Left atrium: no longer neglected

Andrea Rossi, Corrado Vassanelli

Section of Cardiology, Department of Biomedical and Surgical Sciences, University of Verona, Verona, Italy

Key words:
Diastolic function;
Left atrium;
Mitral regurgitation.

Left atrial evaluation is strongly linked to the history of cardiac imaging. In the past, the importance of this chamber has been largely downplayed because cineangiography could not visualize it directly. Nowadays echocardiography can easily assess left and right atrial size and function.

Left atrial enlargement is frequent in many cardiac diseases. A main determinant of left atrial volume is ventricular diastolic function. It has recently been suggested that left atrial volume might be the morphophysiologic expression of chronic diastolic function. In fact the left atrium is exposed directly to left ventricular diastolic pressure through the open mitral valve and because of its thin wall structure it tends to dilate with increasing pressure. Other important determinants of atrial volume are the degree of ventricular remodeling, mitral regurgitation and the presence of atrial fibrillation. The degree of left atrial enlargement is associated with adverse prognosis in different clinical settings. Patients with dilated cardiomyopathy and with a left atrial volume > 68 ml/m^2 have a 3.8-fold risk compared with those with smaller left atrial volume. The predictive value of left atrial volume is independent of left ventricular systolic and diastolic function, mitral regurgitation and atrial fibrillation. This is noteworthy because these factors are both determinant of left atrial volume and have a strong impact on outcome. It might be concluded that left atrial volume represents a powerful predictive marker because it is a window allowing comprehensive evaluation of several factors associated with bad prognosis, which are often difficult to document separately.

(Ital Heart J 2005; 6 (11): 881-885)

© 2005 CEPI Srl

Received April 13, 2005; revision received May 23, 2005; accepted May 24, 2005.

Address:

Dr. Andrea Rossi

Divisione di Cardiologia
Ospedale Maggiore
Piazzale Stefani, 1
37126 Verona
E-mail:
andrea.rossi@univr.it

The left atrium is a muscular contractile chamber located in the inflow path to the ventricle. These chambers are closely related, both anatomically and functionally. The left atrium is fundamental to ventricular filling through its reservoir, conduit and booster pump functions[1], whereas the left ventricle essentially contributes to atrial filling because during systole, ventricular longitudinal fiber shortening forces the descent of the cardiac base, contributing to atrial filling from the pulmonary veins[2,3].

Evaluation of the left atrium is closely linked to the history of cardiac imaging. In the past, the advent of cineangiography allowed direct and sharp visualization of the left ventricle. This resulted in a marked improvement in the understanding of ventricular function. In contrast, the left atrium could not be visualized in the absence of mitral regurgitation, hence its size could not be assessed at cardiac catheterization. This is one of the reasons why the role of the left atrium was largely downplayed in the past and why information which could have been drawn from it was largely hidden.

Nowadays the left atrium is well defined by echocardiography. In previous years the parameter used worldwide to assess atrial size was the anteroposterior diameter of the atrial chamber. But it has only recently become clear that the best way to describe the degree of atrial enlargement is the measurement of volume rather than diameter[4].

Why does the left atrium enlarge?

The left atrium is frequently enlarged in patients with arterial hypertension. This is partly related to the well-known relation between left ventricular hypertrophy and left atrial size. It has been shown that left atrial size has a positive relation with both active (time constant of relaxation)[5] and passive parameters (stiffness constant) of left ventricular diastolic function[6]. However, it is likely that the alteration of passive characteristics is more closely related to atrial deformation. During diastole, except for the period encompassing isovolumic relaxation, the left atrium is exposed directly to left ventricular diastolic pressure through the open mitral valve. Because of its thin-walled structure, the left atrium tends to dilate with increasing pressure. Unlike the left ventricle, in which volume and pressure do not change in the same di-

rection, the relationship between left atrial volume and pressure is quite predictable[7]. Recently, the left atrium has been proposed as a marker of chronic diastolic dysfunction, and Tsang et al.[8] suggest that left atrial size provides information complementary to left ventricular diastolic parameters. Although the ability of the left atrium to integrate the effect of atrial pressure over time is likely but unproven, the idea of using left atrial volume as a marker potentially capable of recording the history of left ventricular filling over a longer time interval is quite appealing. The pathophysiologic reasons for this capacity are to be sought in the relatively lower load dependency of atrial volume compared with other diastolic markers. A chronically enlarged atrium is characterized by an increased amount of fibrosis, which leads to little elastic recoil in response to a fall in pressure[9,10].

