Left atrial physiology

The left atrium modulates left ventricular filling through three components: a phase of reservoir or expansion during systole, a conduit phase during diastole, and an active contractile component (when sinus rhythm is present) during late diastole. This active contractile component of the left atrium has an important role in patients with ventricular dysfunction as a ‘booster pump’ to augment ventricular volume. Augmented left atrial booster function is one of the mechanisms compensating for decreased early filling in patients with reduced left ventricular compliance, whereas a loss of atrial contraction, as a result of atrial fibrillation or ventricular pacing, reduces cardiac output by approximately 15–20%[1,2].

During exercise left atrial reservoir and booster functions are augmented, whereas conduit function is not; increased reservoir function may play an important role in accelerating left ventricular filling by helping to maintain an enhanced atrioventricular pressure gradient during diastole and also by increasing left atrial booster function through an increase in preload[3]. An isolated decrease in left atrial compliance is associated with relative increases in the conduit function of the left atrium. The ability to optimally redistribute left ventricular filling among reservoir, conduit and booster-pump functions is a potentially important adaptation that may occur in the left atrium in response to changing haemodynamics[4].

Frank–Starling mechanism

The stretch of the atrium was controlled by intra-atrial pressure. The Frank–Starling behaviour of the atrium was manifested as a biphasic increase of the contraction force after increasing the stretch level. The development of the contraction force after step increase of the stretch (intra-atrial pressure from 1 to 3 mmHg) was accompanied by an increase in the amplitude of the calcium transients and a decrease in the time constant of Ca²⁺ transient decay. The stretch-activated channel activation led to gradual augmentation of Ca²⁺ transients, which modulated the action potentials through increased Na⁺/Ca²⁺-exchanger inward current. The role of troponin C affinity change was to modulate the Ca²⁺ transients, stabilize the diastolic [Ca²⁺]<sub>i</sub>, and presumably to produce the immediate increase of the contraction force after stretch seen in experiments. The same mechanism that caused the normal physiological responses to stretch could also generate arrhythmogenic afterpotentials at high stretch levels in the model[15].

With a stepwise decrease in the pacing rate from 110 beats . min<sup>-1</sup> to 70 beats . min<sup>-1</sup>, the left atrial dimension increases just before atrial contraction and left atrial systolic shortening increases as well. However, the calculated left ventricular filling volume during atrial systole decreases. The pulmonary venous flow during atrial systole is directed toward the left atrium, and the left atrial influx volume from pulmonary venous flow decreases. With a decrease in the pacing rate, the left atrial Frank–Starling mechanism operates. However, left ventricular filling during atrial systole decreases because of the decrease in pulmonary venous flow to the left ventricle via the left atrium[16].

Left atrial distensibility

Several studies on left ventricular relaxation have been undertaken in the past; however, left atrial relaxation has not been fully evaluated. Peak first systolic velocity, peak atrial systolic velocity and their time-velocity integrals are calculated from the pulmonary venous flow velocity. Multiple regression analysis indicated that the peak first systolic velocity was very closely related to percentage fractional left atrial relaxation, followed by mean pulmonary capillary wedge pressure. The peak first systolic velocity determined from the pulmonary venous flow velocity is closely related to parameters of left atrial relaxation which may be determined by transoesophageal M-mode echocardiography, and the ratio of peak atrial systolic velocity to peak first systolic
velocity is useful for non-invasive evaluation of left atrial pressure[7].

Regional differences in atrial distensibility exist in vivo and may play an important role in modulating systolic and diastolic function of the left atrium[8]. The left atrial appendage is more compliant than the left atrium[9]. The left atrial appendage is more important in left atrial function, in the presence of left atrial pressure and/or volume overload[9]. Pericardiectomy of the left atrial main chamber, and plays an important role in left atrial appendage is more compliant than the left atrium[10].

Greater augmentation in conduit than reservoir function increases left atrial compliance and the early left ventricular systolic and diastolic function of the left atrium[8].

Experience are encouraging and it can be anticipated that, within a short time, transoesophageal echocardiography will play an important role in the management of patients at higher risk of thromboembolism, or vice versa, and the appropriate designation of patients for the planned cardioversion of atrial fibrillation. Moreover, transoesophageal examination of the left atrial auricle by use of two-dimensional and Doppler echocardiography has enabled the cardiologist to judge the function of the left atrial auricle not only from the anatomical aspect, but also from that of pathophysiology. This enabled stratification of patients at higher risk of thromboembolism, or vice versa, and the appropriate designation of patients for the planned cardioversion of fibrillation arrhythmia, even if this state has been relatively prolonged. Current knowledge and experience are encouraging and it can be anticipated that, within a short time, transoesophageal echocardiography will play an important role in the management of patients with atrial fibrillation[17].

The pattern of pulmonary venous flow velocity is useful for understanding the haemodynamic relationship between the left atrium and left ventricle in patients with a variety of diseases. The systolic flow wave, in particular, is considered to be a clinically important parameter that reflects left atrial filling. The peak velocity and time-velocity integral of the systolic pulmonary venous flow velocity, and the percentage left atrial emptying fraction were significantly lower in the dilated failing heart group than in the isolated atrial fibrillation, hypertrophic cardiomyopathy and normal groups. Transoesophageal pulsed Doppler echocardiographic measurements of systemic pulmonary venous flow velocity and the percentage left atrial emptying fraction were significantly lower in the dilated failing heart group than in the isolated atrial fibrillation, hypertrophic cardiomyopathy and normal groups.

Transoesophageal pulsed Doppler echocardiographic measurements of systemic pulmonary venous flow velocity are valid indicators of left atrial filling in patients with atrial fibrillation[18].

