

Hypertension and atrial fibrillation: a bench to bedside perspective

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1. ABSTRACT

Atrial Fibrillation (AF) is the most common cardiac arrhythmia in clinical practice and its prevalence increases markedly with advancing age, worldwide. Almost every primary care physician, internist, or cardiologist, has dealt with stroke or with other complications of AF. Still, its management remains a hot issue for clinicians and the debate over which treatment strategy is the best is ongoing. Moreover, AF increases significantly the total cardiovascular (CV) morbidity and mortality. Despite a great bulk of data in the existing medical literature, the pathophysiology of AF in patients with hypertensive heart disease (HHD) is poorly understood, and the underlying signaling pathways linking hypertension (HTN) to AF remain to be fully elucidated. The scope of this article is to discuss the myocardial anatomical and physiological alterations that occur in HTN, and highlight the proposed electrophysiological mechanisms that cause the hypertensive heart to fibrillate. In addition, we will focus on the latest ESC 2016 guidelines for the risk stratification of AF patients as a tool to guide anticoagulation which represents the mainstay of treatment for AF. Last, the other therapeutic approaches for hypertensives with AF currently adopted for optimal patient management will be reviewed.

2. HYPERTENSION AND ATRIAL FIBRILLATION: THE RISING PREVALENCE OF THE TWO CARDIOVASCULAR “EPIDEMICS”

Hypertension (HTN) is a major risk factor for cardiovascular (CV) disease and the single most

important risk factor for stroke (1). Affecting 972 million people worldwide, HTN is reaching epidemic proportions (2). Some striking statistics estimate that the prevalence of HTN will rise to approximately 1.5.6 billion by the year 2025, especially in rapidly developing countries with limited early routine screening protocols (3,4). Despite the implementation of new clinical guidelines and the broad availability of effective pharmaceutical agents, HTN often goes undetected and inadequately treated, shortening life expectancy by five years during adulthood. (5,6). Without antihypertensive treatment and lifestyle changes, its natural history evolves and HTN progresses to left ventricular hypertrophy (LVH) and heart failure (HF) along with a wide range of structural and functional alterations that result in an arrhythmogenic myocardial substrate (Figure 1) (7).

It is well known that the two conditions often coexist, further increasing global CV risk and the risk of stroke. Similar to HTN, AF is considered to be a CV “epidemic” since its prevalence is expected to at least double in the next 50 years as the population ages (8-10). In 2010, the estimated global prevalence rates of AF per 100.0.00 population for men and women were 596.2. and 373.1., respectively (11). A higher incidence and prevalence rate was observed in developed countries (12). In addition, hospitalization rates for HTN and AF have increased among US adults posing a great health and economic burden on societies, worldwide (13-14). Yet, the treatment of HTN is not currently a focus in the clinical management of



Figure 1. Schematic representation of the link between hypertension and atrial fibrillation.

AF (15). Before examining in detail the management of hypertensive patients with AF, we will review the major pathophysiological mechanisms in HHD that lead to the development of AF. Pathophysiological mechanisms contributing to high blood pressure (BP) are complex and involve many systems. Specifically, genetics, the sympathetic nervous system (SNS), renin angiotensin aldosterone system (RAAS) activation, adaptive and innate immunity and inflammation have been implicated in the pathogenesis of this condition (16-17).

3. HYPERTENSIVE HEART DISEASE LEADS TO LEFT VENTRICULAR HYPERTROPHY AND HEART FAILURE GENERATING AN ARRHYTHMOGENIC MYOCARDIAL SUBSTRATE

HHD is a constellation of structural and functional abnormalities that progress gradually to manifest clinically as symptomatic HF and arrhythmias (7,18). Uncontrolled high BP levels exert an increased load on the left ventricular wall by increasing wall tension according to the law of Laplace. As an adaptive response for the increased wall tensile stress, the left ventricular wall thickens. A reduction in the left ventricular chamber diameter may also be a compensatory mechanism (19). Indeed, BP is the most powerful determinant of left ventricular mass. Moreover, the afterload – the aortic pressure that the left ventricle (LV) has to overcome to eject blood during systole – also increases. Thus, while initially compensatory, over time, cardiac hypertrophy becomes pathological, the heart can no longer meet the increased metabolic demands and its increased mechanical work load, and dilation and HF ensue (20). Volume overload also contributes importantly to the development of cardiac hypertrophy. Although the exact mechanism by which sodium intake influences left ventricular mass is unclear, a high salt intake could expand intravascular volume and increase left ventricular preload (21-22). Wall thickening occurs more commonly in response to pressure overload, and chamber dilation occurs more commonly in response to volume overload (23,27). Left ventricular mass increases following wall thickening or chamber dilation (7). Interestingly, mutations of sarcomeric (or other) proteins, or loss of contractile mass from prior infarction may also lead to hypertrophic growth of the heart (24).

