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Opinion

Left Atrial Enlargement, Arterial Hypertension and Atrial Fibrillation, Another Framingham Clue in the XXI Century

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Received: June 19, 2020; **Published:** July 07, 2020

Arterial hypertension is a systemic condition characterized by elevated blood pressure in the vascular system. Despite the great effort of scientific community to sensitize population to the problem, enforcing the preventive and treatment measures, this condition continues to be responsible for a large portion of global mortality, as it represents one of the major modifiable risk factors for adverse cardiovascular (CV) and cerebrovascular events in both developed and developing countries [1]. Long-term arterial hypertension can cause coronary artery disease, stroke, heart failure, peripheral vascular disease, vision loss, and chronic kidney disease [2]. Left atrial enlargement (LAE) is a marker of left ventricular (LV) pressure and volume overload. The size of the left atrium (LA) is increased in numerous CV disorders and is characterized by alterations in LV structure and function, such as mitral valve or myocardial disease and arterial hypertension [3]. In hypertensive heart disease, LAE is a reliable marker of a chronically elevated LV filling pressure and diastolic dysfunction even in the absence of mitral valve disease [4,5].

A recent international survey estimated that the incidence of systolic blood pressure (SBP) of at least 110 - 115 mm Hg and ≥ 140 mmHg has grown considerably from 1990 to 2015 with a parallel increase of disability-adjusted life years and mortality [6]. The increase of the systolic wall stress caused by high systolic pressures is associated with high peripheral resistance, as occurs in arterial hypertension, determines an adaptive response known as concentric hypertrophy. This phenomenon is mediated by the addition of sarcomeres in parallel and the expansion of the myocyte's area with a consequent increase of the LV mass. Therefore, the LV has a normal volume but increased mass and wall thickness [2]. Framingham study documented that hypertensive patients showed an increase of mass and volume of LV, compared with subjects with normal blood pressure [7]. This phenomenon affects men and women equally, regardless of age, and it is associated with LV diastolic dysfunction (LVDD) and LAE [8,9].

Strong evidence suggests that the presence of LAE portends a clinically significant risk of adverse cardiovascular outcomes for the patient [10]. Substantial biologic plausibility supports the prognostic significance of LA size. However, to maximize the utility of LA size, which is represented more accurately by LA volume than M-mode LA dimensions, an understanding of LA enlargement and its association with preclinical CV disease is important [9].

Current findings suggest that echocardiographically determined LA size may become an important clinical risk identifier in preclinical CV disease and should be assessed as a part of routine comprehensive echocardiographic evaluation. In the past, changes in the morphology of the P wave in the electrocardiogram have been considered useful indications of left and right atrial abnormalities [11,12]. The validity of these assumptions in the estimation of left atrial size has been tested against direct observations at the time of surgery (Saunders., *et al*. 1967; Martins de Oliveira and Zimmerman, 1959), measurements from various radiological views of the heart (Arevalo, Spagnolo, and Feinstein, 1963) and from postmortem studies (Abildskov, 1957). These techniques, however, have significant drawbacks, namely, that x-ray studies measure only gross changes in the atria and postmortem studies are non-physiological [13]. For this reason, the echocardiographic evidence of LAE is an specific sign of hypertensive disease with greater sensitivity and specificity than the electrocardiogram. Therefore, echocardiography -widely available- is a useful diagnostic and follow-up imaging tool for managing AH, especially in presence of suspected cardiac target organ damage [2,9,11]. Nevertheless, in a recent study, LA size in hypertensive patients with electrocardiographic left ventricular hypertrophy is influenced by gender, age, obesity, systolic blood pressure, and left ventricular geometry [14]. Also, ECG showed very low sensitivity but high specificity in detecting LAE as compared to ECHO which is the gold standard. Sensitivity and specificity of ECG for detecting LAE depends upon the number of diagnostic criteria taken into account. Sensitivity of ECG in detecting LAE can be increased by using more criteria [13-15].