Systolic pulmonary venous flow rate increased significantly and reached a plateau, reflecting limited left atrial reservoir function. Diastolic pulmonary venous flow rate increased significantly with an increase in left atrial pressure. During atrial contraction, increases in left atrial active shortening and left ventricular filling.
The recent development of real-time measurement of left atrial size to assess disease states and treatments[21]. Boundary detection may assist in serial non-invasive detection are reproducible. This suggests that automated atrial cavity measurements with automated boundary detection. Instantaneous left parasternal long-axis, and parasternal short-axis views Left atrial areas are taken in the apical four-chamber, and a comparable area section with the largest left atrial area is then selected.

Automated boundary detection echocardiography
Automated boundary detection is a new echocardiographic modality providing continuous on-line measurements of cavitary area throughout the cardiac cycle. Previous reports have indicated that echocardiography with automated boundary detection is useful for the non-invasive estimation of left ventricular volume. The measurement of left atrial volume also provides pivotal information in the clinical setting. Using automated boundary detection, a region of interest is set around the left atrial border and mitral annulus from an apical four-chamber view. Automated boundary detection from the apical four-chamber approach could provide an accurate estimation of left atrial volume change, suggesting the potential value of this method in assessing left atrial function[20]. Acoustic quantification technology evaluates the waveforms of left atrial area changes obtained by automated boundary detection. Left atrial areas are taken in the apical four-chamber, parasternal long-axis, and parasternal short-axis views using automated boundary detection. Instantaneous left atrial cavity measurements with automated boundary detection are reproducible. This suggests that automated boundary detection may assist in serial non-invasive measurement of left atrial size to assess disease states and treatments[22].

The recent development of real-time two-dimensional echocardiographic automated boundary detection suggests that left atrial dimensions can be measured instantaneously to provide on-line assessment of its systolic and diastolic functions (Fig. 1). Instantaneous left atrial cavity area measurement by echocardiographic automated boundary detection is accurate and feasible in patients with diverse cardiac disorders. Patients with atrial fibrillation had a depressed diastolic emptying index and those with significant mitral regurgitation had, in addition, a depressed systolic expansion index. Left atrial functional indexes in both systole and diastole can be derived from quantitative evaluations of left atrial–left ventricular interactions based on non-invasive geometric assessment[23]. Thus Doppler techniques complemented by automated boundary detection provide direct quantitative indexes of left atrial function throughout the cardiac cycle[23,24].

Other echocardiographic indexes
Assessment of diastolic function through measurement of the components of ventricular filling has largely neglected the vigour of atrial systole, in part because this has been difficult to quantify. However, atrial ejection force, defined as that force exerted by the left atrium to accelerate blood into the left ventricle during atrial systole, can be assessed non-invasively by combining two-dimensional imaging and Doppler echocardiography. This index of atrial function, based on classic Newtonian mechanics, provides a physiological assessment of atrial systolic function. Atrial ejection force provides a physiological assessment of atrial systolic function and is a potentially useful index for assessing atrial contribution to diastolic performance. In patients who successfully underwent cardioversion from atrial fibrillation, atrial ejection force improved over several weeks only in the subgroup in which sinus rhythm was maintained[25].

Left atrial kinetic energy can be obtained non-invasively from the formula: \( \frac{1}{2} \times \text{stroke volume} \times p \times V^2 \), where stroke volume=left atrial volume that enters the left ventricle during atrial systole, \( V=\text{transmitral Doppler A velocity and } p=1.06 \text{ g. cm}^{-3} \text{ blood’s density. An excellent correlation was found between left atrial stroke work index and left atrial kinetic energy. The area of the counterclockwise A loop expressing the left atrial external work was used. Left atrial kinetic energy extends the use of transmitral flow Doppler data to include assessment of left atrial work. Left atrial work can be obtained non-invasively with a high degree of accuracy[26].}

Magnetic resonance imaging
Left atrial cine magnetic resonance imaging with 50 ms phases is made in 6–12 contiguous long-axis sections encompassing the entire atrial cavity. A volume–time curve is reconstructed to measure the minimum and maximum volumes as well as the fractional volume change, reservoir function, ejection fraction and mean filling and emptying rates of the left atrium. The image section with the largest left atrial area is then selected and a comparable area–time curve is reconstructed. Left atrial size and function can be studied by reconstructing a phasic atrial area–time curve with cine magnetic resonance imaging. Atrial enlargement and abnormalities of filling and reservoir function can be reliably identified[27].
Retrograde left atrial catheterization

A new type of guiding catheter that is used for retrograde transmural catheterization of the left atrium has been developed in our Institution. The catheter (Stefanadis–Toutouzas®. Special product, 5RE-699 by Cordis Europa) incorporates a steering arm by means of which the catheter tip may be made to curve through an arc of 0–180 degrees, entirely through external manipulation. In this way the tip of the guiding catheter may be positioned below the mitral valve orifice and used for the introduction of a smaller catheter into the left atrial cavity. The technique proved useful in the study of left atrial function (haemodynamic, electrophysiological, secretory). It is also helpful in percutaneous mitral valvuloplasty by permitting retrograde, rather than transseptal, access to the left atrium.

Contraction of the left atrium in diastole generates a pressure wave that moves along the posterolateral wall of the left ventricle, rebounds off the left ventricular apex, and is then directed toward the outflow tract. The left atrial systolic pressure curve consists of two positive waves—a first wave (A) and a second wave (A’). The amplitude of the A wave exceeded that of the A’ wave at normal left ventricular end-diastolic pressures. However, as the left ventricular end-diastolic pressure increased either at rest or during pharmacological intervention such as angiotensin infusion, the amplitude of the A’ wave increased and often exceeded that of the A wave. These results suggest that the second (A’) wave might be attributed to the increased reflection associated with increased left ventricular end-diastolic pressure. The movement of this atrial pressure wave may be detected with pulsed Doppler echocardiography by placing a sample volume in the left ventricular outflow tract. The resulting spectral profile shows the initial A velocity wave and also the A’ velocity wave, which is caused by the atrial pressure wave rebounding off the left ventricular apex. The transit time from the inflow tract to the outflow tract of the atrial pressure wave (A–A’, interval) may be determined from the time axis of the spectral profile by measuring the peak-to-peak separation of the A and A’, velocity waves; it is in the range 25–80 ms. The primary determinant of the A–A’ interval is the elasticity of the left ventricular myocardium. The A–A’ interval is an easily measured non-invasive index of the diastolic function of the left ventricle that reflects its intrinsic elasticity and end-diastolic pressure. It is therefore a quantitative measure of left ventricular wall stiffness and end-diastolic pressure.

