Journal of
HYPERTENSION RESEARCH
www.hypertens.org/jhr

Review
J Hypertens Res (2023) 9(1–2):6–13

How to interpret target organ damage from arrhythmias in patients with arterial hypertension

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Received: February 24, 2023, Accepted: May 4, 2023

Abstract

Chronically elevated blood pressure (BP) leads to pathophysiological alterations in cardiac structure and, consequently, functional deterioration. The spectrum of heart damage manifestations due to hypertension is wide, including left ventricular concentric hypertrophy (LVH), impaired left ventricular diastolic function, left atrial enlargement (LA), and heart failure. The association between hypertension and cardiac arrhythmias, particularly atrial fibrillation, ventricular arrhythmias, and sudden cardiac death (SCD), is well established. The factors predisposing to arrhythmogenesis in hypertensive patients are the following: myocardial ischemia and fibrosis; activation of the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system; LVH; LA; and electrical and structural remodeling. In hypertensive patients, LVH is the most important predictor of supraventricular/ventricular arrhythmias and SCD. The reduction of LV compliance secondary to LVH contributes to diastolic dysfunction of the left ventricle. In addition, impaired diastolic function affects LA passive emptying during diastole, resulting in increased LA pressures and hence LA enlargement. If hypertension is left untreated, diastolic impairment progresses, leading to heart failure with preserved ejection fraction. Aggressive blood pressure management and subsequent LVH regression prevent malignant arrhythmias and SCD. The decline of ventricular arrhythmias and subsequent SCD events after optimal BP control and LVH regression underline LV mass's importance for arrhythmogenic events. This review aims to show how to interpret target organs from arrhythmias in patients with arterial hypertension.

Keywords: hypertension, arrhythmias, target organ damage, left ventricular hypertrophy, sudden cardiac death.

Introduction

Chronically elevated blood pressure (BP) leads to pathophysiological alterations in cardiac structure and, consequently, functional deterioration. The spectrum of heart damage manifestations due to hypertension is wide, including left ventricular concentric hypertrophy, impaired left ventricular

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diastolic function, left atrial (LA) enlargement, and heart failure [1]. Pressure overload and increased afterload occurring in hypertensive patients cause increased wall stress. The compensatory cardiac remodeling is characterized by concentric hypertrophy of the left ventricle due to the parallel addition of sarcomeres, resulting in cardiomyocyte thickening and an increase in left ventricular (LV) mass. Furthermore, increased interstitial and perivascular fibrosis is often observed [2, 3]. The reduction of LV compliance secondary to left ventricular hypertrophy (LVH) contributes to diastolic dysfunction of the left ventricle [4, 5]. In addition, impaired diastolic function affects LA passive emptying during diastole, resulting in increased LA pressures and hence LA enlargement [6]. If hypertension is left untreated, diastolic impairment progresses, leading to heart failure with preserved ejection fraction. The end stage of hypertensive heart disease is characterized by concomitant pressure and volume overload of the LV, dilated cardiomyopathy, and, eventually, reduced ejection fraction [7].

The association between hypertension and cardiac arrhythmias, particularly atrial fibrillation (AF), ventricular arrhythmias (VAs), and sudden cardiac death (SCD), is well established [8–11]. The factors predisposing to arrhythmogenesis in hypertensive patients are the following: myocardial ischemia and fibrosis; activation of the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system; LVH; left atrial enlargement; and electrical and structural remodeling.

LVH is associated with subendocardial ischemia due to the supply-demand mismatch of oxygen and changes to the microvasculature, whereas hypertension per se is a strong independent factor for macrovascular ischemia [12]. Myocardial scar and fibrosis, caused by ischemia, may trigger cardiac arrhythmia and SCD [3], impeding the normal propagation of the electric impulse and, thereby, providing substrate for the reentry mechanism [13]. This review aims to show how to interpret target organs from arrhythmias in patients with arterial hypertension.

