The Left Atrium: From the Research Laboratory to the Clinic

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Abstract

Studies of left atrial (LA) function, until the latter part of the 20th century, were mostly limited to experimental animal models and to studies related to clinical research in the cardiac catheterization laboratory. For this reason, LA function has received considerably less attention than left ventricular (LV) functions, even though evidence suggests that LA myopathy and failure may exist as an isolated entity, precede and/or coexist with LV myopathy. The introduction of echocardiography and Doppler echocardiography in clinical practice has contributed significantly to our understanding of LA function and its interrelationships with the LV, aorta, pulmonary artery and other parts of the cardiovascular system. In addition, LA with the secretion of atrial natriuretic peptides is playing an important role in cardiovascular and neurohumoral homeostasis. Today, it is well known that LA structural and functional abnormalities that are present in many diseases and disorders constitute a powerful prognostic indicator. As technology (echocardiography, magnetic resonance imaging, computed tomography and others) continues to evolve, it is expected that, in the near future, LA structure and function will be routinely used as LV function is used today.

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Introduction

Contraction of the atria has been known since the classic work of Sir William Harvey (1578–1657) on the motion of the heart:

‘And if at this time, the auricles alone pulsating, the point of the heart be cut off with a pair of scissors, you will perceive the blood flowing out upon each contraction of the auricles. Whence it is manifest that the blood enters the ventricles not by any attraction or dilatation of the heart, but by being thrown into them by the pulses of the auricles’ [1].

From then until the later part of the last century, studies of atrial function were limited to experimental animal models in research laboratories and to clinical research studies in cardiac catheterization facilities. Simultaneous recordings of left ventricular (LV) and left atrial (LA) pressure with or without cardiac output measurements provided important information and facilitated the understanding of the physiology and pathophysiology of LA function and its interrelationship with LV hemodynamics [2]. In earlier studies, prior to the introduction of echocardiography in clinical practice, LA size was estimated on fluoroscopy or on routine chest X-rays. P-waves on the electrocardiogram indicated that atrial electrical activity was present. Abnormal P-waves on the electrocardiogram in certain cases suggested LA enlargement and/or intra-

Fig. 1. Phases of LA mechanical function and corresponding LA volume changes. The LA maximal and minimal volumes coincide with the opening and closure of the mitral valve, respectively. The LA volume at onset of atrial systole coincides with the onset of the P-wave on the surface electrocardiogram (from Karayannis et al. [98]).

atrial conduction abnormalities. It was also possible to define atrial fibrillation or flutter, an indication of underlying atrial disease [3]. The introduction of echocardiography and Doppler echocardiography in clinical practice has contributed significantly to our understanding of the functioning of the LA and its interrelationships with the LV, aorta, pulmonary circulation and other parts of the cardiovascular system [4]. The importance of the LA for the regulation of the cardiovascular system and neurohumoral homeostasis and its role as a prognostic indicator in different diseases are well appreciated today.

Physiology and Pathophysiology

The Normal LA

Mechanical Function

The LA is composed of a venous component that consists of the proximal portion of the pulmonary veins, a tubular narrow and hooked appendage, and the vestibule

of the mitral valve together with the septum and the adjacent walls [5]. The LA appendage is derived from the left wall of the primary atrium and functions as a decompression chamber during LV systole and when LA pressure is high.

The LA consists of three phases: the reservoir phase, the passive emptying phase and the active emptying phase (fig. 1) [6].

Reservoir Phase. During LV systole, when the mitral valve ring moves towards the cardiac apex, the LA cavity increases, LA pressure falls and blood flows into the LA from the pulmonary veins [7, 8].

Passive Emptying and Conduit Flow. Early in LV diastole, blood that has been stored in the LA during LV systole (the reservoir phase) flows into the LV. The atrioventricular pressure gradient, partially due to LV relaxation, is the major determinant of blood flow during this phase. Direct flow from the pulmonary veins through the LA into the LV takes place at the same time (conduit volume).

Fig. 2. The LA pressure-volume relationship is composed of two loops: the A loop (expressing LA pump function) and the V loop (expressing LA reservoir function). During the LA filling period, the curve is directed upward and to the right. After reaching maximal pressure and volume of the filling period, it turns clockwise and downward, corresponding to passive LA emptying, and, subsequently, to active LA emptying [2].

