant in the peripheral vascular bed, bronchi, and pancreas. On the other hand, β3 adrenergic receptors are mainly found in the urinary bladder, gall bladder, adipose tissue, and small and large intestines.

Beta-blockers are generally divided into three groups:

- First-generation beta-blockers (propranolol, sotalol) are non-selective agents and inhibit both β1 and β2 adrenergic receptors.

- Second-generation beta-blockers (atenolol, bisoprolol, metoprolol) are cardioselective drugs that bind to β1 adrenergic receptors with higher affinity.

- Third-generation non-selective beta-blockers (carvedilol, labetalol, carteolol) are drugs that additionally exhibit alpha-adrenergic receptor blockade, resulting in vasodilatory effects. Due to this characteristic, they are referred to as "vasodilatory beta-blockers". This vasodilatory activity reduces peripheral vascular resistance while positively contributing to the hemodynamic profile by preserving or improving cardiac output, stroke volume, and left ventricular function.[22]

Beta-blockers bind to β1 adrenergic receptors located in the heart's conduction system and myocyte, preventing the release of norepinephrine from sympathetic adrenergic nerve terminals and the binding of circulating norepinephrine and epinephrine to these receptors. Therefore, they reduce the heart rate (chronotropy), cardiac contractility (inotropy), the conduction velocity of impulses in the heart (dromotropy), and the rate of cardiac relaxation (lusitropy) (Figure 1).

3a. Pharmacological Properties of Beta-blockers

1. Selectivity: Non-selective beta-blockers have equal affinity for β1 and β2 adrenergic receptors, and they block both receptors. Cardiac-selective beta-blockers have a higher affinity for β1 adrenergic receptors.[23]

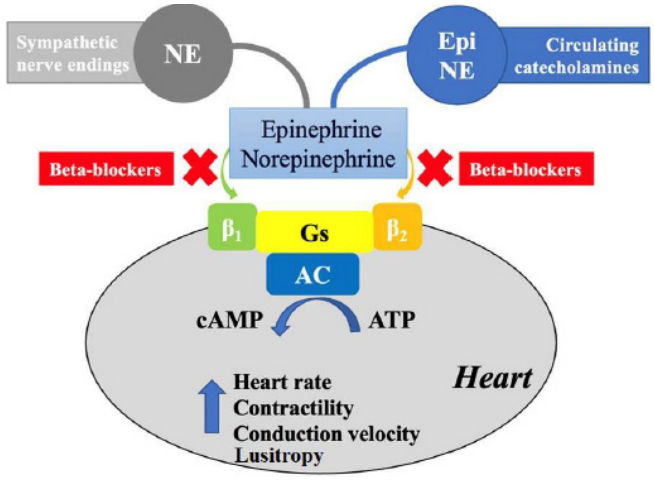

Figure 1: Mechanism of action of beta-blockers in the heart

Epi: Epinephrine, NE: Norepinephrine, AC: Adenylyl cyclase, Gs: Gs-protein

2. Intrinsic sympathomimetic activity: Some beta-blockers, when bound to β-adrenergic receptors, can exhibit partial agonist effects by partially activating the receptor while blocking the binding of norepinephrine. Beta-blockers with intrinsic sympathomimetic activity (ISA) have fewer myocardial depressant, conduction slowing, and bronchoconstrictive effects than other beta-blockers.[23] In addition, ISA may induce arterial vasodilation and increase arterial compliance in the long term, which may lead to additional beneficial effects regarding hypertension treatment.

3. Membrane stabilizing activity: Some beta-blockers exhibit membrane stabilizing activity (MSA) similar to sodium channel blockers (Class I antiarrhythmics). MSA is believed to be more effective against arrhythmias.[23]

4. Lipophilic properties: Lipophilic beta-blockers (acebutolol, carvedilol, labetalol, metoprolol, nebivolol, propranolol) are well absorbed by the gastrointestinal system when consumed orally. These drugs undergo significant first-pass elimination in the liver, resulting in systemic bioavailability ranging from 10% to 75%.[23]

5. Hydrophilic properties: Hydrophilic beta-blockers (atenolol, betaxolol, bisoprolol, carteolol, celiprolol, nadolol, pindolol, sotalol, tertatolol) are minimally metabolized in the liver and primarily eliminated by the kidneys during first-pass metabolism. These agents have weak blood-brain barrier penetration, and their dosages generally do not vary between individuals.

6. Inverse agonism: A beta-blocker that reduces the basal activity of beta receptors to a greater extent than the basal state in the absence of agonists and antagonist agents is defined

as inverse agonism. Some beta-blockers block β-adrenergic receptor activity based on the degree of inverse agonist activity rather than simple receptor blockade. The significance of this pharmacological property in the efficacy of these agents is not yet clear.[23]

The clinical indications and pharmacological properties of commonly used beta-blockers in daily practice are summarized in Table 1.

3b. Side Effects and Contraindications of Beta-blockers

Most of the side effects of beta-blockers are related to their cardiac effects. Bradycardia, hypotension, decreased exercise capacity, and atrioventricular (AV) conduction block are the most common side effects. Beta-blockers are contraindicated in patients with sinus bradycardia or partial AV block. When used together, beta-blockers and cardiac-selective calcium channel blockers (verapamil, diltiazem) should be used with caution because they can cause additive electrical and mechanical depression in the heart.

Non-selective beta-blockers significantly increase the risk of bronchospasm by blocking β2 adrenergic receptor activity in patients with asthma. Therefore, it is advisable to avoid the use of these agents in patients with chronic obstructive pulmonary disease or asthma who present with severe bronchospasm. In patients with diabetes, beta-blockers can mask tachycardia, which is a warning sign of insulin-induced hypoglycemia and should be used with caution in such patients.

4. Beta Blockers as Antiarrhythmic Agents for Nebivolol

Beta-blockers are group 2 antiarrhythmic agents based on the VW classification. Previous studies have confirmed the effectiveness of beta blockers in the treatment of arrythmia.[24] The observations from the Randomized AFFIRM Trial suggested that beta-blockers are the most effective agents for rhythm control in patients with AF.[25] The VALIANT trial showed that beta blockers applied within the first 24 hours decreased early mortality in patients who sustained VT/VF after myocardial infarction.[26] The MADIT-II trial has shown that among patients with intracardiac defibrillators (ICD), those treated with the highest dose of beta-blockers had a decreased incidence of ventricular arrhythmias that ended up with ICD shock compared with patients who did not receive beta-blockers.[27] Recent guidelines recommend beta-blockers for the treatment of supraventricular and ventricular arrhythmias.[28,29]

Nebivolol is a third-generation beta-blocker that exerts NO-mediated vasodilatory and antioxidative actions through β3 receptor agonism.[30] Nebivolol is most beta-1 selective with a long action duration.[31] It does not possess any intrinsic sympathomimetic or membrane-stabilizing activity exists. High beta-selectivity is an advantage of nebivolol in the treatment of advanced chronic obstructive pulmonary disease or asthma compared with the nonselective beta-blockers propranolol, sotalol, and nadolol. Its absorption is not affected by foods, and 98% of it is bound to proteins in the circulation. Hepatic metabolism occurs, and its half-life is approximately 10 hours.[23] Nebivolol and carvedilol do not decrease cardiac output

Table 1: Clinical indications and pharmacological properties of beta-blockers.

Drug/Agent	ISA	MSA	Lipophilic	Hydrophilic	Comment
β1-selective					
Acebutolol	+	+	+		
Atenolol				+	
Bisoprolol					
Esmolol					Short acting Intra/postop HT treatment
Metoprolol			+		
Nebivolol			+		NO release Vasodilator activity
Non-selective (β1/β2)					
Carvedilol		+	+		NO release and α1 blocker
Labetalol	+	+	+		α1 blocker
Nadolol				+	
Penbutolol	+				
Pindolol	+	+		+	
Propranolol		+	+		Beta blocker prototype
Sotalol				+	K+ channel antagonist

HT: Hypertension, ISA: Intrinsic sympathomimetic activity, K+: Potassium, MSA: Membrane stabilizing activity, NO: Nitric oxide

unlike other beta-blockers.[23] There are some data in the literature related to the use of nebivolol for the treatment of arrhythmias. These studies are presented in Table 2.