A canine model of heart failure due to left ventricular dysfunction showed a progressive increase in left atrial chamber dimensions, with a marked increase in the *post-mortem* weights of both atria[11]. The atrial myocytes and the collagen matrix are both involved in these progressive remodeling changes. Atrial myocyte hypertrophy contributes to the increased chamber weight. Mechanical stretch with the stretch-activated pathways, growth factors and cytokines such as angiotensin II, endothelin-1, insulin-like growth factor-1, interleukin-6 and gp130[12] might contribute to atrial myocyte hypertrophy through mechanisms similar to those seen in the ventricle.

Changes in the extracellular matrix also contribute to remodeling of the atrial chamber.

Collagen turnover and alterations in collagen organization strongly correlate with left atrial wall tension, suggesting a role for hemodynamic load in determining extracellular matrix changes[11]. However, there are evidences that hormonal activation also plays a fundamental role in the alterations of this compartment. First, extracellular matrix changes might be mediated by angiotensin II, which is increased in the atrial chamber[13]. Infusion of angiotensin II causes marked fibrosis of the atrial wall tissue[14]. In humans, a strong association between collagen I mRNA and angiotensin-converting enzyme mRNA has been found[15]. Moreover, treatment with the angiotensin-converting enzyme inhibitor enalapril significantly reduced atrial angiotensin II levels and fibrosis.

Although many histopathologic similarities between atrial and ventricular remodeling have been observed, there are also some discrepancies. A canine model of heart failure demonstrated that congestive heart failure was associated with substantially more fibrosis in the left atrium (10 ± 1%) than in the left ventricle (0.4 ± 0.1%), and that tissue angiotensin II concentration was higher and the *plateau* was reached faster in the atrium than in the ventricle[16].

Another condition which triggers left atrial dilation is mitral insufficiency. The relationship between the degree of mitral regurgitation and left atrial volume is predictable[17]. Atrial enlargement is considered a consequence of this regurgitation and can be used to define the severity of the disease. Consequently, mitral regurgitation and left ventricular diastolic dysfunction have the same effect of dilating the atrial chamber, but through different mechanisms. In the early stages of an experimental model of mitral regurgitation, a parallel increase in left atrial pressure and volume was observed[18]. However, the later stages of the disease were characterized by a progressive decrease in pressure and a further increase in atrial volume. Consequently it was shown that chronic mitral regurgitation is characterized by a decrease in left atrial chamber stiffness. The histological analysis of left atrial myocardium showed a substantially increased diameter of atrial myocardial fibers but no significant changes in the percentage of fibrosis. This corroborates clinical observations that even severe mitral regurgitation can be associated with an enlarged left atrium with the pressure level within the normal range[19]. Interestingly, it has been suggested that atrial size might reflect hemodynamic overload in specific phases during the course of chronic heart disease, such as during exercise, giving evidence of transient hemodynamic impairment which otherwise would remain silent. Among patients with mitral valve prolapse and no mitral regurgitation at rest, a certain percentage develop regurgitation during effort. Left atrial volume at rest was significantly greater in subjects with exercise-induced mitral regurgitation than in those without[20].