Pathophysiology of the arrhythmias

Increased sympathetic tone and activation of the renin-angiotensin-aldosterone axis are important components of arrhythmogenic substrate development [14]. Overactivity of the SNS plays a key role in arrhythmogenesis by reducing the refractory period of myocytes [15]. Catecholamines promote cAMP formation and thus increase the cytosolic calcium, resulting in hypertrophy, fibrosis, and arrhythmia [16]. Angiotensin II affects the electrical properties of cardiomyocytes, shortening the refractory period and the conduction velocity. On the other hand, aldosterone promotes atrial ionic remodeling and calcium overload due to the opening of ryanodine receptors [17, 18], which may lead to an increase in delayed afterdepolarizations. The changes in action potential described above would predispose to enhanced automaticity, reentrant mechanisms, or/and arrhythmias mediated by triggered activity. Furthermore, aldosterone promotes the accumulation of collagen and, thereby, interstitial fibrosis [19].

Myocardial disarray (loss of parallel alignment of cardiac myocytes), observed mainly in hypertrophic cardiomyopathy and, to a lesser extent, in patients with hypertensive LVH, may contribute to arrhythmogenesis [20]. Moreover, hypertension is associated with gap junction protein abnormalities such as reduced expression of connexin (Cx) 40,43 leading to slower cell-to-cell conduction and generally affecting the propagation of the electrical impulse [21, 22]. Therefore, the abnormal conduction properties of myocardial tissue facilitate cardiac arrhythmia mediated by the phenomenon of reentry.

Regarding electrical remodeling, hypertension and LVH are associated with ion channel imbalance [23]. Intracellular potassium concentration decreases due to a lower density of the Na^+/K^+ pump in hypertrophic myocardium. Hypertension-shear stress causes increased intracellular calcium by activating intracellular calcium release sites [24]. Furthermore, the progression of diastolic dysfunction and, thereby, the distension of LA and pulmonic veins induce electrical remodeling represented by shorter atrial effective refractory periods and greater dispersion of atrial repolarization [25, 26]. Therefore, cardiac myocytes' ensuing altered electrical properties generate a fertile substrate for cardiac arrhythmias.The various elements that contribute to the occurrence of atrial and ventricular arrhythmias are shown in Figure 1.

Hypertension and arrhythmias

Supraventricular arrhythmias

Hypertensive heart disease is associated with supraventricular premature beats (SVPBs). Suboptimal BP control, diastolic dysfunction, left ventricular hypertrophy, sympathetic overactivity, electrolyte disturbances, caffeine and alcohol abuse, and smoking increase the frequency of supraventricular ectopy. Additionally, non-dippers (nocturnal BP reduction <10%) and patients with elevated nocturnal BP present an increased number of SVPBs. As SVPBs are associated with the occurrence of AF and stroke, close monitoring to detect AF, lifestyle modification, and treatment with beta-blockers in an attempt to minimize ectopic beats are essential [11].

Supraventricular arrhythmias (SVTs) [atrioventricular (AV) nodal reentrant tachycardia, atrial flutter,