4a. Beta-blockers for the Treatment of Supraventricular Tachycardias

The use of parenteral beta-blockers is recommended in the treatment of regular narrow-complex supraventricular tachycardias (SVT) if vagal maneuvers and adenosine fail to terminate the arrhythmia. Beta-blockers should not be used in patients with decompensated heart failure. Beta-blockers can also be used to treat wide QRS complex tachycardias if the hemodynamic status is stable.[23]

Beta-blockers may be used to treat inappropriate sinus tachycardia. Combination with ivabradine may be a more effective strategy.[43] Non-selective beta-blockers might be an option for the treatment of postural orthostatic tachycardia syndrome if non-pharmacological therapy fails.[44] Beta-blockers are an option in the long-term treatment of SVT if catheter ablation is not available. Beta-blockers can be used in the treatment of focal atrial tachycardia in hemodynamically stable patients if adenosine fails to control arrhythmia. Both beta-blockers and non-dihydropyridine calcium channel blockers have been recommended for the acute treatment of multifocal atrial tachycardia; however, there is evidence that metoprolol is more effective than verapamil in the treatment of multifocal atrial tachycardia.[45] Selective beta-blockers

Table 2: Data related to the antiarrhythmic effects of nebivolol in the literature.

Reference	Type of study	Subject (number)	Type of arrhythmia	Conclusion	Positive/Negative
Erdil et al.[32]	Human	200	POAF	Nebivolol was found to be as effective as metoporolol.	Positive
Shubik et al.[33]	Human	20	AF	Shown to effectively control heart rate	Positive
Gasser et al.[34]	Human	62	AF	Decrease in the frequency of atrial fibrillation and arrhythmia symptoms in moderate and severe hypertension	Positive
Mulder et al.[35]	Human	2128	AF	Nebivolol had no effect on endpoints in elderly patients with heart failure and atrial fibrillation.	Negative
Hopton et al.[36]	Human	1	CPVT	For patients with gain of function variants in RyR2, carvedilol and nebivolol may be effective treatments.	Positive
Tan et al.[37]	Basic science-animal	-	CPVT	Nebivolol has a RyR2-targeted effect that suppresses VTs induced by Ca2+ release.	Positive
Lu et al.[38]	Animal	Rats and guinea-pigs	VT/VF	It has been shown to significantly reduce reperfusion-induced arrhythmias (VT and VF) in those receiving nebivolol as pretreatment.	Positive
Lu et al.[38]	Animal	Guinea pig	VT/VF	Nebivolol has been found to significantly reduce ischemia-induced ventricular fibrillation (VF). It was determined that it increased the VF threshold depending on the dose of nebivolol.	Positive
Lu et al.[39]	Animal	Guinea pig	VF	Nebivolol increases VF threshold	Positive
Simsek et al.[40]	Human	105	VT	Significant reduction from baseline in QTc dispersion after treatment with Nebivolol in patients with coronary slow flow	Positive
Galetta et al.[41]	Human	25	VT	In hypertensive patients with left ventricular hypertrophy, treatment with nebivolol significantly decreased QT dispersion.	Positive
Nazeri et al.[42]	Animal	Yucatan pigs	Tachycardia induced cardiomyopathy	Both nebivolol and metoprolol failed to prevent cardiomyopathy	Negative

AF: Atrial fibrillation, Ca: Calcium, CPVT: Catecholaminergic polymorphic ventricular tachycardia, POAF: Prevention of atrial fibrillation, RyR: Ryanodin receptor, QTc: Corrected QT, VF: Ventricular fibrillation, VT: Ventricular tachycardia

should be used in the long-term treatment of recurrent and symptomatic multifocal atrial tachycardia. Beta-blockers are recommended for ventricular rate control in patients with macro-reentrant-type atrial tachycardia.[23]

Beta-blockers and cardio-selective calcium channel blockers are recommended for the acute treatment of AVNRT. Beta-blockers can also be used for long-term treatment of AVNRT if catheter ablation is not available.[23] Beta-blockers are also advised in the acute treatment of AV reentrant tachycardia (AVRT) if vagal maneuvers and/or adenosine have failed to terminate the arrhythmia. Beta-blockers should be used with caution in the long-term treatment of AVRT if there is evidence of preexcitation.[23] Beta-blockers are contraindicated in patients with preexcited AF.

4b. Beta-blockers in Patients with Atrial Fibrillation

AF is one of the most common arrhythmias in clinical practice. Beta-blockers are the main agents used for ventricular rate control in patients with AF. Beta-blockers depress conduction in the AV node, and they can also be used in patients with compensated heart failure, unlike verapamil and diltiazem. Beta-blockers are more effective for rate control in patients with AF during exercise than cardiac glycosides.[46] The prophylactic use of beta-blockers is recommended for the prevention of postoperative AF development following cardiac surgery.[47] Nebivolol was found to be as effective as metoprolol in preventing postoperative AF in patients who underwent coronary artery bypass surgery.[32] Shubik et al.[33] reported that nebivolol effectively controlled the ventricular rate in patients with ischemic heart disease and chronic AF. They observed that a 5 mg daily dose was sufficient for most patients to achieve the desired ventricular rate.

The SENIORS trial demonstrated the effectiveness of nebivolol in decreasing the rates of mortality and hospital admissions compared with placebo among patients aged ≥70 years with a history of heart failure.[48] However, nebivolol treatment failed to reduce the rate of primary endpoints in elderly patients with stable heart failure and AF during a follow-up period of 21 months.[35] Nebivolol therapy also failed to reduce the incidence of AF during follow-up, raising questions related to the antiarrhythmic effects of the drug. A meta-analysis evaluated the effectiveness of beta-blockers in reducing the incidence of AF in patients with heart failure. Previous studies have evaluated the effects of beta-blockers that have proven efficiency in the treatment of HF and reported that beta-blockers significantly reduced the incidence of new-onset AF by 27%.[49] The cause of the discrepancy between the results of the SENIORS trial and this meta-analysis might be related to the older age of the study population in the SENIORS trial, who had a higher prevalence of AF (35%).

4c. Beta-blockers for Ventricular Arrhythmias

Effective treatment of underlying cardiac diseases and comorbidities is the mainstay of prevention of ventricular arrythmia and SCD. Beta-blockers are the only agents consistently proven to reduce the incidence of life-threatening arrhythmias and SCD.[29] Hence, they are considered the first-line agents to be used in the management of ventricular arrhythmias and prevention of SCD.[29] However, sotalol should be used with caution in patients with heart failure because of the risk of QT prolongation and potential proarrhythmic effects.[23]

The antiarrhythmic effects of nebivolol on ventricular arrhythmias developed during ischemia and reperfusion have been investigated in a few *in vivo* models. An experimental study on rats and guinea pigs has evaluated the effects of nebivolol on reperfusion and ischemia-induced arrhythmias.[38] Nebivolol significantly reduced the incidence of VT/VF and increased the VF threshold in various *in vivo* experimental models.[39] However, there is no solid evidence in humans regarding the beneficial role of nebivolol in the treatment of ventricular arrhythmias. The two studies that investigated this topic showed that nebivolol reduced QT dispersion in either patients with coronary slow flow after 3 months of treatment[40] or in hypertensive patients after 4 weeks of treatment.[41] Since QT dispersion is a marker of ventricular arrhythmia tendency, the authors concluded that nebivolol could contribute to arrhythmia risk reduction as well as SCD risk reduction.[40,41]

Nebivolol reduced the incidence of SCD compared with placebo in the SENIORS trial.[48] Since most SCDs are related to malignant arrhythmias, it might be suggested that nebivolol may have a beneficial effect on the incidence of ventricular arrhythmias. However, this hypothesis remains hypothesized and should be verified in large-scale randomized clinical trials with adequate statistical power that have ventricular arrhythmia burden reduction as the primary outcome.[30]

4d. Beta Blockers in Hereditary Arrhythmia Syndromes

Beta-blockers are the first-line agents used in the treatment of congenital long QT syndromes, except for LQT3.[50] Mexiletine is the preferred first-line treatment for LQT3 patients with mexiletine-responsive genetic mutations, and whether mexiletine should be administered as a standalone therapy or in combination with beta-blockers is uncertain.[50] Beta-blockers should also be used in patients with genetic mutations that cause a long QT interval, even if the baseline QT interval is within the normal range.[29]

Beta-blockers are effective in preventing ventricular arrhythmias in patients with catecholaminergic polymorphic VT. Beta-blockers without ISA should be used in these patients.[51]

Non-selective beta-blockers are preferred over selective beta-blockers in the treatment of CPVT.[52] Nebivolol has been shown to reduce ryanodine receptor-mediated calcium release, which plays an important role in arrhythmogenesis.[37] This action has been reported to be independent of NOS stimulation. Among the beta-blocker agents, only carvedilol and nebivolol decrease ryanodine receptor-mediated calcium release.[37] Nebivolol has a long elimination half-time and is a promising agent for Ca^{2+}-triggered arrhythmias. Results of clinical studies are needed to evaluate the clinical importance of the abovementioned pharmacological effects.