There is an intriguing relation between atrial volume and atrial fibrillation. Perhaps as a result of its common association with rheumatic mitral valve disease, atrial fibrillation is generally considered to be secondary to atrial enlargement. Actually, in other cardiac disorders such as hypertrophic cardiomyopathy[21] and mitral regurgitation[22], left atrial size was the most powerful predictor of subsequent episodes of atrial fibrillation. In the general population, after adjusting for age, sex, valvular heart disease, and hypertension, a 30% increase in left atrial volume was associated with a 43% greater risk of atrial fibrillation, incremental to a history of congestive heart failure, myocardial infarction and diabetes[23]. However, there are reasons to believe that atrial enlargement might be secondary to structural changes in the atrial wall due to atrial fibrillation. In patients with chronic lone atrial fibrillation, abnormal atrial histology was uniformly found in multiple biopsy specimens. It was compatible with a diagnosis of myocarditis in 66% of patients and of non-inflammatory localized cardiomyopathy in 17%, and was represented by patchy fibrosis in 17%[24]. Furthermore, in an experimental model of sustained atrial fibrillation profound structural changes were found in the atrial myocytes, similar to those seen in ventricular myocytes from chronic hibernating myocardium[25]. These structural changes can lead to atrial enlargement. Sanfilippo et

al.[26] studied a group of patients with atrial fibrillation and no cardiac abnormalities, and particularly with normal atrial volume at baseline. After a mean interval of 20 months, atrial volume had increased to some extent in all patients and the mean left atrial volume for the group had increased from 45 to 64 ml. The symmetrical increase observed in left and right atrial volumes further supports the hypothesis that arrhythmia is the primary factor in the genesis of atrial enlargement.

After acute myocardial infarction, an enlargement of the left atrium is frequently observed. It has recently been demonstrated that after 6 months from the acute event, the main determinant of atrial area change is the degree of left ventricular remodeling[27]. In patients with dilated cardiomyopathy of ischemic and non-ischemic etiology, left atrial enlargement is also common[28]. Besides ventricular remodeling, this condition frequently involves other determinants of atrial enlargement: diastolic dysfunction, mitral regurgitation and atrial fibrillation. In an echocardiographic study of more than 300 patients with dilated cardiomyopathy the determinants of left atrial volume were ventricular volume, diastolic dysfunction, age, atrial fibrillation and the degree of mitral regurgitation. Nevertheless, the most powerful multivariate model showed that the combination of these variables was able to predict only 54% of the variability of left atrial volume. This suggests that, at least in this condition, there might be other determinants of left atrial volume which could not be quantitated. It is possible that in patients with dilated cardiomyopathy, atrial enlargement could also be due to concomitant atrial myopathic disease[29], caused by a more widespread primary pathologic process. Interestingly, left atrial enlargement might also be caused by a reduction of left atrial efficiency due to loss of atrioventricular synchrony. After VVI pacing for 3 months there was a significant increase of left atrial size, which can be reversed reprogramming DDD pacing[30].

Clinical importance of left atrial size

It is well known that left atrial enlargement represents a serious risk in the general population. In a population-based cohort from Framingham, left atrial size was significantly associated with age-adjusted risk for stroke and for death in both sexes. After adjustment for age, hypertension, diabetes, smoking, left ventricular hypertrophy, atrial fibrillation, and congestive heart failure or myocardial infarction, left atrial size remained a significant predictor of stroke in men (relative risk 2.4 per 10-mm increment) and death in both sexes (relative risk 1.3 in men and 1.4 in women)[31].

In randomly selected residents of Olmsted County, it was confirmed that left atrial volume was independently predictive of first ischemic stroke, incremental to age, diabetes, myocardial infarction, and hyperlipidemia, even in patients with no prior atrial fibrillation. Furthermore, a left atrial volume of ≥ 32 ml/m^2 was associated with an increased mortality risk (hazard ratio 1.30, confidence interval 1.09-1.56), independent of age, sex, and stroke status[32].

The clinical importance of left atrial enlargement has also been shown in many cardiac disorders.

In presence of atrial fibrillation without mitral stenosis or mitral valve prosthesis the risk of systemic embolization is notable and is predicted by left atrial size independently of gender and underlying heart disease[33].

In patients with organic mitral regurgitation, left atrial size is one of the most important determinants of outcome. Left atrial diameter is a powerful predictor of heart failure in patients with mitral regurgitation due to flail leaflet[34]. After mitral valve surgery, left atrial size was the only predictor of outcome in the subgroup of patients with severe mitral regurgitation and left ventricular ejection fraction > 75%[35]. Similarly, in patients with aortic stenosis, smaller left atrial size before surgery was associated with symptomatic improvement after valve surgery independently of left ventricular systolic function, mass or the degree of valvular obstruction and preoperative symptoms[36].

