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Mechanical Function of the Left Atrium

New Insights Based on Analysis of Pressure–Volume Relations and Doppler Echocardiography

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THE left atrium (LA) serves three major roles that exert a profound effect on left ventricular (LV) filling and overall cardiovascular performance. The LA is a contractile chamber that actively empties immediately before the onset of LV systole and establishes final LV end-diastolic volume.[1,2] The LA is a reservoir that stores pulmonary venous return during LV contraction and isovolumic relaxation after the closure and before the opening of the mitral valve.[3] Lastly, the LA is a conduit that empties its contents into the LV down a pressure gradient after the mitral valve opens[4] and continues to passively transfer pulmonary venous blood flow during LV diastasis. These contraction, reservoir, and conduit functions of the LA mechanically facilitate the transition between the almost continuous flow through the pulmonary venous circulation and the intermittent filling of the LV.[5]

The contractile activity of the LA was initially described by William Harvey in 1628.[6] This "booster pump" contribution to cardiac output[7–10] normally accounts for approximately 20% of LV stroke volume[11] but becomes increasingly important to the preservation of cardiovascular performance in patients with reduced LV compliance.[12,13] The enhanced significance of atrial systole to LV filling in patients with LV dysfunction is emphasized by the frequently observed development of clinical signs and symptoms of heart failure when LA contraction is improperly timed[14–16] or eliminated with the onset of atrial tachyarrhythmias.[11] These adverse effects are reversed with the subsequent restoration of normal sinus rhythm and LA contraction.[11] The relative impact of LA reservoir function on early LV filling was initially recognized by Henderson *et al.*,[17] and the dependence of reservoir function on LA compliance was later identified by Suga.[5] While these and other early studies provided seminal information about LA function, comprehensive evaluation of LA performance in the normal and diseased heart was limited by lack of effective techniques for reproducibly measuring continuous LA volume and pulmonary venous blood flow until the 1980s. This objective has subsequently been facilitated by the application of pressure–volume theory adapted from LV function analysis and by the widespread use of two-dimensional and Doppler echocardiography. This article critically reviews recent advances in the understanding of LA physiology derived from pressure–volume relations and echocardiography, discusses the mechanical consequences of primary LA dysfunction, examines LA mechanical adaptation to LV dysfunction, and describes current knowledge about the actions of volatile and intravenous anesthetics on LA function *in vivo*.

Left Atrial Pressure and Volume Waveforms

Precise recording of the LA pressure waveform requires the use of a high-fidelity, intravascular pressure transducer. Placement of a micromanometer-tipped catheter into the LA chamber may be conducted directly through the LA body or appendage or indirectly using a proximal pulmonary vein in the experimental laboratory or during open heart surgery. An intraatrial transseptal technique or a retrograde approach through the mitral valve have been used to measure LA pressure in the cardiac catheterization laboratory.[18] The LA pressure waveform is composed of three major deflections during normal sinus rhythm (fig. 1).[19] After the P wave of atrial depolarization is recorded on the electrocardiogram, the LA contracts, causing an a wave that occurs late in LV diastole. This a wave may be enhanced by preload augmentation (*i.e.*, Frank-Starling mechanism) or increases in intrinsic LA myocardial contractility. The rate of deceleration of the a wave is an index of LA relaxation.[20] With the onset of LV systole, ventricular contraction causes a pressure wave to be transmitted in retrograde fashion by closure of the mitral valve, resulting in a small increase in LA pressure (*i.e.*, the c wave). This c wave may be more pronounced in the presence of mitral valve

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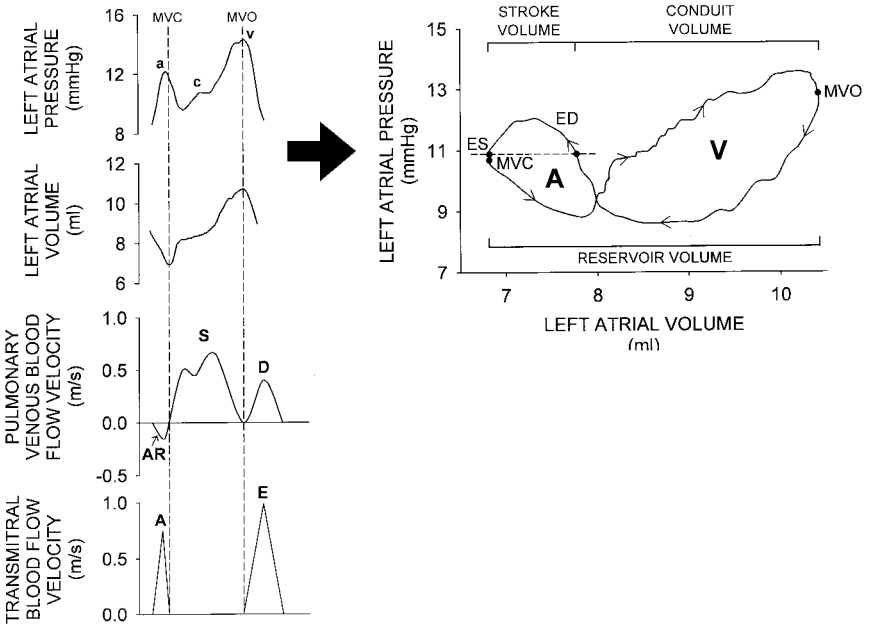