Undoubtedly, LVH plays an important role in chronic adaptation to pressure or volume overload of the systemic circulation. The degree of hypertrophy parallels the severity of overload (25-27). It has been well documented that LVH is an important intermediate phenotype in the progression of HHD and that it is independently associated with adverse CV outcomes (28-29). According to relative wall thickness (RWT) – the ratio of the left ventricular wall thickness to diastolic diameter, measured by echocardiography – LVH is further classified into concentric and eccentric (30). While the RWT is increased in concentric hypertrophy where new sarcomeres are added in parallel, it remains normal in eccentric cardiac hypertrophy, where new sarcomeres are added in series (31,32). By taking a look inside the cardiomyocyte we will discover several signaling pathways that are critically important in mediating myocardial hypertrophy, including the G-protein coupled receptor (GPCR), the calcineurin/NFAT, MAPK, and the PI3K/AKT/mTOR signaling pathways. Importantly, these signaling pathways control molecular processes, such as cell proliferation, differentiation, survival, migration and other functions of the cell as well (Figure 2) (33-35).

Furthermore, myocyte hypertrophy, collagen formation and fibroblast proliferation, follow the increase in left ventricular wall stress and result in myocardial remodeling with a disproportionate increase in fibrous tissue (23). These changes subsequently reduce left ventricular compliance, leading to diastolic dysfunction, the main hemodynamic feature of HHD and an important factor in the evolution of congestive HF. Structural changes of the coronary arteries and the increase in both interstitial myocardial fibrosis and in myocardial mass contribute to reduce the vascular coronary flow reserve (23). The resultant ischemic heart disease (IHD) that often follows HF may lead to myocardial scarring and systolic left ventricular dysfunction, and also promote potentially malignant arrhythmias and sudden cardiac death (SCD). Importantly, there is also an increased risk for AF, an important risk factor for congestive HF and thromboembolic CV complications (36,37). More specifically, structural remodeling results in electrical dissociation between muscle bundles and in local conduction heterogeneities facilitating the initiation and perpetuation of AF. This electroanatomical

