International Journal of Cardiology 237 (2017) 60–63

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Short communication

Hypertension, left ventricular hypertrophy, and sudden cardiac death

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ARTICLE INFO

Article history:
Received 22 February 2017
Accepted 1 March 2017
Available online 3 March 2017

Keywords:
Atrial fibrillation
Hypertension
Hypertensive heart disease
Left ventricular hypertrophy
Sudden cardiac death
Ventricular arrhythmias

ABSTRACT

Hypertension (HTN) is the most common cause of hypertensive heart disease, which comprises of left ventricular hypertrophy (LVH), left atrial enlargement, diastolic dysfunction, functional mitral regurgitation and neurohormonal changes. All of these lead to significant arrhythmias such as atrial fibrillation (AF) as well as ventricular arrhythmias, and are known risk factors for sudden cardiac death (SCD). The association between LVH and SCD is well established, especially in the presence of myocardial ischemia, fibrosis and scar tissue, and AF. Inflammation, fibrosis and oxidative stress, as well as ischemia play a significant role and are the leading pathways to remodeling, arrhythmias, and SCD. Aggressive HTN control may lead, at least in part, to regression of LVH and thus lower the risk of AF and SCD. Therefore, LVH is a powerful, independent predictor of AF, ventricular arrhythmias and SCD, and is significantly underrecognized. Further investigation of the relationship and management of diastolic dysfunction, LVH and genetic factors and their association with SCD is certainly warranted.

1. Introduction

Hypertension (HTN) is among the most common, non-communicable disease in the world. Approximately 80 million people (32.6%) in the United States [1] and one billion worldwide suffer from HTN [2], and the prevalence may be even higher as the diagnosis is based on an objective test (i.e., blood pressure measurement). Long-term HTN leads to hypertensive heart disease, and is the result of anatomical and functional changes in the cardiovascular system (which is a cardiovascular sequelae of HTN) and is defined as left ventricular hypertrophy (LVH), left atrial enlargement, left ventricular diastolic dysfunction, functional mitral regurgitation and neurohormonal changes [3]. All of these changes are known predisposing factors to atrial fibrillation (AF), ventricular tachycardia (VT)/ventricular fibrillation (VF), and sudden cardiac death (SCD) [4]. LVH can be divided as; 1) physiological LVH, mostly due to adaptation and increased cardiac workload following intense physical activity (most commonly seen in athletes), and 2) pathological LVH due to intrinsic causes (genetic disorders) such as inherited cardiomyopathies or extrinsic causes such as pressure overload (HTN, aortic stenosis) or volume overload (mitral regurgitation, aortic insufficiency) [5]. In this review we will discuss the risk of LVH and its association with arrhythmias, SCD, and mechanisms of arrhythmogenesis in LVH. The general epidemiology of SCD is well discussed elsewhere in this issue.

Data from the Framingham Heart Study [6] and other population studies indicate that LVH increases prevalence of premature ventricular complexes, couplets, non-sustained VT, and subsequently increases the risk of SCD. Later, the Oregon Sudden Unexpected Death Study (Oregon SUDS) confirmed that LVH serves as an independent increased risk of SCD [7].

LVH increases the risk of ventricular arrhythmias (VAs) by 5.5% compared to those without LVH at 1.2%. Similarly, the presence of LVH increases the incidence of VT/VF by 2.8-fold [8]. HTN increases the risk of AF by 40–50% [9].

1.1. HTN and LVH

LVH is the most common sequelae of HTN and is the result of cardiac cell remodeling and hypertrophy. It is a strong risk factor for cardiovascular events and all-cause mortality, specifically arrhythmias and SCD [10].

A large body of evidence exists and indicated the relationship between HTN and LVH [5,10]. Further studies also revealed that LVH increases the risk of atrial and VAs and SCD [9–11].

LVH is an adaptation to chronic afterload pressure, which leads to pathological changes in structure and function of a cardiovascular system.