Active Emptying (Pump Function). As the LA contracts, the LA pressure increases and an atrioventricular pressure gradient develops that facilitates blood flow from the LA to the LV. LA systolic function is governed by the same factors that govern LV systolic function, namely the diastolic myocardial fiber length (the Frank-Starling mechanism), afterload and myocardial contractility [8–12]. The autonomic nervous system exhibits a positive inotropic effect via the release of catecholamines; this activates the β_1 - and β_2 -adrenoreceptors and exerts a negative inotropic effect via the muscarinic receptors [12]. The renin-angiotensin system also plays an important role because angiotensin I and angiotensin II exert a positive inotropic effect mediated via the angiotensin 1 receptor [13].

Due to the presence of two emptying phases, the LA pressure-volume relationship is composed of two loops: the A loop that expresses LA active emptying (pump function) and the V loop that expresses passive LA emptying [2]. During the LA filling period, the curve is directed upward and to the right. When the maximal pressure and volume of the LA have been reached, the curve turns clockwise and downward, corresponding to passive LA emptying, and, subsequently, to the active LA emptying phase (fig. 2). In addition to its mechanical function, the LA has endocrine and regulatory functions.

Endocrine Function

The atria synthesize atrial natriuretic peptide (ANP), which is stored in specific intramyocyte granules as the prohormone. During release into the circulation, final

processing yields the biologically active C-terminal and N-terminal fragment ANP [14, 15]. Lesser quantities of ANP are also secreted directly from the ventricle. Brain natriuretic peptide (BNP), a ventricular hormone, is co-stored in small amounts with ANP in atrial granules. Both ANP and BNP exhibit a wide spectrum of effects protecting the cardiovascular system from volume and pressure overload and, with only a few exceptions, oppose the effects of the sympathetic nervous system and the renin-angiotensin-aldosterone axis [16, 17]. The most important factor governing ANP secretion is the mechanical stretching of the atria (see below: 'Neurohumoral Interrelationships' and fig. 9). In addition, two endothelium-derived paracrine factors, endothelin and nitric oxide, play an important role in modulating ANP secretion; endothelin stimulates this secretion while nitric oxide inhibits it [15].

Regulatory Function

Cardiopulmonary baroreceptors located in the atria and pulmonary veins contribute to the regulation of cardiac output since they regulate venous return, pulmonary arterial and venous pressure, and pulmonary capillary blood flow [18]. Atrial baroreceptors also contribute to the control of vasopressin, a vasoconstrictive hormone that acts on the kidneys and stimulates the conservation of solute-free water [19, 20]. Afferent nerve impulses from baroreceptors in the LA (inhibitory), aortic arch and carotid sinuses (excitatory) travel via the vagus nerve and also contribute to the regulation of systemic osmolality [21, 22].

Fig. 3. Mechanisms of atrial remodeling.

LA Remodeling

Aging, neurohumoral activation and chronic atrial stretch activate a variety of signaling pathways that lead to histological changes in the atria. These changes include myocyte hypertrophy, fibroblast proliferation and complex alterations of the extracellular matrix including fibrosis. All these histologic changes that may affect LA function (electrical, contractile) are defined as ‘atrial remodeling’ (fig. 3) [23, 24]. These alterations can also disrupt electrical interconnections between muscle bundles that may result in shortening of atrial refractoriness, reentrant wavelength and local conduction heterogeneities. Under these conditions, electrical ectopic activity originating from the pulmonary veins or other sites in the atria can trigger episodes of atrial fibrillation. Data suggest that differences may exist between LA and LV remodeling [25]. It appears that a more intense inflammatory infiltration, cellular apoptosis and fibrosis occur in the atria than in the ventricles. Cell apoptosis, mitogen-activated protein kinase and activation of TGF- β are also greater in the atria than in the ventricles.

LA Contribution to LV Filling

The relative contribution of LA function to LV filling depends on the diastolic functional properties of the LV and the functional capacity of the LA. Generally, the relative contribution of the reservoir, the passive emptying and conduit flow and the active emptying (pump function) of the LA to LV filling are approximately 40, 35 and 25%, respectively [26]. At the early stages of LV diastolic dysfunction, the relative contribution of the LA active emptying (pump function) increases while the passive emptying and conduit flow decrease [26, 27].