Fig. 1. Left atrial (LA) pressure and volume waveforms (*left*) and the corresponding steady state LA pressure–volume diagram (*right*) during a single cardiac cycle. Also illustrated are corresponding schematic pulmonary venous and transmitral blood flow velocity waveforms (*left*). The a wave of LA pressure corresponds to atrial contraction, the c wave represents the small increase in LA pressure that occurs early during left ventricular (LV) isovolumic contraction, and the v wave identifies the increase in LA pressure associated with LA filling. In contrast, the conformation of the LA volume waveform is monophasic. The resulting LA pressure–volume diagram inscribes a figure-of-eight pattern. The arrows indicate the time-dependent direction of movement around the diagram. The A portion of the diagram (*left loop*) incorporates active LA contraction and temporally proceeds in a counterclockwise fashion. The V portion of the diagram (*right loop*) represents passive LA reservoir function and proceeds in a clockwise manner over time. Mitral valve closure and opening (MVC and MVO, respectively) are also depicted on the individual waveforms and the LA pressure–volume diagram. Left atrial end-diastole (ED) was defined as the time point at which LA pressure (immediately before LA contraction) corresponded to LA end-systolic (ES) pressure (horizontal dashed line). Left ventricular isovolumic contraction, ejection, and the majority of isovolumic relaxation occur during the time between MVC and MVO illustrated on the LA pressure–volume diagram. The pulmonary venous blood flow waveform consists of an atrial reversal (AR) wave that corresponds to atrial contraction, a biphasic S wave that occurs during LV systole, and a D wave that occurs in conjunction with opening of the mitral valve (LV diastole; see text). The corresponding atrial systole (A) and early LV filling (E) waves of transmitral blood flow velocity are also illustrated. The AR and D waves of pulmonary venous blood flow velocity occur in conjunction with the A and E waves of transmitral blood flow velocity, respectively.

prolapse because excessive leaflet motion into the body of the LA occurs during early LV isovolumic contraction. During late LV isovolumic contraction, LV ejection, and the majority of LV isovolumic relaxation, pulmonary venous blood progressively fills the LA and gradually increases LA pressure, resulting in the LA v wave. This v wave may be accentuated during mitral regurgitation or reductions in LA compliance.[21]

Measurement of continuous LA volume has been successfully performed using a variety of techniques. Left atrial volume is often estimated invasively from long and short axis dimensions measured using epicardial orthogonal sonomicrometry assuming prolate ellipsoid LA geometry.[22] Left atrial volume determined using this method has been shown to correlate closely with true LA volume measured using water displacement–atrial cast studies,[23] but its use is restricted to the experimental laboratory. Noninvasive assessment of continuous LA volume in humans has been conducted using two- or three-dimensional[24] echocardiography with automated boundary detection,[18,25,26] tissue Doppler echocardiography,[27] radionuclide angiography,[28,29] cine computed tomography,[30] and magnetic resonance imaging.[24,31] In contrast to the LA pressure waveform, the LA volume waveform is essentially monophasic. Minimum LA volume occurs immediately after the completion of LA contraction and corresponds closely to the closure of the mitral valve. Maximal LA volume is observed immediately before the mitral valve opens. When combined with high-fidelity measurement of LA pressure, these determinations of continuous LA volume allow assessment of LA function in pressure–volume phase space.