CONCLUSION

Beta-blockers are commonly used to treat arrhythmias. The antiarrhythmic effects of beta-blockers are related not only to beta adrenergic blockade but also to specific pharmacological actions associated with individual beta-blocker agents. Nebivolol has unique NO-mediated vasodilatory and antioxidative actions. Nebivolol has also been shown to reduce ryanodine receptor-mediated calcium release, which is known to play an important role in arrhythmogenesis. Although clinical data are limited, we believe that nebivolol might be a promising agent for the treatment of arrhythmias because of its unique pharmacological actions in addition to its effective and specific beta-1 adrenoreceptor-blocking action. Results of large-scale clinical studies with appropriate designs are needed to evaluate the clinical antiarrhythmic effects of nebivolol.

Ethics

Authorship Contributions

Surgical and Medical Practices: B.G., A.N.Ç., A.K., A.Ö., Ç.Ö., Ü.Y.S., O.C.Y., Ç.Y., Concept: B.G., A.N.Ç., A.K., A.Ö., Ç.Ö., Ü.Y.S., O.C.Y., Ç.Y., Design: B.G., A.N.Ç., A.K., A.Ö., Ç.Ö., Ü.Y.S., O.C.Y., Ç.Y., Data Collection or Processing: B.G., A.N.Ç., A.K., A.Ö., Ç.Ö., Ü.Y.S., O.C.Y., Ç.Y., Analysis or Interpretation: B.G., A.N.Ç., A.K., A.Ö., Ç.Ö., Ü.Y.S., O.C.Y., Ç.Y., Literature Search: B.G., A.N.Ç., A.K., A.Ö., Ç.Ö., Ü.Y.S., O.C.Y., Ç.Y., Writing: B.G., A.N.Ç., A.K., A.Ö., Ç.Ö., Ü.Y.S., O.C.Y., Ç.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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RESEARCH ARTICLE

DOI: 10.4274/ijca.2024.92486
Int J Cardiovasc Acad 2024;10(2):31-35

Characteristics of Patients Attending a Cardiology Outpatient Clinic: A Focus on the Turkish Healthcare System

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Abstract

Background and Aim: This study aimed to characterize the clinical and demographic characteristics of patients and to shed light on the Turkish healthcare system.

Materials and Methods: A total of 580 consecutive patients were enrolled in this study. The patient demographic and clinical characteristics and complaints were recorded. Blood samples were taken from the antecubital vein after an overnight fast.

Results: The mean age of the study population was 56.20±15.35 years, 321 (55.3%) of whom were female, 24.8% of whom had diabetes, 55.5% of whom had hypertension, 35.4% of whom had hyperlipidemia, and 24.6% of whom had coronary artery disease (CAD). The major complaints of the patients were chest pain (157, 27.1%), control of their chronic diseases (114, 19.4), prescription of drugs (101, 17.4%), palpitation (63, 10.9%), high blood pressure (46, 7.9%), dyspnea (35, 6.0%), and other complaints (21, 3.6%). Four (0.7%) patients had no complaints, and 39 (6.7%) patients were referred from other clinics for cardiological examination. Compared with men, women more often presented to the cardiology outpatient clinic with complaints of palpitations, whereas men more often presented to the clinic for prescription of drugs. Men had a greater incidence of hyperlipidemia, CAD, and peripheral arterial disease; higher levels of glucose and creatinine; and lower total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol concentrations.

Conclusion: Most patients went directly to outpatient clinics without visiting primary or secondary health centers.

Keywords: Primary health care, tertiary care centers, cardiology

INTRODUCTION

Since the introduction of the Health Transformation Program in 2003, the healthcare system in Turkey has undergone many fundamental changes.[1] The Turkish healthcare system consists of three levels. Primary healthcare services include basic preventive services and outpatient diagnostic and treatment services provided by family health centers. Secondary health services include hospitals where outpatient and inpatient treatment modalities are available. Tertiary healthcare covers a wide range of healthcare providers, including branch hospitals, teaching hospitals, and university hospitals.[2]

The family medicine system is the basis of primary health care. The aim is to establish a closer and better doctor-patient relationship. Everyone is registered with a family doctor in the area where they live because the aim is to diagnose, treat, and follow up at the primary care level. Another main function of the family medicine system is the implementation of a

To cite this article: Yıldız C, Erdem S, Özel Yıldız S, Günver MG, Yurtseven E, Turhan Çağlar FN. Characteristics of Patients Attending the Cardiology Outpatient Clinic: A Focus on the Turkish Healthcare System. Int J Cardiovasc Acad. 2024;10(2):31-35

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Received: 25.01.2024
Revised: 12.03.2024
Accepted: 25.03.2024
Published Online: 02.07.2024

referral chain. The purpose of preventive measures, diagnosis, and treatment of patients at the primary level is to prevent overcrowding in hospitals. Hospital outpatient clinics are full of patients whose problems can be solved at the primary level of the healthcare system. This situation generates unnecessary expenses and reduces the quality of services provided by hospitals. Moreover, it is a large mistake to perceive this system as a one-way referral chain. In reality, the referral chain includes the return of patients to their referral centers. A major reason for an ineffective referral system is the lack of mandatory control and regulation across primary, secondary, and tertiary healthcare services. Because of this lack, patients can directly go to the outpatient departments of secondary and tertiary hospitals.

In this study, we characterized the clinical and demographic features of patients who presented to the cardiology outpatient clinic of a tertiary hospital. We attempted to evaluate the percentage of patients who could have had their problems resolved by primary or secondary healthcare services and to shed light on the Turkish healthcare system.

MATERIALS AND METHODS

A total of 580 consecutive patients who presented to the cardiology outpatient clinic of a tertiary hospital between April 2023 and June 2023 were enrolled in the study. This study had no exclusion criteria. The patient demographic and clinical characteristics and complaints were recorded. The study was approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision no: 2023-07-04, date: 03.04.2023) and was conducted according to the Declaration of Helsinki. Informed consent was obtained from the participants.

Diabetes mellitus (DM) was defined as the use of antidiabetic medication or a fasting glucose level >125 mg/dL. Hypertension (HT) was diagnosed when a patient used antihypertensive drugs or had a systolic or diastolic blood pressure greater than 140 mmHg or 90 mmHg. Hyperlipidemia (HL) was diagnosed when the low-density lipoprotein cholesterol (LDL-C) level was >100 mg/dL in patients with coronary artery disease (CAD) or 130 mg/dL in other patients. Patients with regular follow-up at the cardiology clinic were defined as having chronic disease, including HT, chronic coronary syndromes, heart failure, arrhythmias, and cardiac implantable devices. Blood samples from the patients were drawn from the antecubital vein after an overnight fast. Biochemical and hematological evaluations of the collected samples were performed using an AU 2700 (Beckman Coulter Inc., California, USA) and a Sysmex XE 5000 (Sysmex Medical Int., Kobe, Japan).

Statistical Analysis

The normality of the data was determined by assessing the skewness and kurtosis and using the Kolmogorov-Smirnov test. The data with Gaussian and non-Gaussian distributions are expressed as the mean ± standard deviation and median and interquartile range, respectively. Comparisons of the two groups were made by the use of independent samples t-test or Mann-Whitney U test according to the distribution of the data. Categorical data are expressed as numbers and percentages and were compared using the chi-square test.