Evaluation of LA Structure and Function

Echocardiography

LA enlargement is a strong prognostic indicator for future cardiovascular events [4, 28–35]. Indeed, it is anticipated that early detection of LA dysfunction will provide insight into the pathophysiology and clinical management of several diseases in which LA dysfunction may be present. Although echocardiographic quantitation of LA size measurements tend to ‘underestimate’ when

Fig. 4. LA volume calculation using 2D echocardiography. **a** Biplane area-length method using the formula $V = 8(A1)(A2)/3\pi(L)$, where V is volume, A1 and A2 represent the LA planimetry in the apical 4-chamber (A4C) and 2-chamber (A2C) views, respectively, and L is the shortest length from the middle of the plane of the mitral annulus to the superior aspect of the LA. **b** Modified single-plane Simpson's rule, assuming the stacked disks are circular, using the formula $V = \pi/4(h)\Sigma(D)$, where V is volume, h is the height of the disks and D is the orthogonal axis of the disks.

compared with magnetic resonance imaging (MRI) or computed tomography techniques [36, 37], echocardiography remains the simplest, least invasive and most cost-effective method. Estimation of LA size and function can be obtained by 2-dimensional (2D) echocardiography [38]. The use of real-time 3-dimensional echocardiography (RT3DE), recently introduced as a new technique for the assessment of LA volume and LA ejection fraction, may provide additional information. Doppler analysis of the transmitral and pulmonary vein flow, tissue Doppler assessment of LA myocardial velocities and deformation indices also provide important information.

Conventional Echocardiography

The anteroposterior diameter (calculated by M-mode or 2D echocardiography), although the most widely used measurement of LA size in clinical practice, is no longer considered an adequate representation of the true LA dimension because it relies on several geometric assumptions and often results in an underestimation of LA size. On the other hand, echocardiographic measurements of LA volume using 2D echocardiography or RT3DE rely on fewer geometric assumptions than the anteroposterior diameter [39] and have been validated against cine-computed tomography, contrast ventriculography and MRI [37, 40, 41]. Thus, it is recommended that LA volume measurements be based either on an ellipsoid model or the Simpson's method in 4-chamber and 2-chamber api-

Table 1. How to overcome common pitfalls in order to accurately measure LA volume

Step	Suggestions
LA imaging quality	use high-resolution samples
Maximal LA volume	if the two length measurements from the orthogonal planes are >5 mm, then repeat measurements
Maximal LA volume	measure just before mitral valve opening
LA area planimetry	exclude atrial appendage and confluences of pulmonary veins
Long-axis LA length	measure from midpoint of mitral annulus plane to midpoint of posterior LA wall

cal views (fig. 4), even though LA border visualization is suboptimal in some cases. The size of the LA varies during the cardiac cycle, but only the maximum LA size and volume are routinely measured. Table 1 shows how to avoid pitfalls in order to accurately measure LA volumes during daily clinical practice [42].

3D Echocardiography

The use of RT3DE has been recently introduced as a new technique. RT3DE is a safe, noninvasive imaging modality that may prove to be a promising tool for assess-

ing atrial size. RT3DE collection of LA volumes is conducted in 4 cycles during a breath hold. Particular care is taken to ensure that the entire LA is included within a pyramidal 3D image. LA volume measurements by RT3DE are derived from semiautomated tracings of the LA endocardium, thus passive and active LA volumes can be calculated. LA enlargement occurs in 3D, but not uniformly: the medial-lateral LA expansion is less prominent than the longitudinal and anteroposterior expansion, so a one-dimensional assessment (M-mode) is likely to be an insensitive assessment of LA size. Interestingly, changes in LA volume during the cardiac cycle may not be observed directly on 2D echocardiography, because the shape of the LA changes during the cycle. On the other hand, LA volume measurements by RT3DE correlate closely with those obtained on multidetector computed tomography [43] and MRI [37, 44] as opposed to 2D echocardiography methods [45]. However, despite the good correlation between RT3DE and MRI measurements of LA volumes, echocardiography tends to underestimate LA volumes when compared to MRI [45, 46].

Doppler Image Deformation Indices

LA function can be assessed by pulsed-wave Doppler measurements from the mitral inflow pattern and from the pulmonary vein flow velocity pattern. Peak A-wave velocity from the mitral inflow velocity pattern is often considered a measure of LA function; however, it can be affected by age and loading conditions. Accordingly, an increase in the reversal of flow into the pulmonary veins (A-wave) suggests both elevated LV filling pressures along with augmented LA contraction. However, transthoracic echocardiography cannot detect all 4 pulmonary veins; only the velocity pattern of the right superior pulmonary vein flow can be recorded. LA function can also be expressed as the atrial systolic contribution to the total mitral inflow time velocity integral (TVI) = (mitral A-wave TVI)/(mitral E-wave TVI + mitral A-wave TVI).