Restrictive cardiomyopathy is typically characterized by ventricular diastolic dysfunction and atrial enlargement. In this disease, left atrial size is a major marker of prognosis. In particular, a left atrial diameter > 60 mm was associated with death (hazard ratio 2.3) independently of age, gender and NYHA class[37].

Increased left atrial volume is a powerful predictor of mortality after acute myocardial infarction and provides prognostic information incremental to clinical data and conventional measures of left ventricular systolic and diastolic function. In particular, left atrial volume normalized for body surface area predicted mortality with an hazard ratio of 1.05 per 1 ml/m^2 change (95% confidence interval 1.03-1.06) after adjustment for clinical factors and left ventricular function[38].

In the SOLVD registry and trial population of patients with dilated cardiomyopathy, left atrial diameter was a marker of prognosis with a risk ratio of 1.84 (95% confidence interval 1.08-3.15) independently of left ventricular ejection fraction, left ventricular mass, NYHA class and age[39]. However, patients with dilated cardiomyopathy frequently have complications which might potentially explain both left atrial dilation and adverse outcomes such as atrial fibrillation, mitral regurgitation or diastolic dysfunction of the left ventricle. In a study[28] of more than 300 patients with dilated cardiomyopathy, left atrial volume was found to be a powerful marker of prognosis with a hazard ratio of 1.02 per 1 ml/m^2 change (95% confidence interval 1.015-1.026). This result was maintained after adjustment for atrial fibrillation, mitral regurgitation and the presence of restrictive mitral filling. The prognostic power of left atrial volume was confirmed in the subgroups of patients with and without atrial fibrillation, mitral regur-

gitation and restrictive mitral filling. Among the subgroup of patients with particularly severe left ventricular dysfunction (ejection fraction < 30%), 90% of patients with left atrial volumes < 68.5 ml/m^2 survived after 150 months, as against only 44% of patients with larger left atrial volumes.

Left atrial volume has been shown to correlate with brain natriuretic peptide levels[40]. Brain natriuretic peptide increases with the severity of heart failure and has been demonstrated to be a powerful marker of prognosis in patients with left ventricular dysfunction[41]. However, left atrial size predicts prognosis independently of brain natriuretic peptide[42]. Similarly, recent literature showed that left atrial volume had prognostic value independent and incremental to maximal oxygen consumption[43].

Conclusion

The left atrium plays a fundamental role in cardiovascular pathophysiology through a complex relationship with the ventricular chamber. Left atrial enlargement is mainly related to diastolic impairment of the left ventricle, but mitral regurgitation or atrial fibrillation also has a role in determining the degree of atrial dilation. Recent studies emphasize that left atrial size is a powerful marker of prognosis in different cardiac diseases and in the general population. Consequently, left atrial area and volume should be included in the echocardiographic assessment of cardiac function in different cardiac diseases.