RESULTS

The mean age of the study population was 56.20±15.35 years, 321 (55.3%) of whom were female and 259 (44.7%) of whom were male. One hundred forty-four (24.8%) patients had DM, 321 (55.5%) had HT, 205 (35.4%) had HL, 141 (24.6%) had CAD, 102 (17.5%) had atrial fibrillation, 33 (5.7%) had heart failure, 17 (2.9%) had peripheral arterial disease, and 152 (26.2%) were smokers. The mean body mass index (BMI) of the patients was 27.68±5.23 kg/m^2. Ten patients (1.7%) were underweight, 167 (28.8%) had a BMI in the normal range, 242 (41.7%) were overweight, and 161 (27.8%) were obese. The main complaints of the patients were chest pain (157, 27.1%), disease monitoring (114, 19.4%), prescription of medication (101, 17.4%), palpitations (63, 10.9%), HT (46, 7.9%), dyspnea (35, 6.0%), and other complaints (21, 3.6%). Four (0.7%) patients had no complaints, and 39 (6.7%) patients were referred from other clinics for cardiologic examination. The biochemical parameters of the patients were as follows: thyroid-stimulating hormone (TSH): 2.7±5.13 µIU/mL, glucose: 113.53±42.50 mg/dL, creatinine: 0.83±0.38 mg/dL, total cholesterol (TC): 192.70±48.43 mg/dL, triglyceride (TG): 150.50±95.16 mg/dL, LDL-C: 113.57±39.73 mg/dL, and high-density lipoprotein cholesterol (HDL-C): 51.38±23.05 mg/dL. Two hundred thirty-six (40.7%) patients were using angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, 316 (54.5%) patients were using beta-blockers, 156 (26.9%) patients were using calcium channel blockers, 75 (12.9%) patients were using spironolactone, 66 (11.4%) patients were using loop diuretics, and 197 (34%) patients were using statins.

We did not find any differences between women and men with respect to age, BMI, number of overweight or obese patients, presence of atrial fibrillation, heart failure, DM, HT, TSH, or TG levels. Compared with men, women applied more frequently to cardiology outpatient clinics with complaints of palpitations, whereas men applied more frequently to clinics for drug prescription ($p<0.001$). Men had a greater incidence of HL, CAD, and peripheral arterial disease ($p<0.001$, $p<0.001$, and $p=0.007$, respectively); higher levels of glucose and creatinine ($p=0.001$ and <0.001, respectively); and lower TC, LDL-C, and HDL-C concentrations ($p<0.001$ for all) (Table 1).

Table 1: Comparison of clinical and biochemical features between women and men.

	Women (n=321)	Men (n=259)	p-value
Age (years)	55.40±15.55 57 (44.5-67)	57.20±15.07 59 (48.75-67)	0.082
BMI (kg/m^2)	27.90±4.96	27.42±5.17	0.232
BMI classification (n, %)			0.224
Underweight	4 (1.2)	6 (2.3)	
Normal	84 (26.2)	83 (32)	
Overweight	144 (44.9)	98 (37.8)	
Obese	89 (27.7)	72 (27.8)	
Complaints (n, %)			<0.001
Palpitation	52 (16.2)	11 (4.2)	
Chest pain	89 (27.7)	68 (26.3)	
Drug prescription	42 (13.1)	59 (22.8)	
Follow-up	56 (17.4)	58 (22.4)	
Dyspnea	21 (6.5)	14 (5.4)	
High blood pressure	29 (9)	17 (6.6)	
No complaint	2 (0.6)	2 (0.8)	
Referred from other clinics	19 (5.9)	20 (7.7)	
Other	11 (1.9)	10 (3.9)	
Diabetes mellitus (n, %)	74 (23.05)	70 (27)	0.334
Hypertension (n, %)	170 (52.9)	149 (57.5)	0.159
Hyperlipidemia (n, %)	82 (25.5)	121 (46.7)	<0.001
Smoking (n, %)	71 (22.2)	81 (31.5)	0.045
Coronary artery disease (n, %)	37 (11.7)	104 (40.4)	<0.001
Rhythm (n, %)			0.064
Sinusal	273 (85)	205 (79.2)	
Atrial fibrillation	48 (15)	54 (20.8)	
Perhiperal arterial disease (n, %)	4 (1.2)	13 (5)	0.007
Heart failure (n, %)	15 (4.7)	18 (6.9)	0.241
TSH (µIU/mL)	2.67±3.73 2 (1.1-3.1)	2.77±6.85 1.8 (1.2-2.56)	0.402
Glucose (mg/dL)	107.38±38.14 100 (91-109)	121.19±46.34 105 (94-134)	0.001
Creatinine (mg/dL)	0.75±0.44 0.70 (0.60-0.80)	0.94±0.28 0.90 (0.80-1.00)	<0.001
Total cholesterol (mg/dL)	203.81±44.13 201 (173.75-235)	179.28±50.08 173 (140-214)	<0.001
Triglyceride (mg/dL)	143.03±91.81 134 (92-174.50)	154.69±99.14 131 (94-180)	0.842
LDL-C (mg/dL)	121.01±37.60 119 (93-146)	104.55±40.47 96.5 (71-131.75)	<0.001
HDL-C (mg/dL)	55.27±13.22 54 (45-63)	46.65±10.65 43 (37-50)	<0.001

BMI: Body mass index, TSH: Thyroid stimulating hormone, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol

DISCUSSION

Our study revealed that almost 17% of the patients visited the cardiology outpatient clinic for drug prescriptions. It also showed that only 6.7% of the patients were referred from other clinics, which means that most patients applied directly to the outpatient clinic.

Primary care, with its contributions to the health of the population, should be considered an integral part of the health system. It is linked to better functioning of the overall health system. By providing preventive care, primary care can reduce the burden of preventable disease and death.[3] A well-functioning primary care system is associated with lower mortality rates.[4] Shi et al.[5] showed that the presence of primary care physicians in the healthcare system is associated with lower mortality rates, whereas an increase in the number of specialists is associated with an increase in population mortality. In their study, a subgroup analysis also showed that only the presence of family physicians was associated with lower mortality rates than the presence of general internists and pediatricians. A study conducted in England showed that all-cause mortality among people aged 15-64 years was lower in places with a greater number of general practitioners.[6] In Spain, the introduction of primary care services has been associated with a reduction in mortality from HT and stroke.[7] In addition to better health services and outcomes, the presence of a family medicine system has been associated with a linear decline in total health care system costs.[8,9] All of these data underscore the importance of the family medicine system.

Although Turkey has recognized the importance of the primary care system and implemented a health transformation program, the structure and delivery process of this system in Turkey have been found to be weaker than those in European countries.[10,11] The main weaknesses of the Turkish system were a lack of quantitative and qualitative human resources, many patients, and a low number of primary care visits.[12,13] The system does not require patients to apply for primary care services. As a result, patients can apply to any hospital without consulting a family physician, leading to an inefficient primary care system.[1,2,12,13] The percentage of patients who applied for primary care services was 35%, indicating the dominance of hospital care.[13] The increasing number of government and private hospitals is another factor contributing to the high number of patients admitted to hospital outpatient clinics.[14] A study by Paul et al.[15] demonstrated that more than half of the patients visited a cardiologist for non-cardiac problems. Ada and Ünal[16] investigated the relationship between primary healthcare services and emergency department visits in Turkey. They found that the number of emergency department visits did not correlate with the number of people per family physician and suggested strengthening the role of primary health care services to reduce the number of inappropriate emergency department visits. Öcek et al.[17] expolarized whether primary care service could achieve the cardinal functions and found that the family medicine model in Turkey was not able to integrate with community health services, specialist services, or social services. Our results were consistent with previous reports indicating that a significant percentage of patients who presented to hospital outpatient clinics could have actually received diagnostic and treatment services at primary care centers. We showed that 17.4% of the patients presented to the cardiology outpatient clinic for medication prescriptions and that only 6.7% of the patients were referred from other clinics for cardiological examinations. A total of 19.4% of patients visited the outpatient clinic for follow-up. According to our results, almost two-thirds of the patients could have solved their problems in primary or secondary health centers. Direct referral of these patients to tertiary centers causes unnecessary congestion and reduces the quality of care provided by physicians. The World Health Organization recommended that Turkey improve the coordination between general practitioners and specialists working in secondary services, strengthen the gatekeeping role of primary health centers, and introduce incentives for the better performance of primary services.[18]

In our study, 55.3% of the patients presenting to the cardiology outpatient clinic were female. Although the number of women was higher than that of men, the number of men diagnosed with CAD was higher. Biological differences between women and men are referred to as sex differences and result in differences in the presentation of cardiovascular disease.[19] For decades, cardiovascular disease research has focused primarily on men, leading to the underestimation of sex differences in cardiovascular disease. Studies have shown that women have a lower burden of obstructive CAD and a worse prognosis than men.[20] Women present with atypical symptoms, including weakness, fatigue, dyspnea, and palpitations, and recognition of both acute and chronic ischemic heart disease is often different or delayed in women.[21] Our findings may represent the underdiagnosis of women with CAD. We also evaluated the complaints of women and men. Women were more likely to visit outpatient clinics with complaints of palpitations and dyspnea, whereas men were more likely to visit outpatient clinics for medication prescriptions and to manage their chronic heart disease.