Tissue Doppler imaging (TDI) allows the characterization of intrinsic myocardial wall velocities with a high sampling rate. There is an excellent correlation between mitral annulus A' and atrial function [47]. The TDI measurements should be obtained during end expiration with an average of three sinus beats, and the sample volume should be placed on the atrial side of the mitral annulus at the basal interatrial septum from the apical 4-chamber view. Indeed, it has been shown that TDI analysis prior to cardioversion can predict the recurrence of atrial fibrillation [48]. Color TDI has also been validated for the assessment of global and regional LA function [49]. However,

the effects of angle dependency remain a technical challenge when peak velocities are measured. Moreover, the overall cardiac motion and rotation and the contraction of adjacent myocardial segments can significantly affect the estimation of regional velocities.

Strain and strain-rate imaging provide data on myocardial deformation by estimating spatial gradients in myocardial velocities. Several studies have been performed using this imaging technique for the assessment of atrial function [50–52]. Compared to TDI, this technique is relatively unaffected by the motion of the heart and the contraction of adjacent segments. Images are obtained using a narrow sector because of the thin atrial wall. Images of the lateral and septal walls are obtained at a high frame rate (200 Hz) from the 4-chamber view. Anterior and inferior walls from the 2-chamber view can also be used. It is critical to align the atrial wall parallel to the Doppler beam so that signal noise and angle artifacts are avoided.

Deformation or strain measurement using TDI velocity is affected by adjacent structure and tethering of neighboring segments. 2D speckle-tracking strain imaging utilizes acoustic speckle tracking, so perfect alignment of the ultrasound beam is not necessary. This has been validated against sonomicrometry and tagged MRI [52]. Quantitative curves representing all segments are expressed for each 2D speckle-tracking strain imaging variable. The regional LA strain and strain-rate curves can be assessed at different points during the cardiac cycle allowing the relaxation and contractile functions of each LA segment to be analyzed in detail [50, 51]. Indices of active and passive LA function as assessed by strain are affected by age and loading conditions. Furthermore, the frame rates and the quality of the 2D images may influence the results [53].

Other Methods

Today, echocardiography is the most useful and practical method for the evaluation of atrial structure and function in research and daily clinical practice [4, 38, 45]. Other methods can be used, but their value (with the exception of MRI and computed tomography) is limited.

Physical Examination

Physical examination is not very useful in defining LA functional abnormalities. An S4 gallop suggests that LA mechanical function is present and that the LA is contracting against a high LV end-diastolic pressure [54].

Electrocardiogram

The presence of P-waves in the electrocardiogram suggests that atrial electrical activity is present. P-wave amplitude and duration in a standard 12-lead electrocardiogram provides indirect information related to intra- and interatrial conduction times, and may also point to LA enlargement. A high-resolution electrocardiogram of the P-wave duration and amplitude in the X, Y and Z planes provides more accurate information than a standard-lead electrocardiogram [3]. Electrophysiologic studies using intra-atrial recordings from multiple areas can precisely define atrial conduction times, sinus node function and atrioventricular node function. In addition, atrial arrhythmias can be induced by programmed electrical stimulation in patients prone to these arrhythmias.

Chest X-Ray and Fluoroscopy

The LA can be seen and its size can be estimated in anteroposterior and/or lateral views on a routine chest X-ray. Fluoroscopy with barium swallow was used extensively in the past, prior to the introduction of echocardiography in clinical practice for the evaluation of LA size, especially in patients with mitral valve disease. Today, however, its use for this purpose is very limited [54].

Computed Tomography and Cardiac MRI

Computed tomography and cardiac MRI provide excellent images of the atria with impressive anatomical detail [55, 56]. MRI with electrocardiographic gating is the most accurate method for the evaluation of LA volumes at different times during the cardiac cycle. MRI is superior to 2D echocardiography for the evaluation of LA volumes, although LA volumes obtained from RT3DE correlate well with those obtained from MRI; however, MRI is still considered the gold standard [46]. In addition to LA volume measurements, MRI can be used to define and quantitate myocardial fibrosis using delayed contrast enhancement techniques. The use of delayed contrast enhancement is based on the different kinetics of gadolinium in the fibrotic myocardium compared to the normal myocardium; myocardial fibrosis appears as a hyperintense area. It has been shown that a good correlation exists in the degree of fibrosis defined by histopathology with that detected by MRI. The degree of fibrosis as defined by MRI is a predictor of recurrence of atrial fibrillation after ablation [57–61].