The Left Atrial Pressure–Volume Diagram

As a result of the multiple deflection morphology of the LA pressure waveform, the steady state LA pressure–volume diagram consists of two loops arranged in a horizontal figure-of-eight pattern that incorporates both the active (A loop) and passive (V loop) components of LA function (fig. 1).[3] Beginning at LA end-diastole, the active component of the diagram proceeds in a counterclockwise fashion during atrial systole as blood is ejected from the LA into the LV through the mitral valve. In contrast to the observations in the LV pressure waveform that facilitate the definition of end-diastole, precise identification of LA end-diastole has varied between investigators. An easily detectable nadir in LA pressure may not always occur immediately before the onset of LA contraction as a result of continuous pulmonary venous return during diastasis. Left atrial end-diastolic pressure may be defined as the pressure occurring immediately before atrial contraction that corresponds to the LA end-systolic pressure[32] or may be chosen to occur at a fixed time point before peak LA pressure.[33] For the sake of this review, we will use the former definition of LA end-diastole pressure and its corresponding volume (EDV). Despite these relatively minor differences in the definition of LA end-diastole, most investigators have

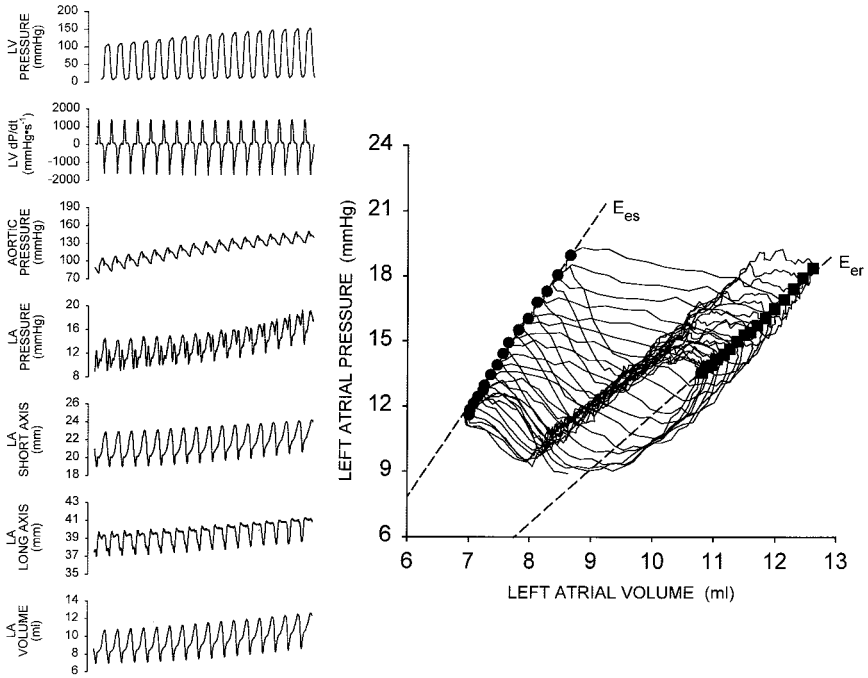

Fig. 2. Continuous left ventricular (LV) pressure, LV dP/dt, aortic pressure, left atrial (LA) pressure, LA short and long axis dimensions, and LA volume waveforms (*left*) and corresponding LA pressure–volume diagrams (*right*) resulting from intravenous administration of phenylephrine (200 μg) in a dog. The LA maximum elastance (solid dots) and end-reservoir pressure and volume (solid squares) for each pressure–volume diagram were used to obtain the slopes (E_{es} and E_{er}) and extrapolated volume intercepts of the LA end-systolic and end-reservoir pressure–volume relations using linear regression analyses to quantify myocardial contractility and dynamic chamber stiffness, respectively. Reprinted with permission.[33]

reported remarkably similar values of LA stroke volume using pressure–volume relations *in vivo*. Left atrial end-systole marks the end of atrial contraction and is most often defined by minimal LA volume. Maximal LA elastance (*i.e.*, the ratio of LA pressure to volume[34]) during contraction has also been used to define of LA end-systole in the normal heart analogous to definition of LV end-systole commonly used in LV pressure–volume analysis.[35,36] We will define LA end-systolic pressure and volume (ESV) at minimal LA volume in this review.

Identification of LA end-diastole and end-systole on the LA pressure–volume diagram facilitates the calculation of LA stroke volume (*i.e.*, EDV − ESV) and emptying fraction (*i.e.*, stroke volume/EDV). Although frequently used to describe LA contractile function, these ejection phase measures of LA pump performance are highly dependent on LA loading conditions and may not be used as strict quantitative indices of LA inotropic state. After the mitral valve closes, LA filling occurs during LV systole and isovolumic relaxation. Left atrial pressure and volume progressively increase as the chamber expands during the reservoir phase, forming the bottom portion of the A loop and the upper portion of the V loop. The area of the A loop represents active LA stroke work[37] analogous to LV stroke work defined as the area inscribed by the LV pressure–volume diagram.[38] Under normal circumstances, a small amount of blood contained within the LA at end-diastole refluxes into the pulmonary veins during atrial systole. This retrograde pulmonary venous blood flow does not usually appear in the LA pressure–volume diagram because the peristaltic-like configuration of atrial contraction and the unique valve-like anatomy of the pulmonary vein–LA junction minimize atrial regurgitation at normal LA pressures.[39] However, increases in the amount of this atrial regurgitant blood flow into the pulmonary veins occur during increases in LA pressure that may falsely elevate LA emptying fraction by reducing minimal LA volume as depicted in the LA pressure–volume diagram.