References

1. Rossi A, Zardini P, Marino P. Modulation of left atrial function by ventricular filling impairment. Heart Fail Rev 2000; 5: 325-31.
2. Barbier P, Solomon SB, Schiller NB, Glantz SA. Left atrial relaxation and left ventricular systolic function determine left atrial reservoir function. Circulation 1999; 100: 427-36.
3. Barbier P, Solomon S, Schiller NB, Glantz SA. Determinants of forward pulmonary vein flow: an open pericardium pig model. J Am Coll Cardiol 2000; 35: 1947-59.
4. Lester SJ, Ryan EW, Schiller NB, Foster E. Best method in clinical practice and in research studies to determine left atrial size. Am J Cardiol 1999; 84: 829-32.
5. Matsuda M, Matsuda Y. Mechanism of left atrial enlargement related to ventricular diastolic impairment in hypertension. Clin Cardiol 1996; 19: 954-9.
6. Briguori C, Betocchi S, Losi MA, et al. Noninvasive evaluation of left ventricular diastolic function in hypertrophic cardiomyopathy. Am J Cardiol 1998; 81: 180-7.
7. Appleton CP, Galloway JM, Gonzales MS, Gaballa M, Basnight MA. Estimation of left ventricular filling pressure using two-dimensional and Doppler echocardiography in adult patients with cardiac disease. Additional value of analyzing left atrial size, left atrial ejection fraction and the difference in duration of pulmonary venous and mitral flow velocity at atrial contraction. J Am Coll Cardiol 1993; 22: 1972-82.
8. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. Am J Cardiol 2002; 90: 1284-9.
9. Hoit BD, Shao Y, Liang-Miin T, Patel R, Gabel M, Walsh RA. Altered left atrial compliance after atrial appendectomy: influence of atrial and ventricular filling. Circ Res 1993; 72: 167-75.
10. Pepi M, Marenzi GC, Agostoni PG, et al. Sustained cardiac diastolic changes elicited by ultrafiltration in patients with moderate congestive heart failure: pathophysiological correlates. Br Heart J 1993; 70: 135-40.
11. Khan A, Moe WG, Nili N, et al. The cardiac atria are chambers of active remodeling and dynamic collagen turnover during evolving heart failure. J Am Coll Cardiol 2004; 43: 68-76.
12. Hirota H, Chen J, Betz UA, et al. Loss of a gp130 cardiac muscle cell survival pathway is a critical event in the onset of heart failure during biomechanical stress. Cell 1999; 97: 189-98.
13. Li D, Shinagawa K, Pang L, et al. Effects of angiotensin-converting enzyme inhibition on the development of the atrial fibrillation substrate in dogs with ventricular tachypacing-induced congestive heart failure. Circulation 2001; 104: 2608-14.
14. Sun Y, Ramires FJ, Weber KT. Fibrosis of atria and great vessels in response to angiotensin II or aldosterone infusion. Cardiovasc Res 1997; 35: 138-47.
15. Ohmichi N, Iwai N, Shimoike H, et al. Assessment of the angiotensin II-forming pathway in human atria. Heart Vessels 1997; 12 (Suppl): 116-29.
16. Hanna N, Cardin S, Leung TK, Nattel S. Differences in atrial versus ventricular remodeling in dogs with ventricular tachypacing-induced congestive heart failure. Cardiovasc Res 2004; 63: 236-44.
17. Rossi A, Golia G, Gasparini G, Prioli MA, Anselmi M, Zardini P. Left atrial filling volume can be used to reliably estimate the regurgitant volume in mitral regurgitation. J Am Coll Cardiol 1999; 33: 212-7.
18. Kihara Y, Sasayama S, Miyazaki S, et al. Role of the left atrium in adaptation of the heart to chronic mitral regurgitation in conscious dogs. Cir Res 1988; 62: 543-53.
19. Braunwald E, Awe WC. The syndrome of severe mitral regurgitation with normal left atrial pressure. Circulation 1963; 27: 29-35.
20. Stoddart MF, Prince CR, Dillon S, Longaker RA, Morris GT, Liddell NE. Exercise-induced mitral regurgitation is a predictor of morbid events in subjects with mitral valve prolapse. J Am Coll Cardiol 1995; 25: 693-9.
21. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. Circulation 2001; 104: 2517-24.
22. Kernis SJ, Nkomo VT, Messika-Zeitoun D, et al. Atrial fibrillation after surgical correction of mitral regurgitation in sinus rhythm: incidence, outcome, and determinants. Circulation 2004; 110: 2320-5.
23. Tsang TS, Barnes ME, Bailey KR, et al. Left atrial volume: important risk marker of incident atrial fibrillation in 1655 older men and women. Mayo Clin Proc 2001; 76: 467-75.
24. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. Circulation 1997; 96: 1180-4.
25. Ausma J, Wijffels M, Thone F, Wouters L, Allessie M, Borgers M. Structural changes of atrial myocardium due to sustained atrial fibrillation in the goat. Circulation 1997; 96: 3157-63.