Combined Methods

From simultaneous recordings of the electrocardiogram and the A-wave spectral Doppler, the LA preejec-

Table 2. Etiology of LA myopathy

Dilated cardiomyopathy
Heritable
Acquired
Lone atrial fibrillation
Metabolic-endocrinologic disorders and diseases
Hyperthyroidism
Diabetes mellitus
Obesity
Aging
Other

tion period (time from the beginning of the P-wave on electrocardiogram to the onset of the A-wave on Doppler) and the LA ejection time (onset of the A-wave on Doppler to the end of the A-wave) can be calculated. These indices are not used in clinical practice, but in certain research studies where atrial hemodynamics are utilized, they may be very useful [3].

Detection of LA fibrosis using cardiac MRI techniques is associated with reduced LA deformation during the reservoir phase of the cardiac cycle. Thus, it appears that tissue characterization by cardiac MRI and functional strain analysis will play a pivotal role in the overall assessment of atrial structure and function in the years to come [57].

Atrial Myopathy

Heritable Cardiomyopathies

Atrial myopathy can be defined as any structural or functional abnormality (mechanical-electrical) involving the atria. This definition also includes patients with lone atrial fibrillation. The causes of atrial myopathy are shown in tables 2 and 3. Cardiomyopathies that affect the ventricles may also affect the atria. Cardiomyopathies could be inherited or acquired. Atrial myopathy that precedes atrial fibrillation has been described in a heritable cardiac conduction and myocardial disease due to a lamin A/C mutation (The Ohio State University Family) [3]. The definition of atrial myopathy prior to the development of atrial fibrillation was based on analyses of atrial structure and function using electrical, anatomical and electromechanical criteria. In this study group, significant differences were found in P-wave amplitude and duration on standard and high-resolution electrocardiographic anal-

Table 3. LA myopathy: volume and pressure load

Volume load
Mitral regurgitation
Atrial septal defect
Other
Pressure load
Mitral stenosis
LV hypertrophy
Arterial hypertension
Stiff aorta
Aortic stenosis/regurgitation
Combine volume and pressure load
Hypertrophic cardiomyopathy
Other

yses that indicated reduced atrial electrocardiographic voltage and increased inter/intra-atrial conduction times. Echocardiographic and Doppler echocardiographic analyses showed significant increase in LA maximal volume and LA acceleration times. Simultaneous recordings of the electrocardiogram and Doppler echocardiogram showed a significant increase in the LA preejection period and an increase in the LA ejection time consistent with abnormal LA function. All these changes occurred prior to the onset of atrial fibrillation, which developed over a 10-year follow-up period. The presence of atrial myopathy was confirmed at autopsy in 1 patient; the atria were dilated and histopathology revealed hypertrophic and atrophic myocytes, striking nuclear changes with variability in size and irregular shapes, scattered myocytes with degeneration, and significant interstitial fibrosis. There was no evidence of inflammation or infiltration in the atrial or ventricular myocardium. Histologic changes were similar in the atrial and ventricular myocardium, but the changes were more severe in the atria.

Acquired Cardiomyopathies

There are several studies demonstrating atrial involvement in patients with acquired dilated cardiomyopathy. Previous studies from our laboratory in patients with aortic stenosis and dilated cardiomyopathy demonstrated that the LA volume was increased in both groups. However, the LA ejection fraction at any degree of LA size was less in patients with primary cardiomyopathy than in those with aortic stenosis. The data suggest a primary involvement of the LA myocardium in patients with cardiomyopathy in addition to that expected from LA dilatation [62–64]. LA

involvement in hypertrophic cardiomyopathy is also well documented. Hypertrophic cardiomyopathy, however, is often associated with mitral regurgitation, so LA involvement in this case may be more related to mitral valve disease rather than to primary myocardial involvement per se.

Lone Atrial Fibrillation

Several studies have challenged the lone atrial fibrillation hypothesis and suggest that atrial myopathy may be present in patients with this disorder [65, 66]. Atrial biopsies obtained from the right atrial septum in patients with lone atrial fibrillation demonstrated abnormal atrial histopathology. Inflammatory changes consistent with myocarditis and/or noninflammatory myopathy were found in the majority of these patients while biopsies from the biventricular myocardium were normal. In certain patients during follow-up, there was an isolated increase in LA size while LV size and function remained normal. The speculation was that atrial myocyte degeneration, necrosis and patchy fibrosis represent an organic substrate that may explain the electrophysiologic mechanisms responsible for lone atrial fibrillation. In other studies, in patients with paroxysmal lone atrial fibrillation, structural and functional abnormalities were present in the atria at times remote from the arrhythmia and while the patients were in sinus rhythm. It was also shown that the recurrence of atrial fibrillation after ablation was related to the degree of atrial fibrosis as defined by MRI. Recurrence of atrial fibrillation was higher in patients with extensive atrial fibrosis than in those with the mild form. It also appears that functional abnormalities of the atrial myocardium, as assessed by strain and strain rate, are directly related to atrial fibrosis. These functional and structural abnormalities in patients with atrial fibrillation are predictors of arrhythmia recurrence after ablation. Thus, noninvasive tissue characterization with cardiac MRI together with functional-strain analysis will help to better define the underlying myopathy in patients with lone atrial fibrillation [57–61, 65, 66]. A genetic predisposition may also be present in these patients [67, 68].