In contrast to the active part of the LA pressure–volume diagram, the passive component (V loop) proceeds in a clockwise direction over time, indicating that alterations in LA pressure and volume occurring during this period of the cardiac cycle result from external forces acting upon the LA. Total LA reservoir volume is easily determined from the pressure–volume diagram as the difference between maximum and minimum LA volumes obtained by direct examination of the A and V loops, respectively.[20] The area of the V loop represents the total passive elastic energy stored by the LA during the reservoir phase[20] and is an index of reservoir function.[40] Static compliance of the LA may be assessed from the pressure–volume diagram by determining the slope of the line between minimal LA pressure of the A loop and maximal LA pressure in the V loop.[41] Decreases in LA compliance are indicated by increases in the slope of this relation. For example, regional myocardial ischemia[42] or severe LV dysfunction[41] produces a decrease in LA compliance that may be quantified using this method. When LV pressure falls below LA pressure near the end of LV isovolumic relaxation (*i.e.*, during early LV diastole), the mitral valve opens, and blood that has accumulated in the LA during the reservoir phase flows down a pressure gradient into the LV. Left atrial emptying during this phase of LV diastole results in a rapid

decline in LA volume that forms the bottom portion of the V loop and also produces a concomitant rapid increase in LV volume. Additional pulmonary venous return also enters the LA during LV diastasis but does not substantially affect LA volume because this blood flows directly through the open mitral valve. Thus, the LA conduit phase is defined between mitral valve opening and LA end-diastole, and LA conduit volume is calculated as the difference between maximum and end-diastolic volumes (fig. 1). The areas inscribed by the A and V loops and the crossover point between these components of the steady state LA pressure–volume diagram are ultimately determined by the complex interrelation between LA loading conditions, LA and LV inotropic state, the rate and extent of LA relaxation, LA passive elastic properties, and blood flow through the pulmonary circulation. For example, an increase in LA preload or myocardial contractility or a reduction in LA afterload produce a corresponding increase in A-loop area consistent with the performance of greater stroke work. In contrast, a reduction in LA compliance decreases the relative size of the A loop by shifting the crossover point to the left.

Acute alterations in LA loading conditions produced by mechanical or pharmacological techniques may be used to assess intrinsic LA myocardial contractility using LA end-systolic pressure–volume relations (fig. 2) in the isolated[34,43] and intact heart.[41,44] Changes in LA inotropic state may be assessed by alterations in the slope (E_{es}) of the LA end-systolic pressure–volume relation[44] in a manner analogous to the well-established evaluation of LV contractility using this method.[45] For example, LA E_{es} has been used to quantify changes in LA inotropic state produced by chronic LV disease[41] (fig. 3) or volatile anesthetics[33] (fig. 4). Similar to the LV end-systolic pressure–volume relation,[46] the LA end-systolic pressure–volume relation has been shown to be a relatively heart rate– and load-independent index of LA contractile state *in vivo*.[34,44,47] The ratio of LA E_{es} derived from these pressure–volume diagrams and LV elastance (E_{LV}; determined using the ratio of LA end-systolic pressure and LA stroke volume) also provides a useful index of mechanical matching# between the LA and the LV that quantifies the relation between the contractile state of the LA and forces resisting its ejection (*e.g.*, LA afterload)[33,41] based on a series of elastic chamber models originally described for LV–arterial coupling.[48,49] For example, LA–LV coupling is markedly attenuated in the presence of reduced LV compliance in patients with heart failure.[41] In addition, this same series of differentially loaded LA pressure–volume diagrams may also be used to determine the dynamic compliance of the LA in response to alterations in load (fig. 2)[22,33,50] similar to the methods extensively validated in the LV.[51] This technique has been used to describe changes in dynamic LA stiffness produced by surgical maneuvers (*e.g.*, pericardectomy,[50] LA appendage excision[22]) and by the administration of vasoactive drugs, including volatile[33] and intravenous[52] anesthetics.