Left atrial pressure–area relationship

In physiological investigations, the pressure–area relation is the most accurate and representative index of left atrial haemodynamic status. Real-time two-dimensional echocardiographic imaging with automated boundary detection to estimate left atrial area changes have been applied. To obtain left atrial pressure, a catheter-tipped micromanometer is introduced retrogradely into the left atrium using the above steerable cardiac catheter developed at our institution. Millar micromanometer and electrocardiogram cables are connected to a VF-1 mainframe computer (Crystal Biotech). Signals of left atrial pressures, as well as signals of left atrial area and electrocardiogram are fed into a personal computer (IBM Pentium 100 MHz) and simultaneously displayed in real-time mode in the monitor of the computer using a multichannel 12-bit analog-to-digital converter (Data Translation Inc.) and commercially available data acquisition software (Dataflow, Crystal Biotech), as we have previously reported. The stored digitized data were analysed by computer algorithm. Thus, a correction of area data is made by aligning the minimal value of the automated boundary detection time–area curve with the peak of the QRS complex of the digitized electrocardiogram. From the area–time and the pressure–time curves the pressure–area relationship was obtained in all patients.

The left atrial pressure–area relationship consists of two loops: the A loop representing left atrial pump function and the V loop representing left atrial reservoir function. The areas of the A and V loops of the pressure–area relationship as well as the left atrial chamber stiffness constant can be calculated.

The elastic characteristics of the left atrial chamber are assessed by the pressure and area relationship corresponding to the period from the nadir of the x wave of the left atrial pressure to the peak of the V wave. Pressure and area data during this period of the clockwise ascending limb of the pressure–area loop are then fitted to the exponential function, \( P = b e^{(-aA)} \), where \( P \) is the instantaneous left atrial pressure and \( A \) is the left atrial area. The least-squares method was used for calculation of \( a \) and \( b \), where \( a \) is the passive elastic chamber stiffness constant (cm⁻²), which determines the slope of the exponential curve and \( b \) is the elastic constant (mmHg⁻¹).

The left atrial stroke work index can be accurately calculated, and a very good correlation has been found with left atrial preload. Left atrial stroke work index was found to be lower in patients with heart failure, whereas the left atrial stiffness constant was increased in patients with heart failure and atrial fibrillation compared with normal subjects. In addition, the increased inotropic state after dobutamine administration resulted in improved left atrial pump function (stroke work index) in normal subjects and patients with heart failure, as well as in decreased stiffness constants in all groups of patients. This method is both safe and reproducible for obtaining the left atrial pressure–area relationship. Left atrial function is impaired in patients with heart failure and in those with atrial fibrillation and may be acutely improved with inotropic agents in both normal and diseased atria.
Creation of pressure–area relationships (loops) can be achieved with the automated border detection signal (corrected in relation to the inherent delay) and pressure recording. In vitro experiments showed that the automated boundary detection delay relative to high-fidelity pressure recordings ranges from 20 to 34 ms and 35 to 57 ms at echocardiographic frame rates of 60 s and 33 s, respectively. The delay is not influenced significantly by the type of transducer used, distance from the target area, or size of the target area. The delay in the automated boundary detection signal, relative to the echocardiographic image, ranges from zero to less than one frame duration, whereas it is delayed one to two frame durations relative to the electrocardiogram processed by the imaging system. To exclude areas outside the left atrial cavity, time-gain compensation and lateral

**Figure 2** Waveforms of left atrial volume and simultaneous left atrial pressure. During left ventricular systole the left atrium fills and the left atrial volume reaches the maximal value ($V_{max}$). Thereafter the mitral valve opens and left atrial passive and active emptying phases follow. Left atrial minimal volume ($V_{min}$) occurs at the end of left atrial systole. Simultaneously with $V_{max}$, the V wave of the left atrial pressure is recorded. The y descent occurs simultaneously with passive emptying while the x descent is recorded during the left atrial filling period. Finally, the A wave occurs simultaneously with atrial contraction (active emptying).

**Figure 3** The left atrial pressure–volume relationship is composed of two loops: the A loop, expressing the left atrial pump function and the V loop, expressing the reservoir function of the left atrium. During the filling period, the curve is directed upward and to the right, and after maximal pressure and volume of the filling period have been reached, the curve turns clockwise and downward corresponding to the passive emptying, and subsequently, active emptying phases.
gain compensation are used much more extensively than during left ventricular automated boundary detection recording\textsuperscript{[35]}. Left atrial elastance

Contractile function of the ex vivo, isolated left atrium has been described by a time-varying elastance \( E(t) \), although this atrial chamber property has not been shown in vivo. In the intact heart, left atrial contraction may be approximated by time-varying elastance with time-dependent changes in \( E(t) \). Left atrial systolic pressure–volume relationships using either the non-isochronal maximum pressure-to-volume ratio or end systole may be useful as an estimate of \( E_{\text{max}} \). They are highly linear and sensitive to calcium-induced changes in inotropic state, and may be useful in identifying left atrial chamber adaptation to chronic haemodynamic loads\textsuperscript{[36]} (Fig. 4).

To characterize the pump function of the left atrium, the instantaneous pressure–volume relationship of the isolated supported left atrium is determined. Elastance is the ensemble of slopes, and \( V_{\text{0P}} \), the volume-axis intercepts resulting from the linear regression of instantaneous pressure on instantaneous volume at multiple instants throughout the cardiac cycle. The systolic portion of the left atrial elastance was insensitive to loading conditions, as was \( V_{\text{0P}} \), which also proved to be similar to the right atrial and right ventricular \( V_{\text{0G}} \) waveforms in its time dependence. These results indicate that elastance and \( V_{\text{0G}} \) adequately represent the instantaneous pressure–volume relationship of the left atrium in systole irrespective of the mode of contraction. Whatever the underlying mechanism might be, the load insensitivity and similarity of the basic shape of the left atrial elastance among different atria suggests that the characterization reflects fundamental features of left atrial contraction\textsuperscript{[37]}.