Metabolic/Endocrinologic Disorders and Diseases

For decades, it has been well known that an association exists between hyperthyroidism and atrial fibrillation. Furthermore, controlling thyroid function results in the restoration of sinus rhythm. The incidence of atrial fibril-

Fig. 5. Effects of aging on the cardiovascular system. The aorta becomes stiffer with age. A stiff aorta will result in a decrease in LV compliance and an increase in LA work. It will also result in an increase in reflected wave velocity and systolic hypertension, which may result in an increase in LV work and mass. Aging may also have direct detrimental effects on the entire cardiovascular system (modified from [71]).

lation is also higher in patients with diabetes mellitus and obesity; LA enlargement is usually present in these patients [69].

Stiff Aorta and Aging

Previous studies from our group demonstrated that aortic function and LA work, as defined by an increase in LA kinetic energy, were directly related to age whereas the parameters of LV size and function were unaffected [70–72]. It is also well documented from many studies that the aorta becomes stiffer with age. Stiffening of the aorta affects LV compliance and impairs early LV filling [70]. In cases of impaired LV filling, LA volume at the beginning of LA systole increases and LA active stroke volume increases. The effects of a stiff aorta on LV relaxation, LA volume and LA work may add to the direct effects of aging on the LV and LA (fig. 5) [71].

Valvular heart disease, especially mitral stenosis or mitral regurgitation, have direct effects on LA volume and pressure. Aortic stenosis or aortic regurgitation may affect the LA indirectly through their effects on LV structure and function [73, 74].

Atrioventricular-Aortic-Pulmonary-Valvular and Neurohumoral Interrelationships

Atrioventricular-Aortic-Pulmonary-Valvular Interrelationships

The LA is connected to the LV via the mitral valve and to the pulmonary circulation via the pulmonary veins (fig. 6); therefore, it is reasonable to expect that any change in ventricular structure and function will affect atrial structure and function, and that alterations in the volume, pressure and work of the LA will influence the pulmonary circulation. An increase in LV mass due to arterial hypertension or stiff aorta will impair LA emptying prior to LA systole, resulting in an increase in LA volume and work (fig. 7) [71, 72]; such changes are the result of chronic adaptation to LV structural and functional alterations.

Stiffening of the aorta has significant implications for the entire cardiovascular system. The ejection of blood in the aorta during LV systole generates a pressure wave that is perceived in the periphery as the arterial pulse. The aortic pulse wave velocity (PWV), defined as the speed in which the pulse wave travels in the aorta, is directly re-

Fig. 6. LA interrelationships. The LA is connected to the LV; mitral valve disease and factors that affect LV structure and function will also affect LA structure and function. The LA is connected via the pulmonary veins to the pulmonary circulation and may therefore affect pulmonary artery hemodynamics.

lated to the elastic properties of the aortic wall. A decrease in the elasticity of the aortic wall causes an increase in the PWV and an increase causes a decrease in the PWV. When the pulse wave reaches the periphery, it returns to the ascending aorta. Normally, the reflected waves reach the ascending aorta early in diastole; this results in the formation of the diastolic wave that facilitates coronary flow. When the elastic properties of the aorta are diminished and the PWV is increased, the reflected waves from the periphery return earlier to the ascending aorta and fuse with the systolic portion of the pulse pressure, resulting in a late peak of the systolic pressure and the disappearance of the diastolic wave (fig. 8); this may have significant implications for coronary perfusion and LV performance.

Indeed, LV-vascular coupling is an important determinant of LV performance. In patients with LV dysfunction without appropriate adaptation of the vasculature, overall circulatory performance may not improve and/or may be diminished, despite positive inotropic intervention. Furthermore, stiffening of the aorta may impair LV

relaxation and early diastolic ventricular filling, resulting in an increase in LA volume at the beginning of atrial systole. Studies on patients with arterial hypertension have shown that changes in aortic and LA function occur parallel to alterations of LV mass (fig. 7). As LV mass increases, the LA volumes, the duration of LA systole and the LA work increase, while the elastic properties of the aorta decrease [71, 72]. The studies have suggested that changes in aortic function and LA work related to age also run parallel and occur prior to demonstrable changes in LV structure and function (fig. 5). These close interrelationships between the LA, LV and aorta would make integrated studies of their functions appropriate in order to better understand the interrelationships in the cardiovascular system.