Doppler Echocardiographic Evaluation of Left Atrial Function

Analysis of the pulmonary venous blood flow velocity waveform is commonly used with or without concomitant evaluation of transmitral blood flow velocity to determine the severity of LV diastolic dysfunction,[53] quantify the degree of mitral regurgitation,[54–56] or estimate pulmonary capillary occlusion and mean LA pressures.[57–60] The pattern of pulmonary venous blood flow velocity also provides important information about the active and passive mechanical behavior of the LA in the normal and diseased heart (fig. 1). Measurement of the pulmonary venous blood flow velocity may be conducted invasively in the experimental laboratory using Doppler flow probes placed around[61] or implanted within[62] a pulmonary vein immediately proximal to the LA chamber. However, pulmonary venous blood flow velocity is most often determined noninvasively using transthoracic or transesophageal pulse wave Doppler echocardiography as previous studies[61,62] have demonstrated an excellent correlation between this modality and invasively derived techniques. Transesophageal echocardiography has evolved into the preferred noninvasive method for pulmonary venous blood flow velocity analysis[63] because the anatomical proximity of the right and left upper pulmonary veins to the esophagus provides optimal imaging windows with minimal ultrasound scatter by intervening tissue. It is important to note that patterns of pulmonary venous blood flow velocity have been shown to be highly dependent of LA loading conditions, LA contractile state, and LV function,[61,64] and conclusions about alterations in LA function derived using this methodology require interpretation within the constraints of these potential limitations.

The normal pulmonary venous blood flow velocity waveform is composed of a single small negative deflection that illustrates retrograde flow from the LA into the pulmonary veins (the atrial reversal [AR] wave; figure 1) and two large positive deflections that depict forward flow from the pulmonary veins into the LA chamber.[65] Another model of pulmonary venous blood flow analysis using four separate deflections that also incorporates specific flow during diastasis has also been proposed.[66] The first positive deflection (S wave) occurs during LV systole and isovolumic relaxation when the mitral valve is closed and displays a biphasic morphology.[61,63,67] The

Coupling or mechanical matching uses a definition of the cardiovascular system as a series of elastic chambers to describe the efficiency of transfer of blood from one chamber to another (such as between the LA and the LV or between the LV and the arterial circulation). For example, LV–arterial coupling is described as the ratio of LV to effective arterial elastance derived from pressure–volume relations.

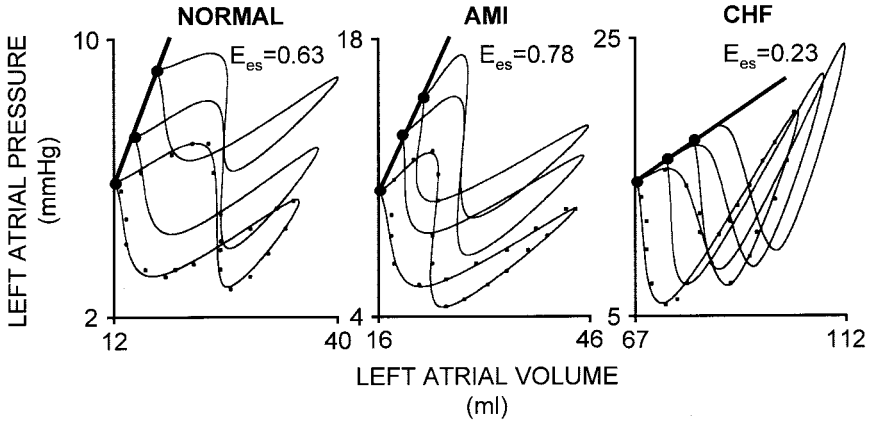

Fig. 3. Left atrial (LA) end-systolic pressure–volume relations (solid lines) obtained by volume administration in typical patients with normal cardiac function (*left*; controls) and those with acute myocardial infarction (AMI; *middle*) and congestive heart failure (CHF; *right*). A compensatory increase in LA contractility (E_{es}) is observed in patients with acute myocardial infarction. In contrast, patients with end-stage congestive heart failure demonstrate reduced LA E_{es}. Adapted with permission.[41]

magnitude and velocity–time integral of the S wave are indices of LA reservoir function that closely correlate with reservoir volume measured using the steady state LA pressure–volume diagram. For example, reductions in LA compliance observed during primary atrial disease states[21] cause declines in S-wave velocity indicative of compromised reservoir function.