HTN-induced LVH begins with adaptive hypertrophy and eventually leads to myocardial decompensation and failure, where a more complex electrophysiological substrate is involved in arrhythmogenesis. The natural history and progression of LVH constitutes of three stages; 1) preclinical manifestations with normal LV systolic function and grade 1 diastolic dysfunction, 2) stable stage where myocardial cells

Abbreviations: AF, atrial fibrillation; HTN, hypertension; LVH, left ventricular hypertrophy; SCD, sudden cardiac death; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia.

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http://dx.doi.org/10.1016/j.ijcard.2017.03.002
0167-5273/

undergo left ventricular remodeling and the LVEF remains normal; however, diastolic dysfunction progresses from stage one to two and three, and 3) overt dysfunction where advanced heart failure with a decreased LVEF is evolving. There is also an increased risk of arrhythmias during stages 2 and 3.

1.2. AF and SCD

AF is an independent and underrecognized risk factor for SCD. Several epidemiological studies have reported the association of HTN, AF, and SCD excluding stroke [11]. Briefly, the presence of an irregular heart rate (R-R interval) during AF as well as the presence of structural heart disease, particularly CAD and scar tissue, HF, and cardiomyopathies are a dangerous combination for development of VT/VF [11–13].

Hemodynamic causes of LVH include:

1. Pressure overload: Pressure overload is characterized by concentric LVH, normal left ventricular chamber (cavity) size and systolic function.
2. Volume overload: Volume overload is characterized by enlarged left ventricular chamber (cavity) size and LVH.

1.3. Geometric pattern of LVH

The geometric patterns of LVH due to the hemodynamic causes (above) leads to either concentric or eccentric LVH.

1.4. LVH and arrhythmogenesis

The pathophysiological mechanisms of LVH leading to arrhythmogenesis are well illustrated in Fig. 1 and are due to an increase in myocardial cell size (cell hypertrophy), without an increase in the myocardial cell numbers, which in turn leads to an increase in fibroblasts, interstitial collagen accumulation, fibrosis, diastolic dysfunction, myocardial remodeling, cellular abnormalities, myocardial structural disarray and arrhythmogenesis [14].

2. Inflammation, fibrosis, myocardial scar and arrhythmogenesis

It is now well recognized that HTN, diabetes mellitus, obstructive sleep apnea and the other novel risk factors for AF VT/VF and SCD are the result of inflammation and fibrosis that leads to the final common pathway of "remodeling" and arrhythmias [15].

2.1. Cardiac fibrosis

In general, approximately 20% of myocardial tissue encompasses cardiac fibroblasts. Myocardial fibroblasts produce extracellular matrix structure and proteins.

Under abnormal conditions such as cardiac aging, HTN, diabetes mellitus, obstructive sleep apnea, ischemia and infarction, obesity, and the like, fibroblasts proliferate and replace normal myocardial cells, which leads to fibrosis. Increased numbers (proliferation) of fibroblasts are direct contributors to arrhythmogenesis [15–17].