Study Limitations

Our study was a single-center study, and the sample size was relatively small. We did not follow up with the patients for long-term outcomes.

CONCLUSION

The majority of the patients could have had their problems solved through primary or secondary healthcare services. The direct application of patients to tertiary centers leads to congestion in outpatient clinics, which reduces the quality of patient care. Screening at the general practitioner level and an appropriate referral system can reduce the extreme burden of patients on cardiologists in the outpatient cardiology clinic.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision no: 2023-07-04, date: 03.04.2023) and conducted according to the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from the participants.

Authorship Contributions

Concept: C.Y., S.Ö.Y., F.N.T.Ç., Design: C.Y., S.E., S.Ö.Y., M.G.G., E.Y., Data Collection or Processing: C.Y., S.E., S.Ö.Y., M.G.G., E.Y., F.N.T.Ç., Analysis or Interpretation: C.Y., S.E., S.Ö.Y., M.G.G., E.Y., F.N.T.Ç., Literature Search: C.Y., M.G.G., F.N.T.Ç., Writing: C.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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RESEARCH ARTICLE

DOI: 10.4274/ijca.2024.91885
Int J Cardiovasc Acad 2024;10(2):36-41

Predictors of Percutaneous Lead Extraction Major Complications: A Tertiary Center Experience

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Abstract

Background and Aim: Over the years, transvenous lead extraction (TLE) procedures (TLEP) have been increasing because of factors such as infection, loss of device function, and lead-related complications. This study aimed to evaluate the factors affecting major complications during TLEP.

Materials and Methods: Between January 2011 and May 2023, patients who underwent TLE of cardiac implantable electronic devices were included in the study. The demographic and procedural features of all patients were evaluated according to major complications.

Results: A total of 121 consecutive patients (192 leads) underwent TLEP. The mean age was 63 ± 17.3 years, and 76% were male. Most leads were active fixation leads (67%) and 74 procedures (61%) required an extraction device. The mean lead dwell time was 5.6 ± 5.2 years. Major complications were observed in 16 procedures (13.2%) and 5 of them (4.1%) resulted in exitus. When we compared the groups according to the major complication, the rates of chronic obstructive pulmonary disease (4 vs. 3; $P = 0.020$), existence of passive fixation leads (PFL) (24 vs. 9; $P = 0.013$), and device indication ($P = 0.012$) were higher in the complication group. Multivariate analysis revealed that only the presence of PFL was associated with major complications. (odds ratio 4.486, 95% confidence interval 1.365-14.748; $P = 0.013$)

Conclusion: The present study showed that the presence of a PFL is a predictive factor for major complications.

Keywords: Percutaneous lead extraction, transvenous lead extraction, cardiac implantable electronic devices

INTRODUCTION

Transvenous lead extraction (TLE) is an important part of the management of patients with cardiac implantable electronic devices (CIED). TLE is considered a high-risk procedure because of its mechanical nature and its association with potential mortality.[1] The purpose of TLE is to eliminate lead-related undesirable effects without damaging the surrounding tissue. For example, in the 2023 European Society of Cardiology Guidelines for the management of endocarditis, complete system extraction without delay is recommended with a class 1 indication in the case of infective endocarditis associated with CIED.[2] When the decision is made to remove the device, the primary approach is to perform this procedure percutaneously.[1] With advancements over the years, several methods are available today, from manual traction to excimer laser extraction. While the extraction process can be performed by manual traction if performed shortly after implantation, fibrosis that develops around the lead over time makes this

To cite this article: Tiryaki MM, Yapan Emren Z, Emren V, Özdemir E, Kocabaş U, Kırış T, Karaca M, Nazlı C. Predictors of Percutaneous Lead Extraction Major Complications: A Tertiary Center Experience. Int J Cardiovasc Acad. 2024;10(2):36-41

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Received: 28.03.2024
Revised: 28.05.2024
Accepted: 03.06.2024
Published Online: 02.07.2024

procedure difficult. Therefore, it may be necessary to use various special equipment such as locking stylets, rotational mechanical dilators, and excimer lasers. The most lethal complication during percutaneous extraction is vascular or cardiac perforation. Studies have reported life-threatening major complications between 0.4% and 3.5% and mortality rates during the procedure between 0.19% and 1.8%.[3] To mitigate the risk, patient selection and predictive factors should be well evaluated.[4,5] Most studies in the literature related to the procedure consist of single-center experiences. Therefore, sharing experiences is important to increase expertise and prevent complications.

In this study, we aimed to evaluate the factors affecting the major complications experienced during the procedure by evaluating the patients who underwent extraction at our clinic. In this way, it is aimed to contribute to the literature on predictive factors against possible major complications during the procedure in patients who decide to undergo percutaneous extraction.

MATERIALS AND METHODS

Study design and patient population

This study was conducted by retrospectively evaluating consecutive patients who underwent TLE of CIED leads in a tertiary care center between January 2011 and May 2023. Demographic characteristics of the patients (age, gender, patient history), additional clinical factors, CIED information, echocardiographic findings, and events experienced during the procedure were retrospectively scanned from the hospital database. The 30-day and 5-year mortality status of the patients was obtained by scanning the national health registry system. Patients were divided into two groups: Group 1 consisted of patients with major complications and group 2 consisted of patients without major complications.

Patients whose medical records and procedural information could not be accessed were not included in the study.

The study design met the criteria of the Declaration of Helsinki and was approved by the ethics commission of the İzmir Katip Çelebi University Non-Interventional Clinical Studies Institutionel Review Board (decision no: 0579, date: 23.11.2023).

Lead extraction procedure and definitions

All procedures were performed by two cardiologists with cardiac surgery backup. All patients were administered sedation and local anesthesia during procedures with blood pressure monitoring. Patients with bradycardia were implanted with a temporary pacemaker through the femoral vein before the procedure. Transesophageal echocardiography was routinely performed to rule out the presence of vegetation in patients scheduled for extraction due to infection. If vegetation is detected, treatment is planned in accordance with the characteristics and clinic within the current guidelines.

The primary approach was gentle manual traction. The CIED pocket was explored under sterile conditions using blunt dissection. The generator and leads were separated from the tissue. If the leads had active fixation, they were unscrewed from the myocardium. Then, gentle traction was applied. If this was not successful, the fibrous adhesions surrounding the leads were dissected using mechanical systems such as locking stylets and rotational mechanical dilators sheaths (Cook Medical, Bloomington, IN, USA). The excimer laser was not applied. The locking stylet was placed toward the distal implantation site to fix the lead from the distal end. If the lumen's integrity was damaged or locking stylets could not be advanced to the distal portion of the leads, a bulldog system was employed for lead fixation. After lead fixation, a mechanical dilator sheath was advanced over the lead and stylet complex. The distal blades of the mechanical dilator sheath were used to separate the leads from the fibrous tissue. In pacemaker (PM) dependent patients who underwent the TLE procedure (TLEP) due to infection, a new PM was implanted at the contralateral site after having negative blood cultures for 72 h, which were obtained within 24 h of the TLEP.

Device indications are divided into three groups. First, atrioventricular (AV) node blockage includes total AV block, Mobitz type 2 block, and syncope with bifascicular block. Second, tachycardia-related arrhythmias include primary and secondary prophylaxis for ventricular arrhythmias. Third, bradycardia-related arrhythmias include sick sinus syndrome, sinus bradycardia, and slow-response atrial fibrillation. Procedural success was defined as the complete removal of all targeted leads from the vascular space. Major complications were defined as complications that were life threatening, resulted in death or persistent significant disability, or required significant surgical intervention to prevent such outcomes. The indications for lead extraction were infection, generator pocket erosion, lead dysfunction, patient's desire, chronic pain, unclear source of the systemic infection, and interference with other devices.

Statistical analysis

SPSS version 26 was used for statistical analysis. (SPSS Inc., Chicago, IL, USA). Continuous variables were reported as the mean ± standard deviation or median (interquartile range) based on normality distribution, and categorical variables were reported as counts and percentages. Student's t-test and Mann-Whitney U test were used to compare mean and median values between the two groups. The chi-square test was used

to compare categorical variables. Logistic regression analyses, univariate and multivariate analyses, were used to evaluate the factors affecting complications separately and together.