The relationship of instantaneous pressure to volume measured at multiple identical time points in the contraction cycle is quasi-linear during most of atrial systole and diastole. A linear regression formula \( P(t) = K(t)[V/V_{\text{0G}}(t)] \) is therefore fitted to the pressure and volume data, where \( K(t) \) and \( V_{\text{0G}}(t) \) of the regression formula are the slope and the volume axis intercept in the pressure–volume plane, respectively, when the atrium beats spontaneously at a regular sinus rhythm with no inotropic intervention. \( K(t) \) increased during systole and decreased during diastole, whereas \( V_{\text{0G}}(t) \) decreased during systole and increased during diastole.

\begin{equation}
y = 1.0353x - 30.591 \\
R^2 = 0.9973
\end{equation}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{The elastance at end-systole of the left atrium expresses the pressure (mmHg) developed by left atrial contraction per unit of left atrial volume change (ml). End-systolic elastance \( E_{\text{es}} \) is calculated by the slope of the linear regression line fitted on the pressure–volume data during end-systole of three different loaded left atrial pressure–volume loops. The volume axis intercept \( V_{\text{0}} \) represents the theoretical value of the left atrial volume at zero pressure. Left atrial pressure–volume loops are generated by altering loading conditions.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Doppler tracings of the blood flow velocity of the left atrial (LA) appendage in a patient with atrial flutter. Positive waves represent contractions of the appendage while negative waves represent the filling period of the auricle. ECG = electrocardiogram.}
\end{figure}
Enhancement of contractility with epinephrine or Ca\(^{2+}\) significantly increases the value of K at the end of systole, but it does not significantly affect either K at the end of diastole or VD at the end of systole and diastole\(^{30}\).

**Left atrial function in disease states**

**Atrial fibrillation**

During atrial fibrillation, synchronized atrial contraction is lost and cardiac output declines. Concomitantly, atrial pressure increases. The increase in atrial pressure counteracts the decline in stroke volume after induction of atrial fibrillation and thereby represents an important compensatory mechanism\(^{39}\). Furthermore, instantaneous diastolic atrial compliance decreased in both right and left atria after induction of atrial fibrillation\(^{40}\).

Left atrial size is an important factor in the development of atrial fibrillation and in determining the long-term result of cardioversion. The pathophysiological mechanism most consistent with this is that a chronic haemodynamic burden initially produces left atrial enlargement which in turn predisposes to atrial fibrillation\(^{41}\). Atrial enlargement can occur as a consequence of atrial fibrillation. The maintenance of sinus rhythm, therefore, may prevent atrial enlargement and its adverse clinical effects\(^{42}\). The left atrium is also slightly dilated in patients with paroxysmal atrial fibrillation\(^{43}\). Atrial fibrillation occurring in patients with lone atrial fibrillation may cause a slow and progressive increase in left atrial size independent of changes in left ventricular size or function\(^{44}\). Left atrial enlargement is deleterious as it may convey additional stroke risk in patients with atrial fibrillation\(^{45}\).

**Left atrial appendage function**

Recently, attention has been focused on transoesophageal echocardiographic detection of left atrial appendage function to assess the risk of thrombus formation because of potential benefit of anticoagulation therapy. The function of the appendage can be analysed by Doppler echocardiography in sinus rhythm as well as in atrial fibrillation and flutter. This method lacks an adequate definition because of the complexity and temporal variability of the Doppler flow profiles. Left atrial appendage function in atrial fibrillation and flutter can be well characterized by Fourier analysis of Doppler flow. Atrial fibrillation has higher dominant frequencies and greater subharmonic modulation compared with flutter. Moreover, atrial fibrillation gave quasi-periodic contraction patterns typically found in chaotic systems. Fourier analysis of left atrial appendage contraction patterns may therefore have significant promise in providing insights into mechanisms of atrial fibrillation and thromboembolism\(^{46}\). Reduced left atrial appendage function can be a cause for stroke in patients with sinus rhythm even in the absence of mitral valve disease. Thus, reduced left atrial appendage function may identify patients with unexplained stroke who should receive anticoagulation therapy even in the absence of detectable appendage thrombi\(^{47}\).

Both the magnitude and the pattern of left atrial appendage emptying and filling velocities are dependent on loading conditions, and left atrial appendage velocities are influenced to a greater extent by changes in left ventricular than in left atrial appendage function\(^{48}\). Although several flow patterns in the left atrial appendage have been described, mechanical determinants of its function have not been elucidated in human beings. Unless there is an alteration of the loading conditions, left atrial appendage function improves over several days after cardioversion, and its function is related to left atrial mechanical function\(^{49}\). Left atrial appendage flow velocity during atrial fibrillation may be useful for identifying candidates for electrical cardioversion\(^{50}\).

Peak left atrial appendage emptying velocity was found to be statistically related to parameters of left ventricular and left atrial function but not to long-term maintenance of sinus rhythm. No other echocardiographic parameter was identified as a predictor for either the success of cardioversion or the maintenance of sinus rhythm at follow-up. In patients with non-valvular atrial fibrillation of recent onset, peak left atrial appendage emptying velocity appears to be a complex parameter depending on left atrial and left ventricular function but that does not predict either the success rate of cardioversion or long-term maintenance of sinus rhythm after successful cardioversion\(^{51}\).