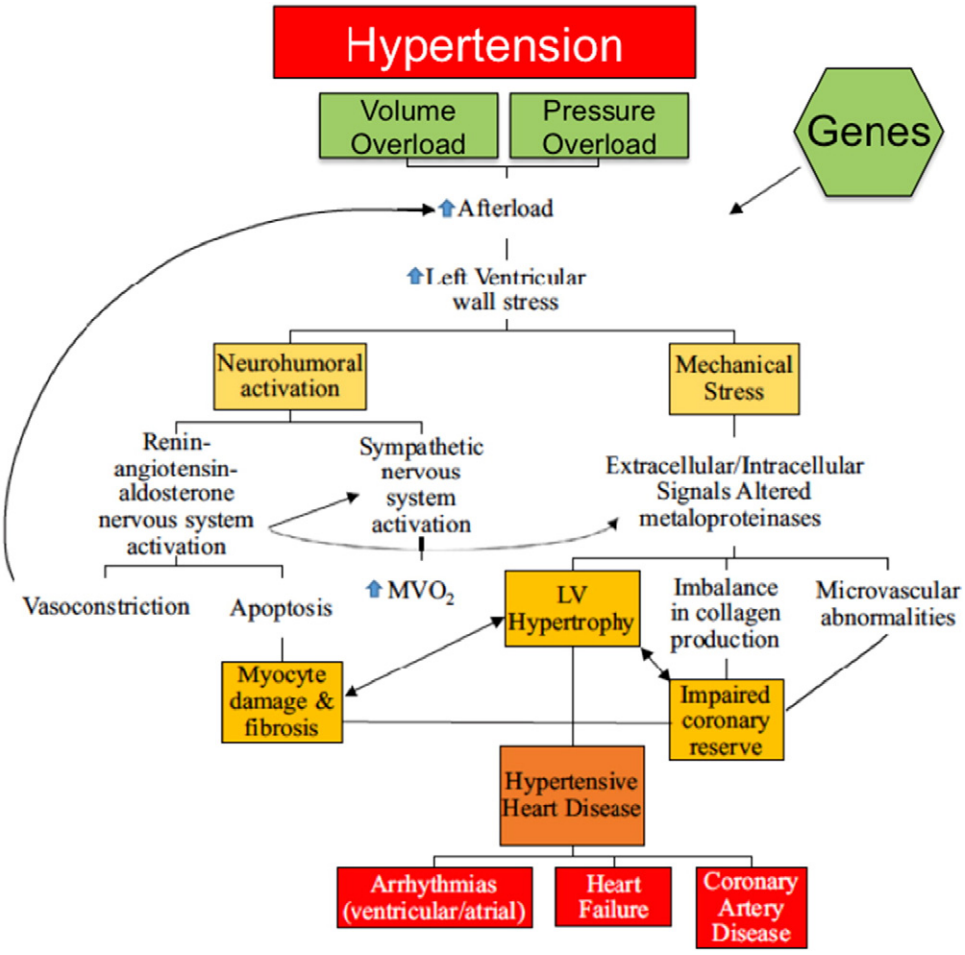

Fig. 1. Pathophysiological pathways of hypertensive heart disease and LVH that lead to arrhythmias, heart failure, and coronary artery disease. Abbreviations: LV-left ventricle; MV02-mixed venous oxygen saturation. With permission from Shenasa M, et al. Card Electrophysiol Clin 2015;7:207–220 [14].

The pathophysiological pathways leading to increased fibrosis is complex and is beyond the purpose of this review. Altered cell signaling that promotes increased number of fibroblast microRNA are known contributors to fibrosis and ion-channel remodeling and are discussed elsewhere [18–20].

In hypertensive patients, the activation of renin-angiotensin-aldosterone system is linked to development of myocardial fibrosis. Therefore, it is conceivable that the use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in patients with HTN reduces fibrosis and the risk of atrial and ventricular arrhythmias and SCD [21].

2.2. Role of anisotropic conduction and myocardial scar

Ample evidence exists that myocardial fibrosis and scar tissue produces anisotropic conduction, which is a substrate for initiation and sustenance of VAs [21,22]. Indeed, irregular heart rate that is present in patients with AF and myocardial structural disease are the hallmarks of facilitating VAs. Antiarrhythmic agents have a differential effect on tissue anisotropy, which further facilitates induction of arrhythmias. Fibrosis and myocardial scar are the result of cellular apoptosis (cell death) and serve as a substrate for reentrant arrhythmias. Myocardial infarction is among the leading cause of myocardial scar, arrhythmias, and SCD.

3. LVH and myocardial ischemia

During progression of LVH, microvascular changes and subendocardial ischemia develop, which results in atrial and VAs and SCD. The mechanism of arrhythmias in LVH and myocardial ischemia is not fully understood.