RESULTS

The study included 121 patients from 2011 to 2023, and 192 leads were removed during these extraction procedures (Figure 1). The mean age was 63 ± 17.3 and 76% were male. The median left ventricular ejection fraction was 45% (30-60). Major complications were observed in 16 procedures, 5 of which were exitus (Figure 2). When comparing the groups based on complication status, baseline variables including age, sex, body mass index, hypertension, diabetes mellitus, coronary artery disease, chronic renal failure, previous stroke, heart failure, and history of open heart surgery were similar between the groups. The demographic characteristics of the patients are summarized in Table 1. Most of the leads were active fixation leads (AFL) (67%) and 74 procedures (61%) required an extraction device. The mean lead dwell time was 5.6 ± 5.2 years. All planned leads were extracted. The features of the patients' CIEDs are shown in Table 2. The indications for the procedures were infection (42%), generator pocket erosion (33%), lead dysfunction (26%) and others (6%) (Figure 3). When comparing the groups based on complication status, chronic obstructive pulmonary disease (COPD) (4 vs. 3, P = 0.020), the presence of passive fixation leads (PFL) (24 vs. 9, P = 0.013), and device indication (P = 0.012) were found to be significant (Tables 1, 2). However, multivariate analysis revealed that only the presence of PFL was statistically significant [PFL (odds ratio (OR) 4.486, 95% confidence interval (CI) 1.365-14.748; P = 0.013), COPD (OR: 4.675, 95% CI 0.816-26.791; P = 0.083), device indication (OR: 1.307, 95% CI 0.596-2.866; P = 0.504), Table 3]. When the mortality status of the patients was evaluated from the national health registry system, it was found that the all-cause mortality rate was 5.7% (7) for 30 days and 42.1% (51) for 5 years. The central illustration summarizes the main findings of this study (Figure 4).

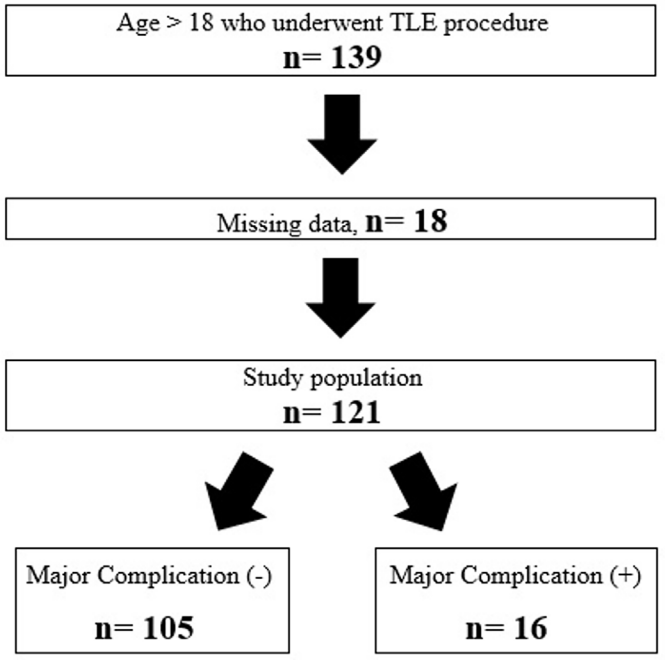

Figure 1: Study population

TLE: Transvenous lead extractionq

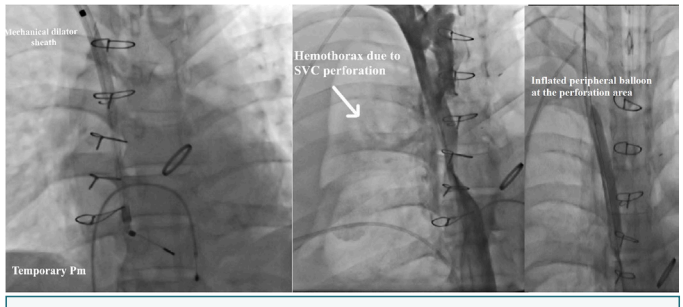

Figure 2: SVC perforation during TLEP

SVC: Superior vena cava, TLEP: Transvenous lead extraction procedure

DISCUSSION

In this study, the causes of complications of TLEP were evaluated. We found that the presence of PFL is an indicator of major complications.

The mechanism of lead fixation is an important factor for TLE procedural difficulty.[6,7] In the literature, there are different opinions about the relationship between lead fixation mechanism and TLE major complications.[8-10] Over the years, fibrous tissue has developed around the electrode, especially at its tip.[11] The shape of the PFL and their mechanical adhesion to the anchor-like tissue increases the contact surface between the lead and the tissue. Studies have shown that PFLs develop stronger adhesions to fibrous tissue.[12,13] In patients with PFL, increased adhesion to fibrous tissue can pose challenges during lead extraction procedures. For this reason, PFLs are more prone to breaking during extraction than AFLs, or they may cause perforation in the tissue.[8] Compared with PFL, AFL can provide an advantage in resolving these adhesions with their ability to activate the tip from outside the heart.[7] Over the years, the use of PFL has decreased, and more AFL have started to be used.[12] Therefore, the dwell time of the PFL is usually longer. Because of this, when deciding to remove the PFL, we decide to intervene in patients who have had a longer time for fibrous tissue and adhesions to develop. In this study, similar to some studies in the literature, it was determined that PFL was a predictor of major complications in our study.[8,10]

Table 1: Demographic characteristics of the patients according to their complication status

Variables	All patients n=121	Complication (-) n=105	Complication (+) n=16	*P*-value
Age (years)	67 (52.5-76)	68 (55-76)	56.5 (37-72.8)	0.090
Gender (male)	92 (76)	77 (73.3)	15 (93.8)	0.075
BMI (<26)	59 (49)	52 (49.5)	7 (43.8)	0.757
Coronary artery disease	50 (41)	46 (43.8)	4 (25)	0.159
Hypertension	58 (48)	53 (50.4)	5 (31.2)	0.152
Diabetes mellitus	31 (26)	28 (26.6)	3 (18.8)	0.487
Chronic renal failure	13 (11)	12 (11.4)	2 (12.5)	0.526
Cerebrovascular disease	8 (7)	8 (7.6)	0 (0)	0.243
COPD	7 (6)	4 (4)	3 (18.75)	0.020
LVEF (%)	45 (30-60)	50 (30-60)	60 (30-60)	0.322
History of OHS	24 (20)	21 (20)	3 (18.8)	0.865
30-day all-cause mortality	7 (6)	2 (1.9)	5 (31.3)	<0.001
5-year all-cause mortality	51 (42.1)	44 (41.9)	6 (37.5)	0.300

BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, LVEF: Left ventricle ejection fraction, OHS: Open heart surgery

Table 2: Procedural characteristics of the patients according to their complication status

Variables	All patients n=121	Complication (-) n= 105	Complication (+) n= 16	*P*-value
Device indication				
AVNB	40 (33.1)	32 (30.47)	8 (50)	0.012
TRA	48 (39.7)	46 (43.81)	2 (12.5)	
BRA	16 (13.2)	11 (10.48)	5 (31.25)	
PM	78 (64.5)	63 (60)	13 (8.13)	0.446
Dual chamber	39 (32.2)	33 (31.4)	6 (37.5)	
Single chamber	38 (29.8)	31 (29.5)	7 (43.8)	
Biventricular	1 (0.8)	1 (1)	0 (0)	
ICD	43 (35.5)	40 (38)	3 (18.8)	0.120
Dual chamber	15 (12.4)	15 (14.3)	0 (0)	
Single chamber	25 (20.7)	22 (20.9)	3 (18.8)	
Biventricular	3 (2.5)	3 (2.8)	0 (0)	
Total lead count	2 (1-2)	2 (1-2)	2 (1-2)	0.844
One lead	56 (46.3)	48 (45.7)	8 (50)	
Two lead	56 (46.3)	49 (46.7)	7 (43.8)	
Three or more	7 (5.7)	5 (4.8)	2 (12.5)	
Dual coil presence	46 (38)	43 (41)	3 (18.8)	0.088
Atrial lead presence	61 (50.4)	53 (50.1)	8 (50)	0.914
Passive fixation lead	33 (27.3)	24 (22.9)	9 (56.3)	0.013
Lead dwell time (years)	4 (1.12-8)	4 (1-8)	5 (2.08-15.5)	0.061
Passive fixation leads	8 (5-14)	5.16 (3.75-7.5)	11 (5-11)	0.049
Active fixation leads	2.12 (0.83-5.25)	2.08 (0.83-5)	2.16 (2-3.5)	0.842
Extraction device usage	74 (61.2)	62 (59)	12 (75)	0.294
Extraction cause				0.372
Infection	51 (42.2)	42 (40)	9 (56.3)	
Generator pocket erosion	33 (27.3)	28 (26.6)	5 (31.3)	
Lead dysfunction	31 (25.6)	29 (27.6)	2 (12.5)	
Others	6 (5)	6 (5.7)	0 (0)	
Operator experience ≥50 cases	14 (11.6)	12 (11.8)	2 (12.5)	0.933