LA function, in a close interdependence with LV function, plays a key role in maintaining an optimal cardiac performance. The LA modulates LV filling through its reservoir, conduit, and booster pump function, whereas LV function influences LA function throughout the cardiac cycle. The LA can act to increase LA pressure in arterial hypertension and can react to increased LV filling pressure (in significant ventricular disease) [5]. LA remodelling is related to LV remodelling and LA function has a central role in maintaining optimal cardiac output despite impaired LV relaxation and reduced LV compliance. Understanding how each component of LA function is influenced by LV performance, and how each LA phasic function contributes to maintain an optimal stroke volume in normal and diseased hearts, is important for interpreting data derived from quantification of LA function [16].

Atrial fibrillation (AF) is a frequently encountered arrhythmia associated with increased morbidity and mortality. Several large population-based prospective studies have shown a strong association between M-mode anteroposterior LA diameter and the risk of new onset AF. In the Framingham Heart Study, every 5 mm increase in LA diameter increased the development of AF by 39%, while the Cardiovascular Health Study showed a four-fold increase in the risk of new AF with LA diameter 0.5 mm [17,18]. A recent prospective study found that not only the maximum LA volume (per tertile, hazard ratio: 1.8) but also the minimum LA volume (per tertile, hazard ratio: 2.4) were independent predictors of first AF or atrial flutter, incremental to clinical and other echocardiographic parameters of AF or atrial flutter prediction. Furthermore, reduced LA reservoir functions, as estimated by total LA emptying fraction, have markedly increased the propensity for first AF or atrial flutter [hazard ratio: 5.4 (1.8 - 16), p50.002], independent of clinical risk factors, LA volume, LV ejection fraction, and diastolic function grades. Evidence from these studies indicates that LA volume encompasses information not captured by clinical data or one-dimensional M-mode assessment and thus represents a superior predictor of outcomes including AF [2,9,19,20]. The 2018 ESH/ESC Hypertension guidelines suggested the use of LA volume instead of linear dimensions, and for the first time proposed the indexation to height2 (h2) [21].

LA size has been shown to predict mortality, both CV as well as all-cause, in the general population. However, in other population-based studies, the association of LA enlargement with mortality has been attenuated when diastolic function, LV mass, or LV hypertrophy has been considered. In contrast, in recent trials such as the LIFE (Losartan Intervention for Endpoint reduction in hypertension) trial, LA diameter/height predicted the risk of CV events independent of other clinical risk factors in hypertensive patients with LV hypertrophy [22]. Similarly, in a very large study of patients referred for echocardiography, LA volume index predicted all-cause mortality independent of LV geometric patterns. The prognostic implication of LA size has also been shown in high-risk subgroups, such as patients with acute myocardial infarction, atrial arrhythmia, LV dysfunction, or dilated cardiomyopathy, and patients undergoing valve replacement for aortic stenosis and mitral regurgitations [9,23,24].

LAE is a predictor of combined fatal and nonfatal cardiovascular events, independently of other contributors to cardiovascular risk, including out of office blood pressure abnormalities and cardiac arrhythmias [2,3,10,19]. We should state, however, that LA enlargement does not further increase cardiovascular risk when LV hypertrophy is present. An echocardiographic examination should carefully assess both LV and LA structures to more precisely quantify the overall contribution of the heart to cardiovascular risk, as well as to identify subjects with normal LV mass who nevertheless have an increased risk because of alterations of LA [25].

There are guidelines available for the diagnosis of LAE, but no therapeutic management geared towards its management. Currently, no known medical therapy is available to reverse the left atrial remodeling. The focus of care and medical treatment in patients with LAE is the identification and treatment of underlying pathologies. The evaluation of atrial function using newer echocardiographic techniques may have important clinical implications in predicting symptom development or risk of arrhythmias in different conditions. The extent of LA remodelling reversibility with medical treatment and the impact of such changes on outcomes require further studies.

Conflict of Interest

None.

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Volume 7 Issue 8 August 2020
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