Recently, experimental investigations have revealed that in a LVH model (guinea pig) when ischemia is imposed by left anterior descending artery occlusion, spontaneous or programmed stimulation-induced premature ventricular complexes provoked sustained VT (Fig. 2) [14]. The challenge remains that it is difficult to evaluate and prove microvascular dysregulation during LVH.

3.1. Cellular basis of arrhythmogenesis in LVH [5,14]

1. Remodeling of myocardial cells, secondary to LVH, takes place both at the cellular membrane and also with interstitial compartment of ventricular myocardium. Prolongation of action potential duration (repolarization) is one of the primary cellular responses to LVH.
2. Myocardial electrical remodeling manifests as prolongation of both QRS duration and QT interval, both of which facilitate the occurrence of reentrant arrhythmias.
3. Intramyocardial conduction delays, which is reflected as QRS fractionation, is known to increase the risk of VAs.
4. Cellular ion channel changes induced by LVH: LVH decreases the density of sodium and potassium pumps, which in turn leads to a decrease in intracellular potassium concentration and prolonged repolarization. In addition, ATP-sensitive potassium channels are more likely to remain open during ischemia in hypertrophied hearts as compared to normal myocytes [23,24], which further prolongs repolarization and facilitates delayed afterdepolarization and triggered activity, causing sustained arrhythmias.
5. Increased intracellular Ca^{2+} and cell membrane capacitance is observed in hypertrophied cells [23,25].
6. Increased anisotropy and non-uniform recovery of excitability in LVH increases the risk of VAs. Human and experimental investigations well demonstrated the role of myocardial anisotropy in the genesis of reentry and VAs [22].
7. Subendocardial myocardial ischemia in the presence of LVH increases the propensity of VT and VF.

Since most patients with LVH demonstrate an increase in the incidence of premature ventricular complexes, couplets and nonsustained VT, use of antiarrhythmic agents, which are known for their proarrhythmic and torsadogenic effect, certainly increase the risk of malignant arrhythmias and SCD, especially in the presence of myocardial scar and irregular heart rate such as AF.

3.2. Genetic factors in LVH and arrhythmogenesis

As part of the myocardial remodeling in response to HTN and LVH, upregulation of Na^{+}/Ca^{2+} exchange current and enhance sarcoplasmic reticulum can facilitate induction of early and delayed afterdepolarizations [25]. Similarly, human population studies and genome-wide association have identified several genes that are involved in LVH and arrhythmogenesis, such as KCNB1, which encodes the voltage-gated potassium channel [25,26].