The second positive deflection (D wave) of the pulmonary venous blood flow velocity waveform occurs immediately after the opening of the mitral valve. This forward pulmonary venous flow occurs as a result of the rapid drop in LA pressure that accompanies early LV filling and is an index of LA conduit function.[63] The peak velocity and velocity–time integral of the D wave are dependent upon the extent of early LV filling.[68] Thus, factors that attenuate early LV filling, such as delayed LV relaxation, may reduce D-wave velocity, indicating that LA conduit function has been adversely affected (fig. 5).[69,70] The velocity of the D wave is also reduced by the mechanical obstruction to early LV filling observed in patients with severe mitral stenosis, indicating that LA conduit function is dependent on normal mitral valve motion.[71]

Left atrial systolic performance is most often noninvasively evaluated using the A wave of transmitral blood flow velocity (fig. 1). The velocity–time integral of the transmitral A wave correlates with LA stroke volume determined from the LA pressure–volume diagram. The atrial reversal component of the pulmonary venous blood flow waveform is also directly related to LA contraction. Peak AR blood flow velocity and its corresponding velocity–time integral have been shown to correlate closely with mean LA pressure and volume, respectively.[59] These data verify that increases in the quantity of atrial regurgitant blood into the pulmonary veins occurs concomitant with elevations in LA pressure associated with increased LA preload, mitral valve disease, or severe LV dysfunction. The AR peak velocity and its velocity–time integral have been combined with peak transmitral A-wave velocity and its respective velocity–time integral to evaluate alterations in LA–LV coupling in patients with elevated LV end-diastolic pressure and LA afterload mismatch resulting from dilated, infiltrative, or hypertrophic obstructive cardiomyopathy.[72,73] These variables may also be used to noninvasively estimate LA $+dP/dt_{max}$ as an index of LA systolic function.[74]

Determinants of Left Atrial Function

Several early investigations compared the mechanical properties of isolated and intact atrial and ventricular myocardium and examined the factors that affect LA contractility. These studies demonstrated that the maximum velocity of shortening of LA myocardium was equal to[75] or greater than[76,77] LV myocardium under similar loading conditions. Left atrial myocardium was also less sensitive to increases in afterload than LV myocardium *in vivo*.[75] Systolic shortening of the LA is primarily dependent on LA preload and inotropic state in the intact heart,[78] but LA emptying fraction is reduced and conduit function enhanced when LA diameter exceeds optimal fiber length.[79] Alterations in autonomic nervous system activity produce characteristic changes in LA inotropic state that are similar to those observed in the LV.[80] For example, increases in LA emptying fraction and LA contribution to LV filling are observed in normal subjects performing a sustained hand grip[81] or rapidly standing from a supine position[82] in part as a result of activation of the sympathetic nervous system. In contrast, parasympathetic nervous system stimulation reduces LA pump performance,[80] although the resulting bradycardia may offset this response by enhancing LA preload and augmenting LA emptying fraction through the Frank-Starling mechanism.[78,83]

In the absence of mitral stenosis, LA afterload is determined primarily by the elastic properties of the LV and the pressure within this chamber. Thus, LA afterload and LA energy expenditure progressively increases as LV diastolic function deteriorates and LV pressure during diastole increases. Up-regulation of the β myosin isoform in atrial myocardium has been observed with increased LA mechanical work[84,85] that further augments the Frank-Starling response to LA dilatation. These compensatory actions enhance LA emptying fraction, but