Left atrial appendage stunning has recently been proposed as a key mechanistic phenomenon in the aetiology of postcardioversion thromboembolic events in atrial fibrillation. Atrial flutter is thought to be associated with a negligible risk of thromboembolic events; therefore anticoagulation is commonly withheld before and after cardioversion in these patients. Left atrial appendage stunning also occurs in patients with atrial flutter, although to a lesser degree than in those with atrial fibrillation. These data suggest that patients with atrial flutter are at risk for thromboembolic events after cardioversion, although this risk is most likely lower than that in patients with atrial fibrillation because of better preserved left atrial appendage function\(^{52}\).

**Cardioversion and left atrial stunning**

Cardioversion of atrial fibrillation transiently increases the risk of embolism, presumably by decreased atrial mechanical function. Almost all patients undergoing chemical cardioversion for atrial fibrillation with amiodarone recovered bilateral atrial mechanical function within 24 h of cardioversion, with normal left atrial
function in 97% of patients and normal right atrial function in 100% of patients on day 7 after conversion to sinus rhythm\textsuperscript{53}. During the 3 months after successful cardioversion of non-valvular chronic atrial fibrillation, left and right atrial reservoir function and left and right atrial active transport function increased progressively, becoming comparable to values in the control subjects\textsuperscript{54}.

Both external cardioversion and internal atrial defibrillation of atrial fibrillation may result in left atrial appendage dysfunction (‘stunning’) and may promote thrombus formation. In contrast, external cardioversion uses lower energy. These findings have important clinical implications for anticoagulation therapy before and after low-energy internal atrial defibrillation in patients with atrial fibrillation\textsuperscript{55,56}. Changes in left atrial appendage pulsed-wave Doppler velocities and changes in grades of spontaneous contrast occur immediately after electrical cardioversion of atrial fibrillation. Restoration of sinus rhythm is in itself the primary objective of treatment. Changes in left atrial and ventricular systolic function appear to be more profound and of longer duration for the left atrial appendage following cardioversion\textsuperscript{58}. After cardioversion, appendage contraction synchronized with the mechanical activity of the atrium\textsuperscript{59}.

After cardioversion of chronic atrial fibrillation to sinus rhythm, there is a gradual increase of 56% in cardiac output over 4 weeks. The increase is caused by the gradual return and increasing strength of left atrial mechanical activity as the atrial myopathy of chronic atrial fibrillation subsides. Cardiac output decreases after cardioversion of atrial fibrillation in more than a third of patients, and the decrease may last a week. Acute pulmonary oedema is uncommon; 50% of cases occur within 3 h of cardioversion, with a mortality of 18%. The reduced cardiac performance after cardioversion probably results from the combination of heart disease and cardiac depressant effects of anaesthetic drugs used. Pulmonary and/or coronary artery emboli and the resumption of right atrial mechanical activity before left atrial mechanical activity may be additional factors in the pathogenesis of pulmonary oedema after cardioversion. Anticoagulant therapy should be continued for a month or longer after cardioversion in those patients who maintain sinus rhythm to prevent thromboembolism\textsuperscript{60}.

Reduced atrial contractility occurs after cessation of atrial fibrillation. Its mechanism is unknown, and no pharmacological treatment exists. It has been suggested that this atrial contractile dysfunction results from intracellular calcium overload due to rapid depolarizations during fibrillation. Atrial contractile dysfunction after short-term atrial fibrillation is reduced by the calcium antagonist verapamil, which suggests that transsarcolemmal calcium influx contributed to this dysfunction\textsuperscript{61}. The recovery of atrial function was influenced by the mode of cardioversion and the size of the left atrium\textsuperscript{62}. Lack of effective mechanical atrial function after cardioversion of atrial fibrillation predisposes to thromboembolic complications and delays improvement in functional capacity. A high proportion of patients recover effective mechanical atrial function within 1 week of cardioversion. Patients who undergo electrical cardioversion display a greater degree and a longer duration of mechanical atrial dysfunction than those who convert pharmacologically or spontaneously\textsuperscript{63}.

Left atrial appendage contraction velocities measured during sinus rhythm in patients after cardioversion from atrial fibrillation are depressed relative to left atrial appendage emptying velocities measured during atrial fibrillation, suggesting that the left atrial appendage is mechanically ‘stunned.’ Even brief (60 min) periods of atrial fibrillation in normal canine hearts result in marked depression of global left atrial systolic function and regional left atrial (left atrial appendage) systolic function upon resumption of sinus rhythm. This ‘mechanical stunning’ of left atrial systolic function appears to be more profound and of longer duration for the left atrial appendage compared with the left atrium as a whole, and may predispose the appendage to blood stasis and thrombus formation\textsuperscript{64}.

Furthermore, cardioversion of atrial flutter is associated with a significant degree of atrial stunning and formation of spontaneous echocontrast\textsuperscript{65}. Atrial stunning and the development of spontaneous echocardiographic contrast is a consequence of electrical cardioversion of atrial flutter to sinus rhythm. This phenomenon is associated with thrombus formation and embolic stroke. Radiofrequency ablation is now considered to be definitive treatment for chronic atrial flutter. Radiofrequency ablation of chronic atrial flutter is associated with significant left atrial stunning and the development of spontaneous echocardiographic contrast. Left atrial stunning is not secondary to the radiofrequency ablation energy application itself. Sustained sinus rhythm for 3 weeks leads to resolution of these acute phenomena. Left atrial stunning occurs in the absence of direct current shock or antiarrhythmic drugs, suggesting that its mechanism may be a function of the preceding arrhythmia rather than the mode of reversion\textsuperscript{66}.

Temporary changes in left atrial appendage flow velocity patterns in patients undergoing electrical cardioversion for chronic isolated atrial fibrillation have been investigated, and the role of active appendage contraction in directing blood flow to the left atrial main chamber and left ventricle was evaluated. These results suggest that appendage and the left atrial main chamber show stunning 24 h after cardioversion, and the atrial systolic emptying wave of appendage flow is generated by active appendage contraction\textsuperscript{67}.