26. Sanfilippo AJ, Abascal VM, Sheehan M, et al. Atrial enlargement as a consequence of atrial fibrillation. A prospective echocardiographic study. Circulation 1990; 82: 792-7.
27. Popescu BA, Macor F, Antonini-Canterin F, et al, for the GISSI-3 Echo Substudy Investigators. Left atrium remodeling after acute myocardial infarction (results of the GISSI-3 Echo Substudy). Am J Cardiol 2004; 93: 1156-9.
28. Rossi A, Cicoira M, Zanolla L, et al. Determinants and prognostic value of left atrial volume in patients with dilated cardiomyopathy. J Am Coll Cardiol 2002; 40: 1425-30.
29. Triposkiadis F, Pitsavos C, Boudoulas H, Trikas A, Toutouzas P. Left atrial myopathy in idiopathic dilated cardiomyopathy. Am Heart J 1994; 128: 308-15.
30. Sparks PB, Mond HG, Vohra JK, Yapanis AG, Grigg LE, Kalman JM. Mechanical remodeling of the left atrium after loss of atrioventricular synchrony. A long-term study in humans. Circulation 1999; 100: 1714-21.
31. Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death. The Framingham Heart Study. Circulation 1995; 92: 835-41.
32. Barnes ME, Miyasaka Y, Seward JB, et al. Left atrial volume in the prediction of first ischemic stroke in an elderly cohort without atrial fibrillation. Mayo Clin Proc 2004; 79: 1008-14.
33. Cabin HS, Clubb KS, Hall C, Perlmutter RA, Feinstein AR. Risk for systemic embolization of atrial fibrillation without mitral stenosis. Am J Cardiol 1990; 65: 1112-6.
34. Ling LH, Enriquez-Sarano M, Seward JB, et al. Clinical outcome of mitral regurgitation due to flail leaflets. N Engl J Med 1996; 335: 1417-23.
35. Reed D, Abbott RD, Smucker ML, Kaul S. Prediction of outcome after mitral valve replacement in patients with symptomatic chronic mitral regurgitation. The importance of left atrial size. Circulation 1991; 84: 23-34.
36. Rossi A, Tomaino M, Golia G, et al. Usefulness of left atrial size in predicting postoperative symptomatic improvement in patients with aortic stenosis. Am J Cardiol 2000; 86: 567-70.
37. Ammash NM, Seward JB, Bailey KR, Edwards WD, Tajik AJ. Clinical profile and outcome of idiopathic restrictive cardiomyopathy. Circulation 2000; 101: 2490-6.
38. Moller JE, Hillis GS, Oh JK, et al. Left atrial volume: a powerful predictor of survival after acute myocardial infarction. Circulation 2003; 107: 2207-12.
39. Quinones MA, Greenberg BH, Kopelen HA, et al, for the SOLVD Investigators. Echocardiographic predictors of clinical outcome in patients with left ventricular dysfunction enrolled in the SOLVD registry and trials: significance of left ventricular hypertrophy. J Am Coll Cardiol 2000; 35: 1237-44.
40. Rossi A, Enriquez-Sarano M, Burnett JC Jr, Lerman A, Abel MD, Seward JB. Natriuretic peptide levels in atrial fibrillation: a prospective hormonal and Doppler-echocardiographic study. J Am Coll Cardiol 2000; 35: 1256-62.
41. Hall C, Rouleau JL, Moye L, et al. N-terminal proatrial natriuretic factor: an independent predictor of long-term prognosis after myocardial infarction. Circulation 1994; 89: 1934-42.
42. de Groote P, Dagorn J, Soudan B, Lamblin N, McFadden E, Bauters C. B-type natriuretic peptide and peak exercise oxygen consumption provide independent information for risk stratification in patients with stable congestive heart failure. J Am Coll Cardiol 2004; 43: 1584-9.
43. Rossi A, Cicoira M, Terraneo C, et al. Il volume atriale sinistro è un importante predittore prognostico in pazienti con cardiomiopatia dilatativa indipendentemente da parametri di tolleranza allo sforzo. (abstr) Ital Heart J 2003; 4 (Suppl 6): 167S.