AVNB: AV node blockage, BRA: Bradycardia-related arrhythmias, ICD: Implantable cardioverter-defibrillator, TRA: Tachycardia-related arrhythmias, PM: Pacemaker

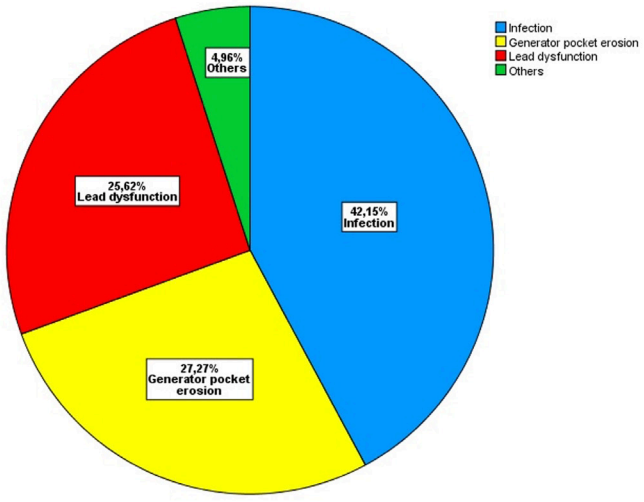

Figure 3: Extraction causes

Table 3: Multivariate predictors of major complications

Variables	Odds ratio	95 %CI lower and upper	*P*-value
Passive fixation lead	4.486	1.365 - 14.748	0.013
COPD	4.675	0.816 - 26.791	0.083
Device indication	1.307	0.596 - 2.866	0.504

CI: Confidence interval, COPD: Chronic obstructive pulmonary disease

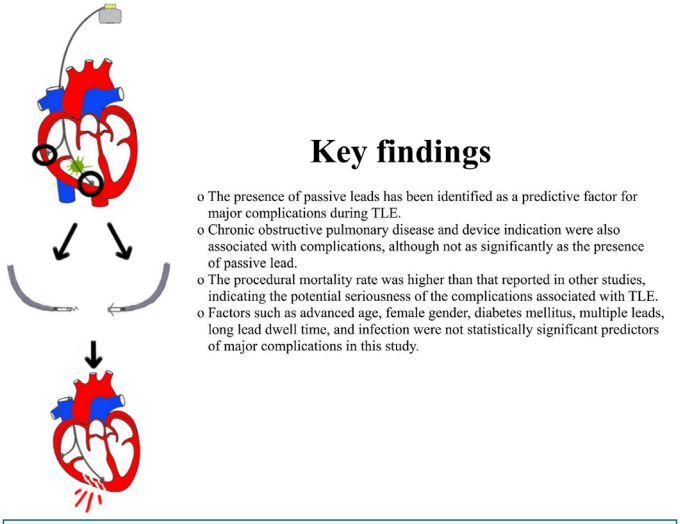

Figure 4: Central illustration of the study
TLE: Transvenous lead extraction

In this study, it was determined that 5 patients (4%) died during the procedure. When the patients who died during the procedure were evaluated, it was determined that three of them had rupture in the superior vena cava during the procedure, one developed tamponade due to right ventricular laceration during the procedure, and one developed tamponade after the procedure. Although pericardiocentesis was performed, the patient could not be saved. Of the patients who died during the procedure, two had dual coils and three had PFL. However, it was not statistically significant. (each $P > 0.05$) Additionally, the lead was broken during the procedure in 4 (3%) patients, and surgical intervention was required in 2 patients. In 2 patients, broken lead was tried to be removed with a snare system. However, because of RV damage and tamponade during the procedure, the patients were transferred to surgical intervention. Even though mortality is the most devastating complication, other major complications that cause morbidity for the patient should not be ignored. In 7 (5%) patients, pleural or pericardial fluid or hematoma requiring intervention was detected.

Previous studies have found advanced age, female gender, diabetes mellitus, multiple leads, long lead dwell time, and infection as common factors contributing to mortality in lead extraction procedures.[3,14] With advancing age, the slowing of the healing process, increased fragility, and vascular calcification may increase the risk of complications related to the intervention. In previous studies, female gender was found to be a risk factor, but the underlying mechanism has not been elucidated. As a general inference, it is thought that the caliber of the vascular structures may play a role.[3,5] As a result of the study conducted by Bashir et al.,[3] diabetes was identified as a new risk factor. Their hypothesis is that diabetes mellitus may play a role in the calcification of leads, similar to atherosclerosis, and this may cause challenges in the removal. As the dwell time of the lead increases and the number of leads planned for removal increases, there may be more adhesion to the tissue and an increase in fibrous tissue, which may make extraction difficult and require the use of more extraction devices. When infection is the indication for extraction, the increased risk of developing sepsis during the intervention process makes this process riskier in terms of mortality. However, in this study, these factors were not significant. TLE is not a simple procedure and has serious complications such as mortality; therefore, there may be bias in patient selection for the TLE procedure, which could affect these findings. While the 30-day mortality rate was 1.6% in Bashir et al.'s [3] study, Bongiorni et al.[5] found that the procedural mortality rate could be up to 2.8%. In this study, the procedural mortality (4%) and major complication rates (13%) were higher than those in other studies in the literature.[3,5] While there are many reasons for this, it may have been due to the fact that lead extraction is often considered a last resort, especially in patients with a high burden of comorbidities, and therefore may have been performed later in the treatment process. In addition, it may have been caused by the persistence to achieve procedural success. In this study, when the experience of the operator who performed the procedure was evaluated, no significant difference was found

between those with more than 50 procedures. This finding may be because of the small size of the study population. When we evaluated long-term mortality according to complication status, we found that TLE complications did not affect 5-year all-cause mortality, similar to the literature.[10]

In conclusion, it should be noted that the procedure carries a risk of complications, including mortality, in patients scheduled for TLE. For this reason, patient selection should be conducted carefully and preferably in a high-volume center with experienced operators.

Study limitations

Our study has several limitations. First, as this was a single-center retrospective study, its findings should be interpreted in light of the common limitations of retrospective studies. In addition, no patients underwent extraction with laser sheaths in this study. Moreover, this study had a small sample size, which may limit the generalizability of the findings.

CONCLUSION

This study showed that the presence of a PFL is a predictive factor for major complications. However, further studies are required to confirm these findings.

Ethics

Ethics Committee Approval: The study design met the criteria of the Declaration of Helsinki and was approved by the ethics commission of the İzmir Katip Çelebi University Non-Interventional Clinical Studies Institutionel Review Board (decision no: 0579, date: 23.11.2023).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: V.E., E.Ö., U.K., T.K., M.K., C.N., Concept: M.M.T., V.E., Design: M.M.T., V.E., Data Collection or Processing: M.M.T., V.E., Analysis or Interpretation: M.M.T., V.E., Literature Search: M.M.T., Z.Y.E., Writing: M.M.T., Z.Y.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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CASE REPORT

DOI: 10.4274/ijca.2024.63935
Int J Cardiovasc Acad 2024;10(2):42-44

Beware of Bubbles: Coronary Air Embolism During Transcatheter Patent Foramen Ovale Closure

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Abstract

Coronary air embolism is a rare and life-threatening side effect of endovascular interventions, mostly due to procedure-related causes. A 51-year-old man presented with a history of multiple transient ischemic attacks. Patent foramen ovale was found, and transcatheter closure was considered necessary. During the intervention, ST-segment elevation in leads II, III, and aVF was observed. Emergency coronary angiography revealed a typical air bubble that occluded the distal part of the right coronary artery. After nitrate intracoronary injection, the air bubble was dissolved, and ST-segment elevations were resolved. The electrocardiogram rhythm had turned to atrial fibrillation, and intravenous amiodarone was administered. The patient was closely monitored until sinus rhythm was restored. In this study, the distal RCA occlusion did not cause important hemodynamic instability but provoked an arrhythmia that was later restored. Thorough preparation of the equipment and proper intra-procedural techniques must be followed to prevent this serious complication.