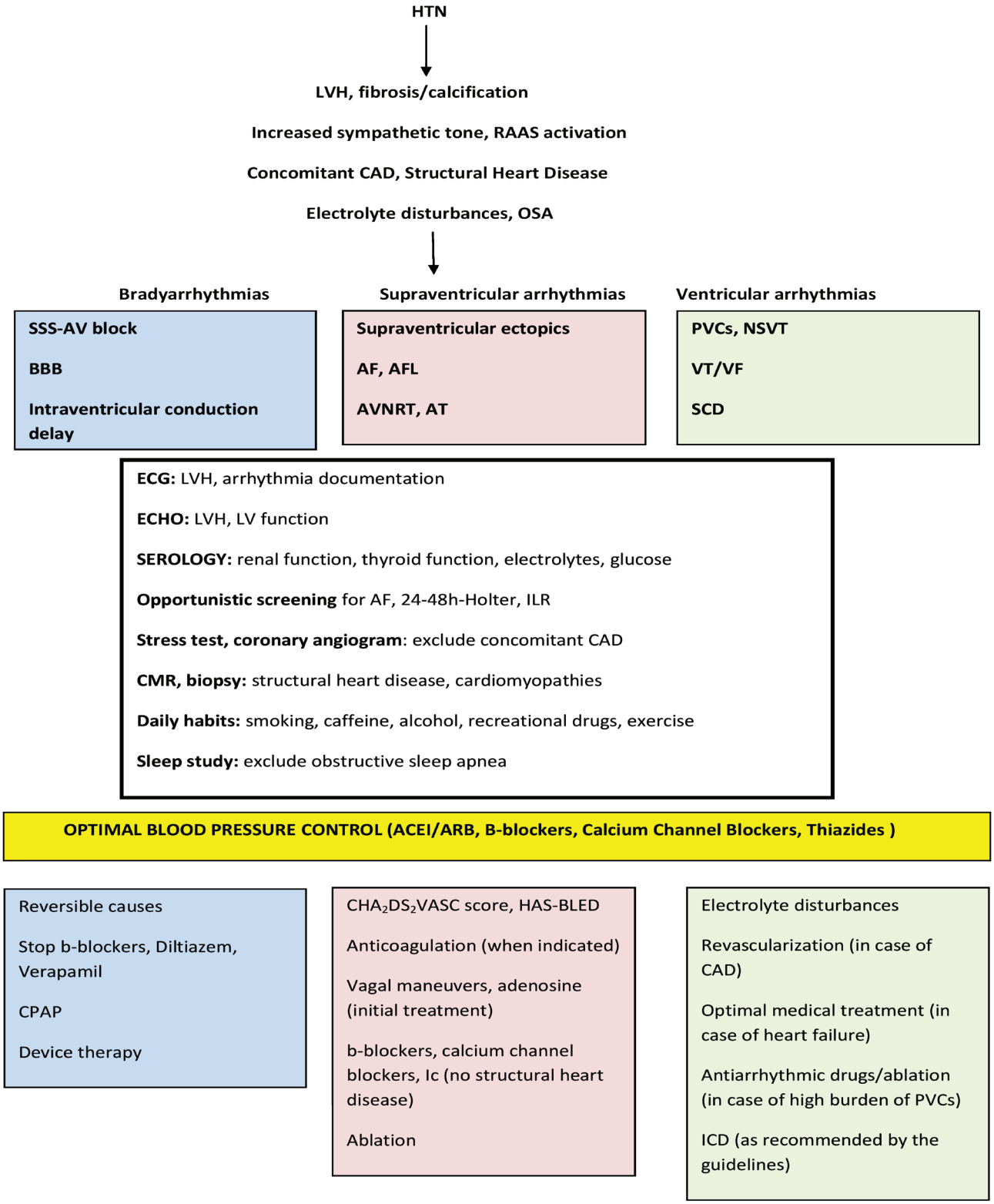

Figure 1. Hypertension and Arrhythmias. Pathophysiology, clinical manifestations and management. HTN: Hypertension; LVH: Left Ventricular Hypertrophy; RAAS: renin-angiotensin-aldosterone system; CAD: Coronary Artery Disease; OSA: Obstructive sleep apnea; SSS: Sick Sinus Syndrome; AV: Atrioventricular ; BBB: Bunble Branch Block; AF: Atrial Fibrillation: AFL: Atrial Flutter; AVNRT: Atrioventricular Nodal Reentry Tachycardia; AT: Atrial Tachycardia; PVC: Premature Ventricular Complex; NSVT: Non-Sustained Ventricular Tachycardia; VT: Ventricular Tachycardia; SCD: Sudden Cardiac Death; ECG: Electrocardiogram; LV: Left ventricle; ECHO: Echocardiogram; ILR: Implantable Loop Recorder; CMR: Cardiovascular Magnetic: Resonance; ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin Receptor Blockers; CPAP: Continuous Positive Airway Pressure; ICD: Implantable cardioverter-defibrillator; CHA2DS2-VASc: Congestive Heart failure, hypertension, Age ≥ 75 [doubled], Diabetes, Stroke [doubled]–Vascular disease, Age 65–74, and Sex [female]; HAS-BLED: Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol.

atrial tachycardia] are common among patients with hypertension and are mainly driven by left ventricular hypertrophy [27]. The incidence of SVT in patients with LVH is 11.1%, compared with 1.1% in patients with normal ventricular geometry. LVH features a 3.4-fold higher risk of precipitating SVT [28]. SVTs in the context of systolic and diastolic heart dysfunction could trigger severe symptoms like pulmonary edema. Medical management with beta-blockers and calcium channel blockers is useful, but catheter ablation is the gold standard treatment for symptomatic patients [29].