**Mitral valve disease**

The importance of the contribution of atrial systole to ventricular filling in mitral stenosis is controversial. The...
cause of reduced cardiac output following the onset of atrial fibrillation may be due to an increased heart rate, a loss of booster pump function, or both. The atrial booster pump contributes less to ventricular filling in mitral stenosis than in the normal heart, and the loss of atrial pump function is less important than the effect of increasing heart rate as the cause of decompensation during atrial fibrillation [68]. The onset of left atrial dilatation in mitral stenosis is the result of an early increase in left atrial pressure. Atrial fibrillation, which develops irrespective of the severity of the mitral stenosis, contributes to a further enlargement of the left and right atria [69].

Patients with mitral stenosis and atrial fibrillation or in sinus rhythm develop systemic emboli. Mitral valve disease, particularly mitral stenosis is frequently associated with left atrial spontaneous echo contrast. It has been also observed that, the more severe the mitral valve disease, the greater the probability of left atrial spontaneous echo contrast. In all cases in which thrombi are found, left atrial echo contrast is found and the risk of embolism is high. In these cases anticoagulant therapy is suggested [70]. A subset of mitral stenosis in sinus rhythm at increased risk of embolization can be suspected by a Doppler transoesophageal echocardiographic left atrial appendage flow profile [71].

It is known that left atrial function is influenced by changes in left atrial afterload. The latter is increased in mitral stenosis as a result of increased resistance to blood flow imposed by the stenotic mitral valve. The left atrial pump function in patients with sinus rhythm and the left atrial reservoir function in those with atrial fibrillation increased significantly after completion of the procedure. Furthermore, left atrial stiffness decreased in both groups. After retrograde non-transseptal balloon mitral valvuloplasty, there is a significant increase in left atrial pump function in patients with sinus rhythm, a significant increase in left atrial reservoir function in patients with atrial fibrillation and a significant reduction in left atrial stiffness in all patients. Marked alterations of the configuration of the left atrial pressure–area relationship occur immediately after successful balloon mitral valvuloplasty in patients with mitral stenosis [33].

During chronic mitral regurgitation, the left atrium enlarges in size and mass, with a more potent booster action. The left atrial chamber becomes more compliant. Thus, the enlarged left atrium appears to exert an important compensatory mechanism in the case of excessive central blood volume by buffering pressure rise in the atrium and by providing an adequate ventricular filling volume [4].

Left atrial V-wave amplitude has been associated with the presence and severity of chronic mitral regurgitation. There is a strong inverse correlation between V-wave amplitude and calculated left atrial compliance. An increase in V-wave amplitude after balloon commissurotomy was associated with an increasing probability of worsening or severe mitral regurgitation. Thus, left atrial V-wave amplitude reflects left atrial compliance and severity of mitral stenosis before balloon commissurotomy. An increase in V-wave amplitude is an insensitive but very specific indicator of worsening or severe mitral regurgitation during stepwise, incremental balloon mitral commissurotomy [72].

Acute onset of mitral regurgitation initially induces a remarkable augmentation of atrial shortening with chamber dilation as a result of optimal use of the Frank–Starling mechanism of the atrial muscle. When mitral regurgitation is progressively increased, the extent of the atrial shortening and expansion is diminished, despite the geometrical advantage of a further increase in atrial diameter, indicating that this extreme dilation no longer provokes the Frank–Starling response and the atrial myocardium is made to operate on a descending limb of function. The amount of regurgitation is highly dependent on the geometry of the mitral orifice and a decrease in regurgitation with vasodilator therapy or with positive inotropic agents may be largely related to a decrease in the size of the left heart cavity. The latter would bring components of the mitral apparatus closer together and increases its competence [73]. In severe mitral regurgitation, isoproterenol and nitroprusside decreased left atrial pressure and diameter, restoring more forceful atrial shortening [74].

**Hypertrophic cardiomyopathy**

Left atrial chamber stiffness was increased in patients with hypertrophic cardiomyopathy and this affected the left atrial reservoir function. This may in turn have affected cardiac output [75]. Moreover, left atrial booster pump failure due to left atrial afterload mismatch exists in hypertrophic cardiomyopathy [76]. Left atrial contribution to left ventricular filling increases after sudden changes of posture in normal subjects and in patients with hypertrophic cardiomyopathy [77]. There is a close relation between left atrial appendage velocity and left atrial contractile function in patients with hypertrophic cardiomyopathy with paroxysmal atrial fibrillation, and these patients have potential risk of cerebral infarction [78].

**Stiff left atrial syndrome**

This clinical syndrome results when left atrial compliance is markedly reduced but left ventricular diastolic function is normal and the mitral valve is neither obstructed nor incompetent. It is characterized by the presence of signs and symptoms of right heart failure. The right heart failure in these patients is the direct result of reduced left atrial compliance. Such patients mostly have enlarged left atria; a large left atrium is not necessarily a distensible atrium and the critical issue so far is the energy required to distend the atrium not its starting volume. Cardiac catheterization revealed a marked V wave but no mitral regurgitation and no
significant mitral diastolic gradient. A clinical diagnosis of a stiff left atrium is made and confirmed at autopsy[79,80].

**Arterial hypertension**

Systemic hypertension is the leading cause of left ventricular hypertrophy. Left ventricular diastolic filling is impaired in patients with hypertensive heart disease. Enlargement of the left atrium might be attributed to the impairment of blood flow from left atrium to left ventricle due to the increased left ventricular stiffness[81]. Multivariable linear regression models show that the relative contributions of the pressure variables to the prediction of left atrial size are substantially less than that of age and, in particular, of body mass index. Furthermore, inclusion of left ventricular mass in these multivariable models eliminated or attenuated the associations of the pressure variables with left atrial size. In logistic analyses, increasing levels of the pressure variables are significantly predictive of left atrial enlargement. Overall, in this population-based study sample, increased levels of systolic and pulse pressures (but not diastolic or mean arterial pressures) are significantly associated with increased left atrial size[82]. Left atrial enlargement has been reported in the obese. Left atrial enlargement is frequent in the normotensive, otherwise healthy obese and correlates well with left ventricular mass. It is not mediated through impairment of left ventricular diastolic function, and probably reflects a physiological adaptation of the heart to the obese state[83].

