

REVIEW**THE LEFT ATRIUM IN HYPERTENSION:
A SYMBOL OF MORTALITY AND MORBIDITY?****Gregory YH Lip, Sridhar Kamath***Haemostasis Thrombosis and Vascular Biology Unit, University Department of Medicine
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The importance of the left atrium in cardiac pathophysiology is perhaps a little undervalued. Indeed, left atrial size and/or function has been implicated in a number of cardiovascular and cerebrovascular disorders as being either causal or as an indirect marker(s) of disease [1].

For example, the Framingham study reported that left atrial enlargement was a significant predictor of stroke in men and death in both sexes; indeed, for every 10-mm increase in left atrial size, the relative risk of stroke was 2.4 in men and 1.4 in women, whilst the relative risk of death was 1.3 in men and 1.4 in women [2]. This relation of left atrial enlargement to stroke and death appeared to be partially mediated by left ventricular mass [1]. In contrast, Di Tullio et al [3] reported that left atrial enlargement was associated with an increased risk of ischemic stroke in an ethnically mixed population, even after adjustment for other risk factors, including left ventricular hypertrophy. Left atrial size is also the principal independent predictor of prognosis in patients with dilated cardiomyopathy, where those with left atrial dilatation have an increase in mortality and a worse clinical outcome [4]. Finally, left atrial enlargement (≥ 4.8 cm) is an independent risk factor for the development of left atrial thrombi in patients with mitral stenosis [5], increasing the potential for stroke and thromboembolism.

With the potential mortality and morbidity associated with left atrial enlargement, its quantification is therefore important. Various methods such as electrocardiography (ECG), echocardiography (both transthoracic and transoesophageal), chest x-ray, cardiac angiography and magnetic resonance imaging of the heart have been used to assess left atrial size. However, the ECG is not as reliable as echocardiography, with no consistent agreement between the ECG diagnosis of left atrial enlargement and the left atrial cavity size as measured by echocardiography [6]. On the chest x-ray, the left atrium is larger than 5.0 cm in diameter if the carinal angle was 100 degrees or greater [7]. Whether left atrial diameter by echocardiography corresponds well with left atrial volume is slightly controversial.

In any case, left atrial volume is not significantly different to left atrial diameter in predicting the recurrence of atrial fibrillation following successful electrical cardioversion to sinus rhythm [8]. The echocardiographic determination of left atrial size both by M-mode and two-dimensional methods have demonstrated a good correlation with cine-angiographic measurements [9].

What could account for the increased morbidity and mortality that is associated with left atrial size? Whilst left atrial dilatation may be a normal development in healthy elderly subjects, an enlarged left atrium plays a significant role in the pathophysiology of atrial arrhythmias, leading to an increase of the latter with age [10]. This observation should be with the caveat that atrial fibrillation, the commonest sustained cardiac arrhythmia, can itself lead to progressive left atrial enlargement [11], which may be independent of changes in left ventricular size or function [12]. Importantly, the presence of atrial fibrillation has been independently associated with an increased mortality, with an odds ratio for death of 1.5 for men and 1.9 in women, which did not vary by age; importantly, most of the excess of mortality attributed to atrial fibrillation occurred soon after diagnosis of atrial fibrillation and there was a significant interaction between atrial fibrillation and sex with respect to mortality [13].

Another factor contributing to the increased risk of stroke with an enlarged left atrium is a prothrombotic state, which has been shown to exist in atrial fibrillation [14], and a correlation between endothelial damage/dysfunction, coagulation factors and left atrial dimension has been demonstrated [15]. Furthermore, atrial endocardial damage is more prominent in mitral stenosis (compared to mitral regurgitation), increasing the likelihood of thrombogenesis [16]. Finally, isolated left atrial enlargement could cause enlargement of the mitral annulus and cause mitral regurgitation [17]. In patients with pure aortic stenosis, echocardiographic evidence of left atrial enlargement, as measured by an increased left atrial dimension corrected for body surface area, appears to reflect a narrower aortic valve orifice, greater left ventricular chamber dimension and greater left ventricular hypertrophy (LVH), thus reflecting more severe aortic stenosis [18]. Occasionally, chronic left atrial enlargement could result in direct pressure over the surrounding

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mediastinal structures and rarely, lead to fatal aorto-atrial, and oesophago-atrial fistula [19].

There may also be an interaction between left atrial pathophysiology and arterial hypertension, one of the commonest risk factors for cardiovascular disease and stroke? Conflicting data exist regarding the influence of blood pressure on left atrial size. The Framingham study [20] demonstrated that increased levels of systolic and pulse pressures (but not diastolic or mean arterial pressures) were significantly associated with an increased left atrial size. However, the inclusion of left ventricular mass in these multivariable models eliminated or attenuated the associations of the various blood pressure variables with left atrial size. Thus, the effect of blood pressure on left atrial dimension could be at least partly mediated by left ventricular hypertrophy secondary to hypertension. Interestingly, left atrial size is more closely related to ambulatory, rather than office, blood pressure measurements, and a high mean night time blood pressure is a powerful marker of left atrial enlargement in arterial hypertension [21].