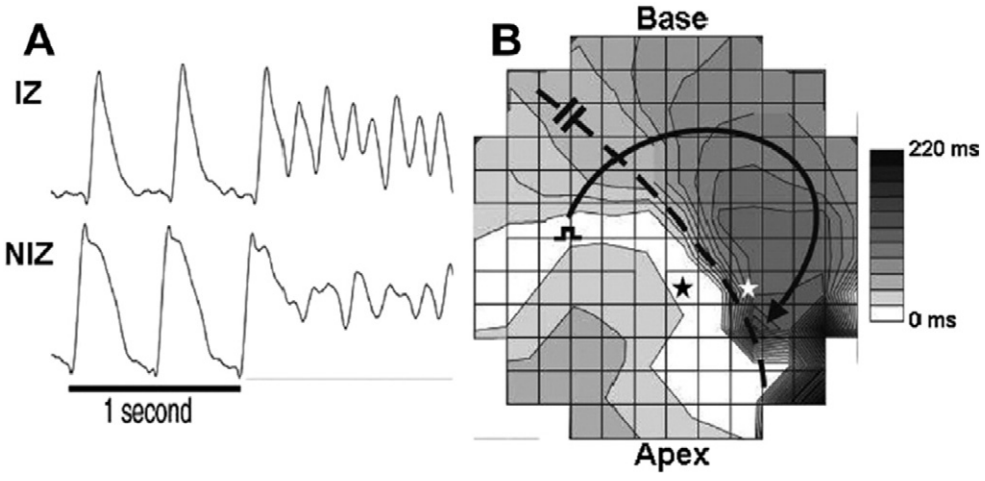

Fig. 2. Optical recordings of membrane voltage obtained from a hypertrophied guinea pig heart after 10 min of left anterior descending artery occlusion illustrates the onset of ventricular tachyarrhythmia (VT). (A) Action potential recordings from 2 sites 2 mm apart on each side of the border between the ischemic zone (IZ) and nonischemic zone (NIZ) (asterisks). The first 3 action potentials are paced at a cycle length of 500 ms. Note the development of a 60-ms conduction delay between the 2 sites, the marked shortening of APD of the IZ site, and the onset of a non-sustained (self-terminating) VT. (B) Epicardial isochronal activation map of the last paced beat before the onset of VT shows development of an arc of conduction block (represented by crowded isochrones) at the border between the IZ and NIZ. A wave front that started at the site of pacing in the right ventricle circulated around the arc of block in a pattern consistent with circus movement reentry. With permission from Shenasa M, et al. Card Electrophysiol Clin 2015;7:207–220 [14].

Other genetic factors such as connexin expression certainly play an important role, but are beyond the scope of this review.

4. Current tests to evaluate LVH

Electrocardiography and echocardiography are the most commonly used tests. Other ECG related methods such as heart rate variability, signal-averaged ECG, and micro T-wave alternans are less commonly used. The diagnostic yields and sensitive have been previously discussed [11,14].

4.1. Cardiac computerized tomography and magnetic resonance imaging

Both provide accurate and high resolution information and images on left ventricular mass, volume, and function. Both are also used to create electrical anatomical mapping, so they are very useful to evaluate myocardial scar characteristics and size before and during ablation procedures. The drawback of cardiac computerized tomography is ionizing radiation exposure.

Cardiac magnetic resonance imaging is considered the "gold standard" for the evaluation and measurement of left ventricular mass and volume.

Advanced methods of cardiac magnetic resonance imaging and sequencing such as fiber tracking and fiber orientation allows characterization of myocardial fibers (fiber orientation) such as diffusion magnetic resonance imaging tractography, which differentiates among LVH due to HTN, hypertrophic cardiomyopathy, and athlete hearts [27].

5. Future directions

- Improved and novel imaging methods such as advanced cardiac magnetic resonance imaging, ECG imaging, electromechanical wave imaging, and diffusion magnetic resonance imaging tractography [27]
- Specific population studies (high-risk versus low-risk individuals)
- Reappraisal of SCD detection methods and epidemiology
- Focus more on inflammation, fibrosis, and biomarkers
- Better ECG markers for risk stratification of SCD in different substrates
- Better risk stratification models
- Better design of future trials

6. Summary

- LVH is a powerful, independent predictor of cardiovascular events and is considered a "silent killer"; however, it is modifiable and reversible.
- LVH is associated with an increased incidence of AF VT/VF, and SCD.
- HTN and hypertensive heart disease results in inflammation and fibrosis, which produces a substrate for inhomogeneity and an increase in the risk of arrhythmias.
- Myocardial fibrosis dissociates the excitable myocardial fibers and changes the biophysical properties of impulse propagation, which is known to increase the anisotropic conduction that predisposes to arrhythmias [22].
- It is important to recognize that inflammation, fibrosis and remodeling that is produced by HTN are different from changes that result in diabetes mellitus, ischemia, etc. Thus, each pathology should be investigated and managed separately.
- HTN begets LVH, LVH begets remodeling, arrhythmias, and SCD.

Conflict of interest

None.

Acknowledgment

We would like to thank Mariah Smith for her assistance in the preparation of this manuscript.

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