Positive correlations of left atrial dimension were found with office blood pressure, average 24-h, average daytime and night-time systolic and diastolic blood pressure, left ventricular mass index, and Doppler-derived E/A ratio. In a multivariate model that included potentially confounding factors, only body mass index, average night-time diastolic blood pressure and male sex were independent predictors of left atrial size in the pooled population. Left atrial size is closely related to ambulatory rather than office blood pressure measurements, and high average night-time blood pressure is a powerful marker of left atrial enlargement in arterial hypertension[84].

Left atrial function makes a large contribution in left ventricular filling, especially in patients with impaired diastolic function. Left atrial function is fundamental in left ventricular filling in hypertensive patients as hypertension results in left ventricular diastolic dysfunction. In hypertensive patients, left atrial reservoir function increases and left atrial conduit function decreases, while left atrial ejection force increases. Antihypertensive treatment with enalapril and/or thiazide, induces normalization of the left atrial function in parallel with left ventricular hypertrophy regression[85]. The increase of left atrial contractility is considered to be urged by the increase of left atrial volume in hypertensive subjects with left ventricular hypertrophy in comparison with normals (Frank–Starling’s law). These data could be explained by the decreased distensibility of the left ventricular chamber in relation to left ventricular hypertrophy[86].

Significant changes in cardiac structure and diastolic function were observed in non-dipper patients with recently discovered hypertension, who, compared with dippers, show changes similar to those in patients with long-standing hypertension. Hypertensives with the observed abnormalities may benefit from active anti-hypertensive treatment, which appears justified even in an early phase of mild hypertension, in terms of potential reduction of end-organ complications as well as cost-effectiveness[87].

Left atrial dilation and enhanced volume transport may facilitate arrhythmias in hypertensive patients. The occurrence of paroxysmal atrial fibrillation in hypertension is associated with enlargement of the left atrium, depression of its contractile function and ‘normalization’ of the pattern of left ventricular filling and is independent of left ventricular hypertrophy and systolic wall stress. The mechanisms linking these variables remain undefined[88].

**Myocardial infarction**

Left atrial function plays an important role in maintaining overall cardiac function during left ventricular ischaemia by reactive hyperactivity. There is an inverse relationship between left ventricular and left atrial performance during left ventricular ischaemia if the left atrium is not affected by the ischaemic events. While left ventricular peak systolic pressure and dP/dt max decreased, left atrial contractility increased significantly. The diminution of the left ventricular ejection fraction during ischaemia is counterbalanced by an increased left atrial booster function resulting in a remarkable augmentation of left ventricular end-diastolic volume. Thus, the left ventricular stroke volume remains almost constant despite a dramatic reduction of the ejection fraction[89].

In left ventricular ischaemia, compensatory augmentation of left atrial contraction enhances left ventricular filling and performance, whereas loss of this atrial transport function exacerbates haemodynamic compromise. In patients with left anterior descending coronary artery stenosis, left ventricular supply or demand ischemia is associated with enhanced left atrial function, manifest as augmented left atrial A loops. However, in patients with proximal left circumflex coronary artery stenosis who develop the same type and degree of ischemia, left atrial branches might have been affected, rendering the left atrial ischaemic and unable to increase its booster pump function[90].

The left atrial contribution to left ventricular function is increased in patients with remote myocardial infarction. This left atrial contribution to the left ventricle is attributed to the Frank–Starling mechanism in the left atrium[90,91]. After myocardial infarction, left ventricular
end-diastolic pressure is higher than mean pulmonary artery wedge pressure because of powerful atrial contraction. The average atrial contribution to left ventricular end-diastolic volume is 12% in normal subjects and 15% in myocardial infarction; its contribution to left ventricular end-diastolic pressure is 20% in normals and 39% in myocardial infarction, and to left ventricular stroke volume, 22% in normals and 35% in myocardial infarction. Atrial contribution to left ventricular stroke volume was 56% in patients with a cardiac index ≤2.0 l/min·m⁻² and 31% in those with a cardiac index >2.1 l/min·m⁻². Atrial contraction contributed 35% to left ventricular stroke volume in patients with normal end-diastolic volume and 10% to end-diastolic volume in patients with increased end-diastolic volume. Thus, in patients with myocardial infarction, atrial contraction made a large contribution to left ventricular filling and stroke volume irrespective of the type of left ventricular functional derangement that was present.

Heart failure

Increased atrial response to early-stage left ventricular filling impairment is characterized by augmented reservoir and pump functions, according to a Starling mechanism, which becomes hardly effective at end-stage ventricular dysfunction when the limits of the atrial preload reserve are reached. At this stage, conduit in the atrium takes precedence. When left ventricular filling pressure was increased, the E/A ratio increased, indicating a filling shift towards early diastole. The reduced atrial contribution during increased preload was explained by the curvilinear shape of the left ventricular pressure-volume curve. At markedly elevated filling pressures, near-maximum left ventricular diameter was achieved before atrial contraction; hence the atrial contribution decreased and the E/A ratio increased. Abnormal left ventricular filling has been observed in patients with heart failure and is characterized by marked heterogeneity of mitral inflow velocity. The initial rise in left atrium contribution to left ventricular filling may represent a compensatory response to the diminution of the rapid early component of left ventricular filling. With further progression of left ventricular dysfunction, the left atrium contribution to left ventricular filling gradually decreases. This reduction may be mediated by increased workload imposed on the left atrial myocardium due to increased left ventricular diastolic wall stress, which, over time, may lead to intrinsic left atrium dysfunction. Investigations of left atrial distensibility have revealed that it plays a major role in atrial function. In congestive heart failure, left atrial distensibility may acutely increase with vaso-dilators or inotropics or may decrease with beta-blockade or volume loading.