Whether left atrial enlargement in hypertension is a direct result of hypertension or a result of underlying left ventricular hypertrophy and subsequent diastolic dysfunction is not entirely clear. The left atrial dimension, left atrial index and the left atrial-to-aortic root dimension ratio are significantly higher in hypertensive patients when compared to normotensives [22]. The left atrial area also appears to correlate well with the left ventricular wall thickness and diastolic dysfunction [23]. During diastole, except for the period of isovolumic relaxation, the left atrium is exposed directly to left ventricular pressures through the open mitral valve. Due to the increased left ventricular stiffness in patients with hypertensive heart disease, left ventricular diastolic filling is impaired, resulting in the impairment of blood flow from left atrium to left ventricle [24]. Because the left atrium is a thin-walled structure, its size would therefore increase with the increase in left atrial pressure. Thus left atrial enlargement is probably the result of the chronicity of a high left atrial pressure, and echocardiographic left atrial enlargement has been considered to be an early sign of hypertensive heart disease [22]; this is supported by the presence of left atrial enlargement on the ECG and/or echocardiography, even before the development of overt hypertensive left ventricular hypertrophy [25]. A dilated left atrium, with its reduced 'atrial transport' function, may predispose patients with hypertension to intra-atrial stasis, increased intravascular thrombogenesis and also provide an additional mechanism for developing atrial fibrillation. Thus, the relationship between hypertension, impaired left atrial function, intra-atrial stasis and thrombogenesis may partly explain the enhanced risk of stroke and thromboembolism in hypertension.

Whether correction of hypertension results in a convincing reduction in left atrial size, and whether it matters clinically, still remains to be convincingly proven. It is possible that antihypertensive drugs differ in their effects on left atrial size. For example, in a comparison of six antihypertensive agents as monotherapy in relation to the reduction of left atrial size in mild to moderate hypertension, hydrochlorothiazide was associated with the greatest overall reduction of left atrial size; the observed reduction of left atrial size with therapy was independent of factors known to influence left atrial size, including left ventricular mass and the reduction of left ventricular mass with treatment [26]. Dernellis et al [27] reported that left atrial reservoir function increases and left atrial ejection force increases as antihypertensive treatment with enalapril and/or thiazide induces normalisation of the left atrial function in parallel to regression of hypertensive left ventricular hypertrophy. It is possible that it is not only the lowering of blood pressure, which determines the degree of LVH regression, but also the interaction of drugs with neuro-endocrine mechanisms such as the renin-angiotensin-aldosterone system and the sympathetic nervous system.

Acute increases in left atrial pressure are not usually associated with left atrial enlargement beyond the upper limit of the normal range [18]. In contrast, there is reduced elastic recoil after chronic atrial distension, resulting in only limited change in size with any changes in left atrial pressure. Furthermore, left atrial enlargement is frequently seen in a number of other conditions. For example, in patients with ischaemic heart disease, the combination of left ventricular enlargement and high left ventricular end diastolic pressures can be related to a decrease in left atrial function [28]. Left atrial enlargement is also observed in the normotensive, otherwise healthy, obese subject and reflects a physiological adaptation of the heart to the obese state [29]. Obesity is also one of the strongest predictor of left atrial size in patients with hypertension and amplifies the relation between left atrial size and left ventricular mass [30]. The relation of left atrial size to atrial fibrillation has been described earlier.

One recent study is worth debating further, as it typifies some of the problems in studying left atrial size in hypertension. Tedesco et al [31] reported a cross-sectional echocardiographic and ambulatory blood pressure study of 164 hypertensives, reiterating previous observations that age and left ventricular mass index are independent predictors of left atrial size. In light of the adverse associations with enlarged left atrial size, the presence of left atrial enlargement in hypertension may contribute to the mortality and morbidity associated with untreated hypertension. Nevertheless the study by Tedesco et al [31] carries a few caveats. As mentioned earlier, whether a single

measurement of left atrial dimension adequately represents left ventricular volume is debatable. Even though left atrial enlargement was significantly greater among patients with LVH in the study by Tedesco et al [31], this group was significantly older compared to the group without LVH. As the authors admit, relationship between the left ventricular diastolic dysfunction and left atrial dimensions was also not studied. Contrary to previous observations, obesity failed to show up as an independent determinant of left atrial dimension, which may be due to the low prevalence of obesity in the study sample. The most significant limitation is that a significant proportion of patients in the study by Tedesco et al [31] had some form of previous antihypertensive treatment either continuously or discontinuously. Whilst there was a discontinuation period of 3 weeks, this is probably not long enough to completely eliminate the influence of prior treatment. These data are complemented by a recent study by Daniels et al [32] who performed echocardiography in 112 children with hypertension, and found that left atrial enlargement was also prevalent in children and adolescents with essential hypertension.

Furthermore, the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) Study of 941 hypertensive patients, age 55 to 80 (mean, 66) years, with electrocardiographic LVH at baseline recently reported that an enlarged left atrial diameter (women, >3.8 cm; men, >4.2 cm) was present in 56% of women and 38% of men ($p < 0.01$) [33]. Such patients had more mitral regurgitation, atrial

fibrillation, and echocardiographic LVH, when compared to those with normal left atrial size. In a logistic regression analysis, left atrial enlargement was related to gender, age, obesity, systolic blood pressure, and left ventricular geometry, independently of left ventricular mass and presence of mitral regurgitation or atrial fibrillation.

Unsurprisingly, the increased left atrial pump function represents a compensatory mechanism in hypertensive patients with LVH. For example, Erol et al [34] – who also found that chronic hypertension (in adults) was associated with an increased in left atrial volumes – also reported a decrease in left atrial passive emptying function, and an increase systolic pump function in such patients.

In conclusion, left atrial size, which is independently associated with a number of modifiable factors contributing to mortality and morbidity, perhaps symbolises the many problem(s) associated with hypertension. Whether the reduction in left ventricular hypertrophy and left atrial size in hypertension confers long term mortality and morbidity benefits needs to be studied in greater detail.

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