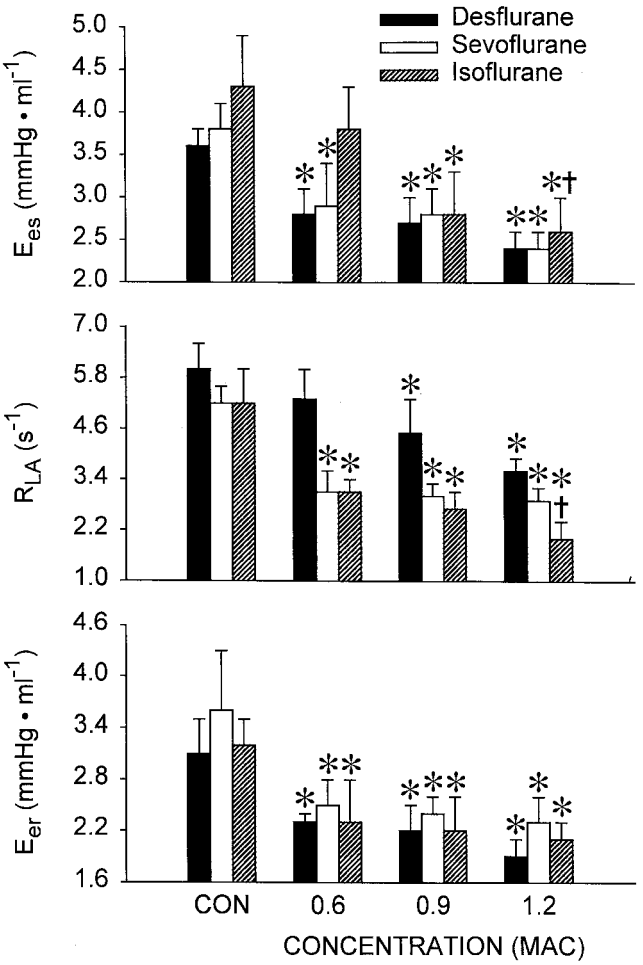

Fig. 4. Histograms depicting the slope (E_{es}; *top*) of the left atrial (LA) end-systolic pressure–volume relation, LA relaxation (R_{LA}; *middle*), and the slope (E_{er}; *bottom*) of the LA end-reservoir pressure–volume relation (dynamic chamber stiffness) under baseline conditions (CON) and during the administration of 0.6, 0.9, and 1.2 MAC desflurane (solid bars), sevoflurane (open bars), or isoflurane (hatched bars). Data are mean ± SEM from eight experiments conducted in acutely instrumented dogs in each group. *Significantly ($P < 0.05$) different from CON; †significantly ($P < 0.05$) different from 0.6 MAC. Reprinted with permission.[33]

increased workload imposed on the LA myocardium by LA afterload mismatch may contribute to the subsequent development of primary LA contractile dysfunction.[47,60,69] For example, an initial increase in LA emptying fraction has been observed early in the course of evolving heart failure,[86] but LA systolic function eventually becomes severely depressed as LV chamber stiffness and LV end-diastolic pressure continue to increase. Conversely, indirect increases in LV compliance produced by chronic arterial vasodilator therapy act to reduce LA afterload and improve the active contribution of the LA to LV stroke volume in patients with LV pressure-overload hypertrophy resulting from essential hypertension.[87] Left atrial remodeling and reduced compliance may also occur in response to LV diastolic dysfunction. These effects contribute to an exaggerated pressure response during small increases in LA volume, restrict pulmonary venous blood flow into the LA during the reservoir phase, and lead to the development of pulmonary edema.

Multiple factors combine to determine LA reservoir and conduit function. Relaxation of the LA chamber and the resultant reduction in LA pressure that occurs immediately after atrial systole facilitates forward flow from the pulmonary veins into the LA during early LV isovolumic contraction.[20,88,89] These events produce the early peak of the biphasic S wave of pulmonary venous blood flow velocity observed with Doppler echocardiography.[67] Left ventricular systolic function also plays a very important role in determining early LA reservoir function. The cardiac base descends toward the apex during LV systole, acting like a piston to draw additional blood from the pulmonary venous circulation into the LA.[20,29] The mitral annulus has been shown to descend approximately 1.3 cm during LV systole in normal subjects, but this annular motion is markedly attenuated in patients with dilated cardiomyopathy, and as a result, early pulmonary venous blood flow may be blunted or absent.[90] Transmission of the right ventricular systolic pressure pulse through the pulmonary circulation contributes to the increases in LA pressure and volume observed later during the reservoir phase[64,91] and has been shown to be responsible for the second peak of the biphasic pulmonary venous S wave.[67]

Intrinsic LA compliance plays a major role in determining reservoir and conduit function by facilitating venous return from the pulmonary circulation.[5] Atrial diseases in which LA compliance is markedly reduced are associated with impaired LA filling.[21,92,93] The LA appendage has been shown to be more compliant than the main body of the LA using pressure–volume relations in isolated[94] and intact LA preparations.[22,32] Temporary clamping[95] or surgical excision[22] of the LA appendage reduced LA compliance, decreased reservoir function as quantified by declines in the pulmonary venous blood flow velocity S/D ratio, and attenuated the rate of LV rapid filling. These data indicate that the LA appendage plays an important role in LA reservoir function, especially during increases in LA pressure or volume.[94,95] The pericardium has also been shown to affect LA distensibility as pericardiectomy increased LA compliance, enhanced early LV filling rate, and augmented conduit to a greater extent than reservoir function in an elegant study using both LA pressure–volume relations and Doppler echocardiographic analyses of transmitral and pulmonary venous blood flow velocities.[50]

Exercise produces characteristic changes in the determinants of LA function in humans. Left atrial myocardial contractility increases and the LA contribution to cardiac output is more pronounced during aerobic exercise[96,97] as a result of sympathetic nervous system activation. Left