Early in congestive heart failure, slowing of left ventricular relaxation reduces the maximal early diastolic left atrial–left ventricular pressure gradient, decreasing the peak early filling rate. As congestive heart failure progresses, this is overcome by an increase in left atrial pressure that augments the early diastolic left atrial–left ventricular pressure gradient, increasing peak early filling rate. Increasing left ventricular stiffness during the development of congestive heart failure progressively shortens the early filling deceleration time and augments the early filling deceleration rate. These observations suggest that the early filling deceleration time reflects left ventricular stiffness.

Restrictive left ventricular filling patterns are associated with diastolic ventricular interaction in patients with chronic heart failure. Volume unloading in the setting of diastolic ventricular interaction allows increased left ventricular filling. Identifying patients with chronic heart failure and restrictive filling patterns may therefore indicate a group likely to benefit from additional vasodilator therapy. Both a reduction in left atrial compliance and atrial systolic function play important roles in heart failure patients with the restrictive transmirtal flow pattern. Among patients with dilated cardiomyopathy, those who had a restrictive or pseudonormal filling pattern are in a higher functional class and had higher filling pressures. Further studies are needed to determine the therapeutic and prognostic significance of left atrial dysfunction, which was common in patients with a restrictive pattern.

Both nitroprusside and dobutamine improve cardiac output in patients with advanced congestive heart failure with different adaptations of left ventricular performance and left atrial function. Nitroprusside seems to restore both atrial and ventricular pump function better. Nitroprusside increases cardiac output, reduces left ventricular filling pressure, and improves left atrial pump volume without variations in left atrial reservoir and conduit volumes. The restoration of preload reserve and improvement of the atrial contribution to left ventricular diastolic filling are shown by the Doppler mitral flow pattern, which moves from a restrictive to a normal pattern. Furthermore, mitral regurgitation decreases in all patients. Dobutamine increases cardiac output, but the effects on pulmonary wedge pressure and mitral regurgitation are variable and unpredictable. Left atrial reservoir and conduit volumes increase whereas left atrial pump volume do not change. Furthermore, Doppler mitral flow shows a persistent restrictive pattern.

After treatment of heart failure, the mitral A velocity significantly increased and there was a distinct attenuation of the difference of the pulmonary venous and mitral A wave duration. These findings are associated with a marked decrease in left ventricular stiffness and an increase in left atrial ejection fraction. The reversible left atrial dysfunction suggests that the initial left atrial dysfunction is due to left atrial afterload mismatch rather than intrinsic left atrial disease, which also contributes to the augmentation of the mitral A velocity after heart failure treatment. Left atrial afterload can be estimated by the effective left ventricular elastance (EELV). Atrioventricular coupling can be calculated by the EELV/Eos ratio (where Eos is the end-systolic
elastance). Early in heart failure, left atrial pump function is augmented but left atrial stiffness increases and work mismatch occurs. With further progression of left ventricular dysfunction, left atrial pump function decreases as a result of increased afterload imposed on the left atrial myocardium[103].

Doppler studies of transmitral flow profiles in heart transplant recipients suggested left ventricular diastolic dysfunction. Left ventricular diastolic dysfunction is not the only possible cause of altered transmitral Doppler profiles in heart transplant recipients. Atrial abnormalities represent a major contributing factor to altered mitral and pulmonary venous flow patterns. Analysis of transmitral Doppler profiles alone are therefore not adequate for analysis of diastolic left ventricular function in heart transplant recipients[104]. Early ventricular filling and therefore passive left atrial emptying may be impaired in patients with cardiac transplantation. As a result, left atrial function may be an important factor in maintaining stroke volume in recipients of orthotopic cardiac transplants. Left atrial contraction contributed 42% to the left ventricular stroke volume in patients who had cardiac transplantation but only 17% in control subjects[105,106].

Studies in the rapid-pacing model of heart failure have shown that left ventricular systolic function normalizes on cessation of pacing and left ventricular diastolic dysfunction persists. Moreover, left atrial systolic function is persistently abnormal, partly owing to persistent left ventricular diastolic dysfunction, residual left atrial hypertrophy and myosin heavy chain isofrom switches[107]. Isolated atrial myopathy, increased atrial stiffness and enhanced conduit function compensate for impaired atrial booster pump and reservoir functions[108]. Left atrial pressure and volume overload resulted in significant up-regulation of beta-myosin heavy chain isoform switches[107]. Left atrial myopathy, increased atrial stiffness and enhanced conduit function compensate for impaired atrial booster pump and reservoir functions[108].

Exposure of isolated rat left atria to a medium which has been subjected to free radicals causes a current-dependent decrease in contractile force. The response to isoproterenol is diminished in atria subjected to oxidative stress and lead to a rightward shift of the concentration response curves. Surprisingly, addition of alpha-adrenoeceptor agonists to atria subjected to electrolysis-generated free radicals led to a rapid decrease in contractile force. Free radicals alter responses to various inotropic stimuli. These alterations may be the result of injured contractile elements, transporter molecules and molecules involved in signal transduction[67].

Conclusions
In disease states the left atrium contributes to failing left ventricular filling and may undergo failure itself. Using combined techniques, left atrial function can be evaluated in normal subjects and in patients at rest and after pharmacological interventions that are common in clinical practice. Left atrial dysfunction is indicated by increased left atrial dimension and pressure and shift of the left atrial pressure–dimension curve with a parallel decrease in left atrial stroke work. Furthermore, non-invasive indices are sensitive to left atrial dysfunction. Changes in left ventricular filling after pharmacological interventions are attributed not only to left ventricular diastolic function improvement but also to co-ordinated changes in left atrial function. Invasive and non-invasive indices of left atrial systolic and diastolic function can evaluate the atrioventricular coupling. Atrial kick was a compensatory response to the decreased early filling. Loss of this atrial function may be due to the increased load of the left atrium which may cause intrinsic left atrial dysfunction. Left atrial dysfunction deteriorates decreased left ventricular filling in patients with left ventricular dysfunction.

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