Keywords: Coronary air embolism, patent foraman ovale, transcatheter patent foramen ovale closure, case report

INTRODUCTION

Coronary air embolism (CAE) is an uncommon side effect of transcatheter cardiac interventions with an incidence ranging from 0.1% to 0.3%. It arises when air is introduced into the coronary circulation due to inadequate flushing of the guiding and diagnostic catheters. Literature provides various consequences related to CAE, ranging from clinically insignificant occurrences to myocardial infarction, cardiogenic shock, and even death.[1] The aim of this paper is to present a rare complication during a patent foramen ovale (PFO) closure intervention.

CASE REPORT

A 51-year-old male presented to our outpatient cardiology clinic for further investigation because of multiple transient ischemic attacks in the preceding year, resulting in transient loss of sight. The patient had no other medical history, except for mild hyperlipidemia. Thrombophilia tests were negative, and carotid ultrasound did not reveal a plaque or clot.

On examination, his body temperature, blood pressure, pulse, and oxygen saturation in the supine position were 36.1 °C, 128/74 mmHg, 75 beats per minute, and 97%, respectively. Physical examination of the lungs was normal, and the heart sounds were of a regular rhythm, without gallop. Electrocardiogram (ECG) was sinus rhythm, without any irregularity.

Transoesophageal echocardiography (TEE) with a bubble test was positive (showed air bubbles into the left atrium) for PFO, with no signs of atrial septal defect and no findings of heart failure or pulmonary hypertension. Cardiac magnetic

To cite this article: Pagiantza A, Belevesli E, Bikakis I, Economou FI. Beware of Bubbles: Coronary Air Embolism During Transcatheter Patent Foramen Ovale Closure. Int J Cardiovasc Acad. 2024;10(2):42-44

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Received: 05.05.2024
Revised: 08.05.2024
Accepted: 03.06.2024
Published Online: 02.07.2024

resonance imaging had normal findings, and the pulmonary vs systemic blood flow ratio (Qp/Qs) was approximately one.

According to the current guidelines for the management of adult congenital heart disease,[2] it was decided to proceed to transcatheter PFO closure. The intervention was performed under general anesthesia and under TEE guidance.

An 8-Fr sheath for PFO closure was inserted via the right femoral vein in the left atrium to deploy a CoCoon 30 mm septal occluder device (Vascular Innovations Co., Ltd.). The patient was on dual antiplatelet therapy (aspirin, 100 mg/day; clopidogrel, 75 mg/day) for 30 days before the procedure and received intravenous heparin (6000 U) after sheath insertion.

After the deployment of the device across the atrial septum (Figure 1), TEE showed that the closure device was in the right place, but the cardiac monitor suddenly showed significant ST-segment elevation in the inferior leads and sinus tachycardia. Emergency coronary angiography revealed an occluded distal part of the right coronary artery (RCA) with a moving air column distal to the occlusion, suggestive of a CAE (Figure 2A).

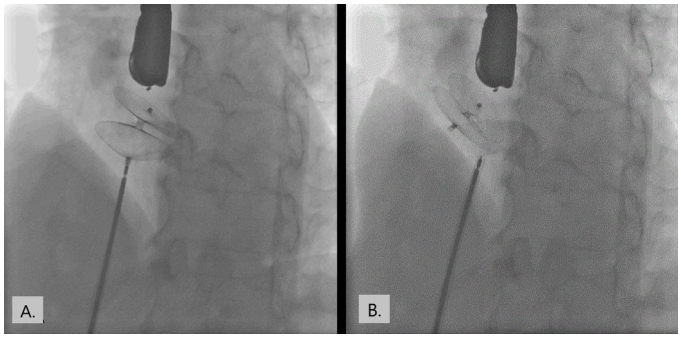

Figure 1: Fluoroscopy. Deployment of a 30 mm CoCoon septal occluder device for transcatheter treatment of patent foramen ovale. The correct placement of the PFO occluder is ascertained by the "Pacman sign" in Figure 1A

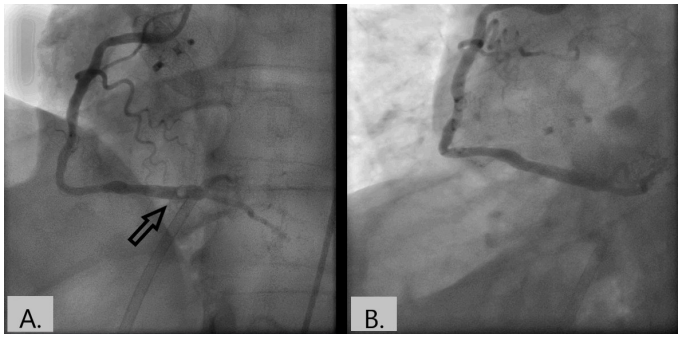

Figure 2: Coronary angiography. Coronary angiography showing an air bubble (arrowhead) obstructing the distal part of the right coronary artery (A) and no obstruction in the right coronary artery after injecting 150 mcg intracoronary nitrate (B)

An intracoronary 150 µcg nitrate injection was administered in the RCA to dissipate the air column. The air column was dispelled, and a TIMI-3 flow was achieved in the RCA with simultaneous resolution of the ST-segment elevations (Figure 2B). Afterwards, the cardiac monitor showed that the patient had atrial fibrillation with a rate of approximately 130 bpm; therefore, he was given IV amiodarone and transferred to the coronary care unit. Four hours later, his rhythm was restored with an ECG with sinus rhythm, no ST-segment elevations, and a rate of 80 beats/min. The rest of the postoperative course was event-free, and the patient was discharged one day later with medical instruction to receive clopidogrel 75 mg once daily and apixaban 5 mg twice daily for a month. Informed consent was obtained from the patient for the publication of this case report in accordance with the ICMJE guidelines.

DISCUSSION

CAE appears to be an uncommon and avoidable side effect of transcatheter cardiac interventions. Inadvertent air introduction into the coronary arteries can occur from a variety of sources, including inadequate cleaning of diagnostic or guiding catheters, air leakage from a malfunctioning manifold system, balloon rupture, air infiltration during balloon catheter insertion or removal, and structural equipment failures.[3,4] In particular, in PFO closure interventions, once the device advances through the delivery sheath, residual or entrapped air is forced into the left atrium, which typically causes an air embolism. This is believed to be the potential mechanism of coronary artery embolism in this study. It is important to note that the operator's experience and skill level are major predictors of the prevalence of this issue.[5]

The volume of air and the place of air that enters the coronary arteries determine the severity of the repercussions associated with air embolism. The clinical symptoms of air embolism can range from asymptomatic air embolism to chest discomfort, hypotension, myocardial infarction, arrhythmias (bradycardia, ventricular tachycardia, ventricular fibrillation, heart block), and cardiac arrest.[6] In this study, we were not able to assess any clinical manifestations because our patient was under general anesthesia.

Angiography is used to diagnose air embolism, but distinct bubbles are rarely observed in the coronary arteries. In some patients, closure of the affected artery might be complete, while the occluded site usually looks vague rather than possessing the distinct arterial cut-off that can be characteristic of an artery blocked by a thrombus. Additionally, it might lead to angiographic appearances of no-reflow or delayed flow. In this case, a typical distinct bubble was observed in the RCA. Given that the right-sided sinus of Valsalva is positioned anteriorly, the RCA is the epicardial coronary artery most frequently impacted by air emboli.[3] This clarifies the appearance of ST-segment

elevation in the inferior leads. Further electrocardiographic findings could include a complete atrioventricular (AV) block due to supplementation of the AV node by the RCA.[7] Apparently, in this case, the bubble was placed distally to the AV node infusion artery, and we did not notice any AV node electric disturbances.

Regarding the treatment of air embolism and its consequences, there is a lack of defined guidelines. Operators should thoroughly prepare the catheterization systems, ensuring that all connections are firm. In most cases, there are few air leaks that have no hemodynamic effects and do not require treatment. Supportive care, including rapid administration of analgesics for alleviating pain, 100% oxygen supplementation, hemodynamic support in case it is needed, and arrhythmia counseling, is provided for all instances of mild to moderately symptomatic patients until the air bubbles naturally dissolve.[1,8] Apart from supportive care, administration of arterial vasodilators like adenosine or nitrates, as in our case, and mechanical techniques such as bubble aspiration with certain catheters and fragmentation and displacement of air bubbles more distally are usually proposed.[9] Preventive care is a fundamental management principle.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Authorship Contributions

Surgical and Medical Practices: I.B., F.I.E., Concept: A.P., F.I.E., Design: A.P., Data Collection or Processing: A.P., E.B., I.B., Analysis or Interpretation: I.B., F.I.E., Literature Search: A.P., E.B., Writing: A.P., E.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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