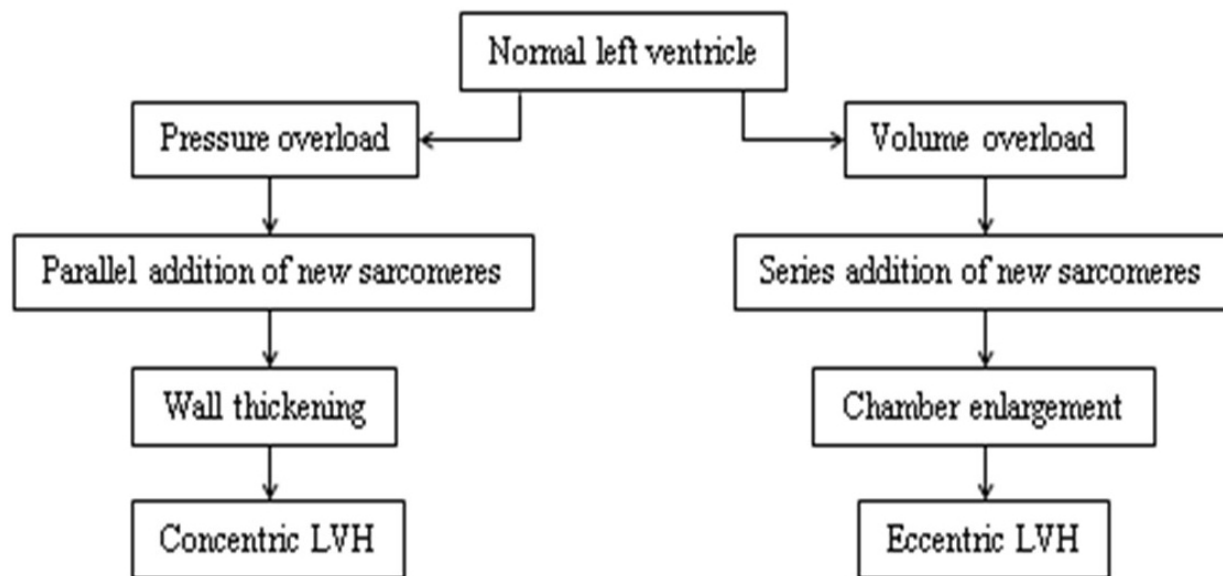


Figure 2. Concentric versus eccentric hypertrophy.

substrate permits multiple small re-entrant circuits that can stabilize the arrhythmia (38).

4. ATRIAL STRUCTURAL AND ELECTRICAL REMODELING ARE THE HALLMARKS OF ATRIAL FIBRILLATION

As diastolic dysfunction progresses, fibroblasts proliferate and differentiate into myofibroblasts to enhance connective tissue deposition and fibrosis. In the hypertrophic myocardium myofibrillar disarray, heterogeneous gap junction distribution, and fibrosis are additional potentially arrhythmogenic components (39). Increased interstitial and replacement fibrosis may lead to electrical myocardial bundles dissociation and conduction block. HF ensues and left atrial structure and function are altered, as well (38). The risk of AF increases with potentially fatal complications. AF-induced atrial remodeling enhances the vulnerability of the heart to AF induction and maintenance; this auto-reinforcing property of AF is often referred to by the term “AF begets AF” (39). It has been demonstrated in experimental animals that as soon as the AF interval passes a critical threshold of 120 ms, it becomes more stable and the duration of AF starts to increase (40). As a result total CV risk is increased with devastating consequences for the hypertensive patient.

In particular, there are three main components of atrial remodeling; the electrical, contractile and structural remodeling. First, AF is a chaotic rhythm caused by an overly rapid production of atrial impulses that cause intracellular calcium accumulation inside the cardiomyocytes, engaging homeostatic defense mechanisms against chronic calcium overload (41). The calcium-dependent calcineurin/nuclear factor

of activated T cells (NFAT) system is then activated. NFAT translocates into the nucleus and suppresses the transcription of the gene encoding Cav1.2, long type calcium channels (LTCCs) (42). A decrease in the action potential duration (APD) is the net result, thereby promoting a re-entry-prone substrate. Enhanced propensity to ectopy is the endpoint of calcium handling instability, which possibly occurs through increased sympathetic activation and cardiac sympathetic hyperinnervation in hypertensive states. The electrical remodeling which is characterized by rapid atrial rates triggering a series of events that create re-entry circuits reverses quickly and completely once the sinus rhythm is restored (38, 44). Second, the intracellular changes upon calcium handling may be responsible for the loss of contractility of the left atrium, inducing thus a contractile remodeling. The stasis of blood in the left atrial appendage contributes to the development of blood clots, promoting thromboembolic events (38,43-44). The third component of atrial remodeling is the structural remodeling which is characterized by the macro- and microscopic alterations that occur in the myocardium as a consequence of AF and its recurrences and contribute long-term to contractile dysfunction and decreased cardiac output (Figure 3) (38,43-44).

Beyond the three main components of atrial remodeling that are central in the generation of AF in hypertensive patients, it is important to note that AF itself, once present, may create ectopic foci, “rotors”, or other stable re-entry circuits, that propagate several independent wavelets through the atrial musculature in a chaotic manner. This is known as the “multiple wavelet hypothesis” and it has been proposed by Moe and Abildskov. The endpoint is the perpetuation of this

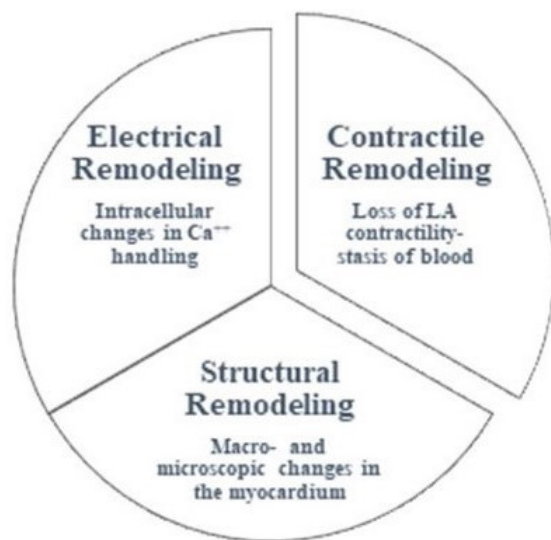


Figure 3. Main components of atrial remodeling.

complex arrhythmia and the increased risk of CV and thromboembolic events (45).