Hypertension and AF are common cardiovascular conditions associated with increased morbidity and mortality. They usually coexist. AF is the most common arrhythmia associated with hypertension and is a manifestation of hypertensive heart disease. The top factors correlated with the occurrence of AF are heart failure, aging, and valvular disease, followed by hypertension. However, because of its higher prevalence in the population, hypertension accounts for more cases of AF than other risk factors and is responsible for 14% of all AF cases [30]. Among patients with established AF, hypertension is present in ≈60% to 80% of individuals. The risk is elevated even in patients with normal upper BP [31]. Diastolic dysfunction, increased atrial pressure due to LVH, and atrial structural and electrical remodeling pave the way for AF. Hypertensive patients with AF carry an elevated risk of systematic embolism, stroke, tachycardia-mediated cardiomyopathy, and heart failure [32]. The determinative role of hypertension in systematic thromboembolism in the context of AF is reflected by the fact that it is the most frequent index included in risk scores, like the CHA2DS2-VASc score.

Moreover, uncontrolled hypertension is related to bleeding complications in patients on anticoagulant therapy. Consequently, optimal BP control is important to minimize the risks of AF-related stroke and oral anticoagulant-related bleeding [27]. Adequate and long-term BP control reduces the repercussions of AF. RAAS inhibitors have antiapoptotic and antifibrotic properties, which may decrease the incidence of AF in hypertensive patients with LVH (VALUE, LIFE studies). Beta-blockers and aldosterone receptor antagonists (MRAs) may also prevent AF in patients with heart failure. AF with rapid ventricular response should be managed with beta-blockers or non-dihydropyridine calcium antagonists (*e.g.*, diltiazem and verapamil) as anti-hypertensive agents.

Furthermore, BP control can lead to better rhythm control and long-term ablation success [33]. In patients with documented AF, hypertension increases the risk of thromboembolic and bleeding events and facilitates the progression from paroxysmal to persistent or permanent AF. Since hypertension is a modifiable risk factor, sufficient BP management is imperative in an attempt to address the detrimental complications of AF.

Ventricular arrhythmias

Ventricular arrhythmias may occur in hypertensive patients. Hypertension is not arrhythmogenic per se, but chronic pressure overload and subsequent hypertrophy contribute to the development of ventricular arrhythmias (premature ventricular contractions, non-sustained ventricular tachycardia, ventricular tachycardia, ventricular fibrillation) and even sudden cardiac death [11]. The extent of hypertrophy is directly related to increased ventricular ectopy. Fibrosis alters the electrophysiological properties of the heart and is considered proarrhythmic. Apart from the substrate, medical treatment of hypertension (thiazides) can lead to electrolyte disturbances (hypokalemia, hypomagnesemia), which can trigger ventricular arrhythmias by prolonging the QT interval and predisposing to early and delayed depolarizations [3]. The Framingham Study demonstrated that LVH electrocardiographically detected is associated with more frequent and complex premature ventricular beats. However, we have to accept that once LVH is detectable by the ECG, the echocardiographic criteria for LVH are already fulfilled [34]. Uncontrolled hypertension was associated with non-sustained ventricular tachycardia in up to 5% of patients during 24-h Holter monitoring [30]. LVH is a strong determinant of SCD due to sustained VT or ventricular fibrillation (VF), especially when coronary artery disease is present. An increase in LV mass of 50 g/m^2 correlated with a 45% higher risk of SCD in hypertensive patients aged >40 years [30]. Catterjee *et al.* indicated that the risk of VT was 2.8-fold greater in patients with LVH compared with patients without LVH (1.2%) [28]. However, it is unclear if a direct relationship exists between LVH and SCD. The increased risk of SCD could be attributed to the microvascular ischemia provoked by the hypertrophied myocardium or to ischemia because of epicardial coronary artery lesions, considering that hypertension is a major risk factor for atherosclerosis. Other factors we must consider, apart from the increased ischemic zone, are wall stress, fibrosis, neurohormonal activation, and altered electrical properties of the cardiomyocytes [3, 35–37]. During an electrophysiological study, hypertensive patients with LVH were more vulnerable to malignant arrhythmias [30]. Even asymptomatic, frequent, and complex ventricular arrhythmias in the absence of coronary artery disease increase mortality by 62% [30]. Aggressive BP management and subsequent LVH regression prevent malignant arrhythmias and SCD. RAAS inhibitors are the treatment of choice, especially when diabetes is present [11].