Pulmonary hypertension is a common complication in patients with mitral valve disease (stenosis and/or regurgitation) and LV dysfunction/failure, with the degree of pulmonary hypertension being mostly related to the severity of these conditions [75]. Regardless of the underlying disease, the main reason for developing pulmonary

Fig. 7. LA volumes, active stroke volume and work as determined by LA kinetic energy (LAKE) in relation to LV mass. LV mass was within 1 standard deviation (SD) above the normal mean in group I, 1–2 SD above the normal mean in group II and >2 SD above the normal mean in group III (modified from [72]).

hypertension is primarily related to the transmission of LA pressure to the pulmonary veins and then to the pulmonary capillary wedge pressure (fig. 6). In certain patients, an increase in pulmonary venous pressure may trigger pulmonary vasoconstriction due to a decrease in nitric oxide, an increase in endothelin and a diminished

effect of ANP. In these cases, pulmonary artery pressure further increases in excess of what is expected from the elevated pulmonary artery capillary wedge pressure. Thus, LA compliance and pressure are important factors that contribute to the development of pulmonary hypertension.

Fig. 8. Schematic representation of reflected waves in the aorta. In a normally functioning aorta, the reflected waves reach the root of the aorta early in diastole, resulting in the formation of the diastolic wave that facilitates coronary blood flow. When the aorta is stiff, the reflected waves reach the aortic root at the end of systole, resulting in the disappearance of the diastolic wave and the development of systolic arterial hypertension.

Neurohumoral Interrelationships

ANP is a 28-amino-acid peptide that is synthesized in the atrial myocytes in response to atrial distension. Angiotensin, endothelin and the sympathetic nervous system also increase ANP secretion. Elevated ANP is found in hypervolemic states associated with LA distension and congestive heart failure. ANP is stored in cardiac myocytes as a prohormone and, during release into the circulation, final processing yields the biologically active C-terminal and N-terminal fragment ANP [14, 15]. ANP is involved in the regulation of sodium and water balance, intravascular volume and atrioventricular filling pressures (fig. 9). There are two major pathways related to ANP function: a vasodilatory effect and a renal effect. ANP directly dilates veins, resulting in a decrease in central venous pressure and ventricular preload. It also dilates arteries, resulting in a decrease in systemic vascular resistance and arterial pressure. Moreover, it increases the glomerular filtration rate and decreases renin secretion (resulting in a decrease in angiotensin II and aldosterone); both of these result in natriuresis and di-

uresis. Low levels of angiotensin II also contribute to vasodilatation and to a decrease in arterial pressure. ANP may also act on the central nervous system via the inhibition of norepinephrine release by sympathetic nerve terminals. BNP, a second natriuretic peptide, is costored in small amounts with ANP in the atrial granules. BNP is mostly synthesized in the ventricles and the brain; it can also regulate volume and pressure overload [15, 16, 76].

LA: A Marker of Poor Exercise Capacity

LV ejection fraction does not correlate with maximal oxygen consumption (VO_2max) [77]. A correlation does exist, however, between exercise capacity and parameters of LV diastolic function in normal subjects and in patients with heart failure [78, 79]. Several studies have demonstrated an inverse relationship between LA size and LA systolic dysfunction severity with VO_2max in patients with heart failure and reduced LV ejection fraction [80–84]. These findings have recently been expanded to patients with preserved LV ejection fraction [85, 86]. In a relatively recent study, the relationship between LA function and exercise tolerance was studied in 486 patients with normal and different degrees of LV systolic dysfunction (49% normal, 36% mild and 15% moderate-to-severe decreased LV ejection fraction). Exercise echocardiography excluded myocardial ischemia in these patients [85]. In a multivariate analysis, total LA strain ($\beta = 0.21$, $p < 0.001$) and E/e' at rest were associated with exercise capacity ($\beta = -0.11$, $p = 0.001$). Other independent parameters related to exercise capacity were age ($\beta = -0.36$, $p < 0.001$), male gender ($\beta = 0.34$, $p < 0.001$) and body mass index ($\beta = -0.23$, $p < 0.001$). The best predictor of exercise capacity in multivariate analysis is the total LA strain. Indices of LA function are related to exercise capacity in patients with heart failure and preserved LV ejection fraction, asymptomatic patients with arterial hypertension and healthy individuals.