Apart from the alterations taking place at the tissue level, cellular changes have also been implicated in the pathogenesis of AF. Recently, researchers have identified several junctional complexes located at the intercalated discs (ID), whose disorganization may play a key role in arrhythmogenesis. IDs are highly organized, electron dense, structures that join the ends of adjacent cardiomyocytes to support synchronized contraction of the heart muscle (46). Gap junctions (GJ), constructed from connexins (Cx), constitute the primary structure of the ID required for intercellular current flow (47). Twenty members of Cx proteins have been identified in human. Of those, Cx43 is the major GJ protein in working human ventricular cardiomyocytes, with much less Cx45 and Cx40 expressed here (48). For the most part, Cx45 is strictly localized to the atrioventricular node and adjoining His bundles, and Cx40 is expressed mainly in the atria and the fast connective tissue of the His-Purkinje system (49). Growing evidence suggests that alterations of intercellular communication through GJs are likely contributing factors to the occurrence of AF. Such alterations may be as simple as microfibrosis interrupting gap junctional communication without a change in Cx quantity or distribution, or as complex as remodeling of the 3 different Cx isoforms to change the makeup of heteromeric/heterotypic GJs (50). However, studies showing causal relationship in the context of pathogenesis of AF are still scarce and further research is needed.

5. ANIMAL MODELS

For more than a century, large animal models have played prominent roles in the study of

the pathophysiology of AF, since they have taught us about mechanisms of this common disease. A variety of animal models exist, including models of lone AF and models of AF in the setting of HTN. Kistler *et al.*, have shown that in sheep with pre-natal corticosteroid-induced chronically, elevated BP is associated with significant atrial electrical and structural remodeling (51). In addition, the spontaneously hypertensive rat (SHR) is a model of systemic HTN that exhibits a progression of HTN and LVH from a stable form with normal cardiac function. The SHR shows a HTN-induced remodeling of the left atrium involving atrial enlargement, interstitial fibrosis, and cellular electric remodeling, which, in the aging SHR, leads to increased vulnerability to burst pacing-induced atrial arrhythmias (52, 53). Further experimental studies, in combination with clinical research, is needed to gain more insight into the mechanisms that underlie AF and control thus this challenging clinical problem.

6. RISK STRATIFICATION IN HYPERTENSIVES WITH ATRIAL FIBRILLATION

Since their INTRODUCTION into guidelines, the CHADS₂ and the CHA₂DS₂VASc scores have simplified the clinical decision for initiating oral anticoagulation (OAC) in patients with AF, which represents the mainstay of treatment for these patients.⁵⁴ The CHADS₂ (Congestive heart failure, Hypertension, Age, Diabetes, Stroke) score assigns one point each for a history of HF, HTN, age>75 years, and diabetes mellitus, whereas it assigns two points to patients who present with a prior history of cerebrovascular stroke or a transient ischemic attack (54). Patients with a zero CHADS₂ score are considered to be at low risk of experiencing stroke, in contrast to those with a score two or greater who are at high risk. Patients assigned only one point at CHADS₂ score are at moderate risk for a cerebrovascular event. As such, patients having a >2 CHADS₂ should be initiated on OAC with either new oral anticoagulants (NOACs) or warfarin, unless there is a contraindication (55). The target international normalized ratio (INR) in AF patients receiving warfarin should be 2.5. (55-56).

The 2016 ESC Guidelines for the management of AF developed in collaboration with EACTS recommend estimating stroke risk in AF patients based on the CHA₂DS₂VASc score (Congestive heart failure, Hypertension, Age, Diabetes, Stroke, Vascular disease, Sex (female)). In general, patients without clinical stroke risk factors do not need antithrombotic therapy, while patients with stroke risk factors (i.e. CHA₂DS₂VASc score of 1 or more for men, and 2 or more for women) are likely to benefit from OAC (44).