Bradyarrhythmias

Patients with hypertension may demonstrate bradyarrhythmias. The exact prevalence is not documented,

and various pathophysiologic mechanisms, such as drug-related arrhythmias, degenerative electrical disturbances, and obstructive sleep apnea, have been implicated [11]. Current guidelines recommend a combination of antihypertensive agents for optimal BP control. While dihydropyridine calcium channel blockers combined with -blockers are a valid option, the use of verapamil or diltiazem with -blockers is discouraged as it can provoke bradycardia and atrioventricular block. A-blockers also have a heart-lowering effect [38].

Furthermore, hypertensive patients receiving agents, including -blockers with predominantly renal clearance (atenolol, bisoprolol), are at increased risk of accumulation of b-blockers and active metabolites that could trigger bradyarrhythmias [27]. BP and fasting glucose levels are independently associated with AV block. A 10 mmHg increase in systolic BP increases the risk of AV block by 22%, and the same percentage applies for every 20 mg/dl increase in glucose levels [39]. Furthermore, LVH has been associated with conduction disturbances like bundle branch block (especially LBBB) and high-degree AV block. The presence of fibrosis and calcification can precipitate sick sinus syndrome [29]. Interatrial, intra-atrial, and inter-ventricular conduction delays are common in hypertension and predispose to AF and SCD. Hypertension with LVH and a wide QRS identifies patients at high risk of heart failure, sudden cardiac death, and cardiovascular mortality [11]. Obstructive sleep apnea is strongly related to bradyarrhythmias; primary treatment with continuous positive airway pressure could eliminate them [27]. Finally, an elevated resting heart rate in sinus rhythm may be a marker for further investigation for cardiac dysfunction, atrial flutter or fibrillation, anemia, hyperthyroidism, and sepsis. Although sinus tachycardia is associated with a worse prognosis in the context of coronary artery disease and heart failure, patients with hypertension and increased heart rate, in the absence of the above comorbidities, may benefit from -blocker therapy [11, 29]. The fact that BP and heart rhythm are interdependent is highlighted by the fact that in cases of sinus sick syndrome or AV block, a compensatory hypertensive response may be observed and is reversed with the appropriate device therapy [27].

Recommendations for arrhythmias monitoring in hypertensive patients

Hypertensive patients are at greater risk of both supraventricular and ventricular arrhythmias compared to the general population. Also, there is an established relationship between hypertension and SCD in patients without known cardiovascular disease [40]. AF is considered a manifestation of a hypertensive heart; thus, patients with hypertension face a high risk of thromboembolic events [39]. The 2020 European Society of Cardiology (ESC) Guidelines for AF propose an opportunistic screening for patients ≥65 years old and a systematic screening for patients ≥75 years old or at high risk of stroke [41]. However, not all hypertensive patients experience arrhythmias, and currently, there are no specific recommendations for arrhythmia monitoring.

A consensus paper by Lip *et al.* published in 2017 [11] highlighted some characteristics from the ECG, echocardiogram, and other comorbidities that indicate a high-risk profile for arrhythmias, and thus, closer monitoring is warranted. The choices for monitoring include ECG, 24 h, 48 h, 72 h, or week Holter monitors, implantable loop recorders (ILRs), cardiac implantable electronic devices (CIEDs), or less documented methods such as radial pulse palpation, arrhythmia detection via BP monitors, smartphones and smartwatches [32].

Echocardiogram

The most important finding from an echocardiogram is LVH. LVH has a proarrhythmogenic electrophysiologic phenotype and predisposes to supraventricular and ventricular arrhythmias. Patients with LVH present early after depolarization and, thus, sustained arrhythmia.

Other findings, like left atrial enlargement and diastolic dysfunction, are indicators of hypertension, and these patients also have a greater arrhythmic burden compared to hypertensive patients without abnormal findings on the echocardiogram (4).