LA: A Marker of Adverse Prognosis

LA dilation is a predictor for the development of heart failure in asymptomatic individuals and a marker of adverse prognosis in patients with established LV systolic dysfunction [87]. It is associated with an increased risk of death in patients with dilated cardiomyopathy, LV dysfunction and postmyocardial infarction [33, 88–90]. In-

Atrial natriuretic peptides and cardiovascular/neurohumoral homeostasis

Fig. 9. Factors determining the excretion of ANP and its effects on the cardiovascular system are shown schematically. GFR = Glomerular filtration rate; RWV = reflected wave velocity.

terestingly, in a study of 273 patients with heart failure (age 62 ± 9 years and 13% female) who underwent echocardiographic analysis and exercise testing with VO_2max determination, LA volume normalized for body surface area (LAV/BSA) was strongly associated with mortality (HR 1.027 and 95% CI 1.018–1.04; $p < 0.0001$). The predictive value of LAV/BSA (HR 1.015 and CI 1.005–1.026, $p = 0.004$) was independent of VO_2max (HR 0.95 and CI 0.91–0.99, $p = 0.01$) and LV ejection fraction (HR 0.89 and CI 0.81–0.97, $p = 0.009$) [91]. The cut-off values for the prediction of adverse cardiovascular events were LAV/BSA >63 ml, LV ejection fraction $<30\%$ and $\text{VO}_2\text{max} <16$ ml/kg/min; the HR for future cardiovascular events in patients who had all three abnormal indices was 38 (CI 11–129) compared to patients who had all three normal indices. The conclusion reached was that LA volume provides powerful prognostic information, incremental and independent of VO_2max and LV ejection fraction [91]. More recently, a large-scale meta-analysis demonstrated that LA dilation is associated with a 2.4-fold increased risk of mortality independent of LV ejection fraction, restrictive mitral filling pattern, New York Heart Association class, age and etiology of ventricular dysfunction in

patients with heart failure and reduced LV ejection fraction [92].

The well-known inverse relationship between LV ejection fraction and mortality has been described mainly in patients with systolic dysfunction. In previous studies, however, patients with heart failure and preserved LV ejection fraction (i.e. up to half of all heart failure patients) were excluded; these patients displayed a similar mortality rate to patients with heart failure and with reduced LV ejection fraction. In a substudy of the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality) trial for which heart failure patients with preserved and decreased LV systolic function were recruited, it was shown that (in the group of patients with an LV ejection fraction $>45\%$) LV ejection fraction did not further stratify patients into a lower- or higher-risk group [93]. In contrast, the degree of LA dilation was associated with an increase in mortality [94–96], suggesting that LA volume may be a better marker than LV parameters for determining adverse prognosis in patients with heart failure, irrespective of the underlying mechanism. Furthermore, LA size and function have also been established as predictors of adverse cardiovascular events in

the general population, in patients with postmyocardial infarction or cardiomyopathy and in valvular heart disease. LA size is also a predictor of new onset and recurrence of atrial fibrillation after conversion to sinus rhythm [97].

Concluding Remarks

LA function has received considerably less attention than LV function, even though evidence suggests that LA myopathy and failure may exist as an isolated entity, precede LV myopathy and/or coexist with LV myopathy. Furthermore, LA structural and functional abnormalities may be present in many diseases and disorders [71–74].

LA emptying is biphasic. The first phase begins with the opening of the mitral valve and ends with the onset of LA contraction (passive emptying). During this phase, blood that has been stored in the LA during LV systole (reservoir phase) flows from the LA into the LV. In addition, during this phase, blood flows directly from the pulmonary veins through the LA into the LV (the conduit

function of the LA). The second phase of active LA emptying begins with the onset of LA contraction and ends with the closure of the mitral valve (with the LA functioning as a pump). Thus, the LA functions as a reservoir, conduit and pump. It also functions as a neurohumoral organ contributing to cardiovascular homeostasis [76]. It is indeed multidimensional and the evaluation of its performance therefore requires multiple parameters.

Recent advances in imaging techniques have contributed significantly to the study of the complex morphology and function of the LA and its interrelationships with the functioning LV, aorta and pulmonary artery. As technology continues to evolve, applications in clinical practice will become easier. It is anticipated that in the near future, LA function will be routinely determined and used as LV function is used today. The determining of LA function simultaneously with LV function, aortic function and pulmonary artery hemodynamics will provide a better understanding of the role of the LA on cardiovascular homeostasis in normal subjects and in patients with cardiovascular diseases.

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