More recently, Singer *et al.*, developed and validated a new AF stroke prediction model using the original Anticoagulation and Risk Factors in Atrial

CHADS ₂	CHA ₂ DS ₂ VASc score
<ul style="list-style-type: none"> • Congestive heart failure → 1 • Hypertension → 1 • Age >75 → 1 • Diabetes → 1 • prior Stroke or TIA → 2 	<ul style="list-style-type: none"> • Congestive heart failure → 1 • Hypertension → 1 • Age >75 → 2 • Diabetes → 1 • prior Stroke or TIA → 2 • Vascular Age → 1 • Sex (female) → 1

Figure 4. Stroke risk scores for AF and points assigned for each variable.

Fibrillation (ATRIA) AF cohort (57). Results From a National Primary Care Database in United Kingdom showed that the ATRIA score performed better than the CHADS₂ and the CHA₂DS₂VASc scores in predicting ischemic stroke risk in AF patients (58). Specifically, it more accurately identified very low stroke risk patients with AF than the CHA₂DS₂-VASc score, which could prevent overuse of anticoagulants (58). Similarly, in a Swedish cohort of patients with AF the ATRIA score predicted ischemic stroke risk better than CHADS₂ or CHA₂DS₂-VASc (Figure 4) (59).

As we have previously mentioned, AF increases stroke risk at least five-fold (60). Since HTN is also the single most important factor for stroke, it is imperative to initiate anticoagulation in patients who are at high risk for a cerebrovascular event. By doing so, we could improve the quality of life of hypertensive patients with AF and increase survival (61). It should be mentioned that the safety and efficacy of NOACs in patients with rheumatic mitral valve disease has not been evaluated and should be further studied (44). A patient's bleeding risk should be taken into account in reaching a decision about anticoagulation, although for most people the benefit of anticoagulation outweighs the bleeding risk.

7. USE OF ANTIHYPERTENSIVE MEDICATION IN PATIENTS WITH ATRIAL FIBRILLATION

Several studies have showed that the use of antihypertensive medication in hypertensive patients with AF, decrease significantly the risk of AF and stroke, mainly by lowering the high levels of systolic BP. In addition, they may also reduce the risk of AF through inhibition of the cardiac remodeling and neurohumoral activation that occurs in the evolution of HHD (62). Specifically, it has been suggested that controlling

activation of the RAAS in addition to controlling BP is associated with a reduced risk of AF, and as such, these medications are preferred over other classes of antihypertensives, unless contraindicated (63).

In hypertensive patients with co-existing CV disease, such as coronary heart disease or or HF, beta-blockers are the preferred class of antihypertensives since they contribute to rate control and increase survival through a reduction in cardiac work load. Yet, recurrences of AF are frequent even under beta-blocker prophylaxis (64).

8. SUMMARY

HHD progresses to left ventricular hypertrophy and HF along with structural and functional abnormalities at the myocardium, which promote an arrhythmogenic substrate and SCD. Myocardial scarring, excessive fibrosis or remodeling that accompany HTN may trigger malignant arrhythmias, such as AF. Scientists have recently focused on the pathophysiology of AF by studying the alterations occurring at the tissue, as well as, at the cellular level. New insights and deeper understanding of pathophysiology of AF in patients with HTN could lead to the advent of new therapies and better management of this fatal rhythm disturbance.

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Abbreviations; AF, atrial fibrillation, BP, blood pressure, CDC, Centers for Disease Control and Prevention, CV, cardiovascular, GJ, gap junction, Cx, connexin, HF, heart failure, HHD, hypertensive heart disease, HTN, hypertension, ID, intercalated disc, IHD, ischemic heart disease, LTCC, long type calcium channel, LV, left ventricle, LVH, left ventricular hypertrophy, NFAT, nuclear factor of activated T cells, NOAC, new oral anticoagulant, OAC, oral anticoagulation, RAAS, renin angiotensin aldosterone system, RWT, relative wall thickness, SCD, sudden cardiac death, SNS, sympathetic nervous system

Key Words: Atrial Fibrillation, Hypertension, Left Ventricular Hypertrophy, Signaling Pathways, Atrial Enlargement, Myocardial Remodeling, Intercalated Disc Remodeling, Stroke, Risk Stratification, Anticoagulation, Rate Control, Rhythm Control, Invasive Therapies, Review

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