Electrocardiogram (ECG)

P wave morphology on the surface ECG is of great importance in patients who suffer from hypertension. For example, increased p-wave duration, a low-amplitude p-wave (0.1 mV), or an advanced interatrial block (Bachmann-Bundle block) can be markers of AF. Also, frequent premature atrial beats (PACs) could be a sign of AF, and ECG monitoring is warranted [32].

Frequent premature ventricular beats (PVCs), couplets, or non-sustained ventricular tachycardia can be signs of LVH, aortic stenosis, or coronary artery disease. In addition, the co-existence of PVCs and LVH can increase the risk of AF, so prolonged ECG monitoring is needed [11].

The detection of LBBB and LVH on surface ECG is a warning marker of heart failure, SCD, and cardiovascular death, according to the LIFE study of 9131 hypertensive patients receiving aggressive antihypertensive therapy (losartan). QRS complex duration was

independently associated with SCD after a median 5-year follow-up period [42].

Dipping pattern of arterial hypertension

Normally, BP is lower at night compared to daytime (≥10% and <20%, dipping profile). Hypertensive patients who present a decrease in BP of 10% (non-dipping profile) or even a rise (reverse dipping) during the night are at greater risk of target organ damage and major cardiovascular events [39]. They also present more frequent episodes of supraventricular and ventricular arrhythmias among other hypertensive patients [31].

Comorbidities

Patients with recent ischaemic stroke receive 72-hour ECG monitoring, but patients with cryptogenic stroke should undergo extended cardiac arrhythmia monitoring to detect AF [32, 41]. The EMBRACE trial and CRYSTAL-AF study demonstrated that 30-day continuous arrhythmia monitoring and implantable cardiac devices, respectively, are superior to short durations of cardiac monitoring in patients with cryptogenic stroke [43, 44].

Obstructive sleep apnea (OSA) can cause resistant hypertension and bradyarrhythmias during sleep, even with a normal conduction system. After successful treatment with continuous positive airway pressure (CPAP), cardiac rhythm disorders are controlled without medical treatment or device implantation. In conclusion, cardiac monitoring before and after CPAP treatment can lead to the early detection and reversal of possible cardiac arrhythmias [11].

Other comorbidities, like increased BMI, chronic kidney disease and cardiovascular diseases (*e.g.*, coronary and peripheral artery disease), predispose to arrhythmias, and thus, they demand closer cardiac monitoring [32].

Symptoms

Hypertensive patients who present palpitations, presyncope, or syncope are considered patients with suspected arrhythmia, and a 12-lead ECG is recommended. A 24- to 48-hour Holter should be considered if it is unavailable or the results are inconclusive. If a diagnosis is not confirmed and the patient is highly symptomatic or presents CHA2-DS2-VASc ≥2, 30-day monitoring may detect the arrhythmia; otherwise, an ILR is warranted. A further individualized approach depends on the duration and severity of symptoms [11].

Conclusions

Hypertensive heart disease refers to structural and functional changes in the left atrium, left ventricle, and coronary arteries as a result of chronically elevated BP. Hypertensive heart disease can manifest as heart failure, coronary artery disease, arrhythmias and even sudden cardiac death. Hemodynamic changes, sympathetic and renin-angiotensin-aldosterone system (RAAS) activation, electrical and structural remodeling, fibrosis, electrolyte disturbances, and genetic factors serve as substrates for the development of atrial and ventricular arrhythmias.

In hypertensive patients, LVH is the most important predictor of supraventricular/ventricular arrhythmia and SCD. Episodes of AF are more frequent in patients with LVH. SCD is related to LVH, and as the left ventricular mass increases, the risk of SCD increases too. The decline of ventricular arrhythmias and subsequent SCD events after optimal BP control and LVH regression underline LV mass's importance for arrhythmogenic events. Drugs like thiazide diuretics can cause electrolyte disturbances, prolonging the QT interval and cause ventricular arrhythmias. A dose-dependent increase in fatal arrhythmias and subsequent SCD is observed. A regular follow-up of serum electrolytes, particularly calcium and potassium, and ECG is recommended.

Conflict of interest

The authors declare no conflict of interest.

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