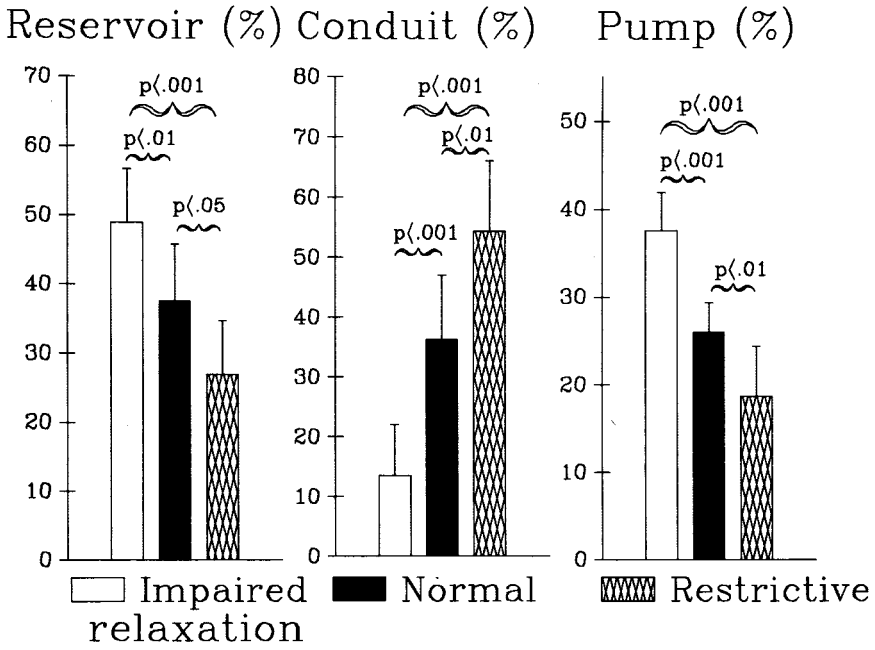

Fig. 5. Histograms illustrating the percent contribution to left ventricular (LV) filling volume of left atrial (LA) reservoir, conduit, and contractile function evaluated with pulmonary venous blood flow Doppler echocardiography in patients with normal, impaired relaxation, and restrictive LV filling patterns. Note that impaired relaxation is characterized by increases in LA reservoir and contractile function but conduit function is reduced. In contrast, a restrictive LV filling pattern is associated with enhanced conduit function and reduced reservoir and contractile contributions to total LV filling volume. Reprinted with permission.[69]

atrial reservoir but not conduit function is augmented during exercise as quantified by pulmonary venous blood flow velocity measurements.[97] This increase in LA reservoir function combines with a pronounced reduction in minimum LV pressure resulting from enhanced LV isovolumic relaxation[98] to produce a larger LA–LV pressure gradient during early LV filling,[97] thereby augmenting LV stroke volume and cardiac output during exercise. In contrast, a compensatory increase in conduit function has been observed concomitant with LA dilatation in well-conditioned athletes at rest compared to normal subjects.[99]

Increases in LA volume and reductions in passive LA emptying have been observed in healthy elderly subjects (aged $>$ 70 yr) studied using a combination of transmitral Doppler and two-dimensional echocardiographic techniques.[100] Dilatation of the LA produces a compensatory increase in LA ejection force[101] and augments active LA contribution to LV filling.[100,102,103] Left atrial storage fraction (defined by the ratio of storage volume of the LA during reservoir phase to total LV stroke volume) increases in elderly patients in association with LA dilatation and is inversely related to LV ejection fraction.[104] The LA dilatation observed in elderly patients may contribute to increases in LA wall stress and eventual LA contractile dysfunction.[105]

Mechanical Consequences of Left Atrial Dysfunction

Stiff Left Atrium Syndrome. An isolated reduction in LA compliance that occurs independent of mitral valve disease or LV dysfunction is the pathognomonic finding in patients with stiff LA syndrome.[21,106] Left atrial dilatation is a common associated finding in this syndrome, but the increase in LA volume does not coincide with observed decreases in LA compliance.[107] Left atrial reservoir function is severely compromised as a result of the noncompliant LA. Cardiac catheterization typically reveals a large LA pressure v wave without evidence of mitral regurgitation or a significant mitral valve gradient.[106] Patients with this disorder invariably develop pulmonary hypertension, pulmonary edema, and right ventricular failure because LA filling is profoundly impaired, initially during exercise but later at rest as well.[21] A time-varying load model of the pulmonary vasculature supported these clinical observations and indicated that isolated reductions in LA compliance cause increases in pulmonary and LA pressures that are similar to those observed in stiff LA syndrome.[108] Severe fibrosis and calcification of the LA are characteristic autopsy findings in these patients.[21]

Atrial Fibrillation. Loss of LA contraction with the onset of atrial fibrillation is commonly associated with a reduction in cardiac output. An early study by Mitchell and Shapiro[11] demonstrated that several compensatory mechanisms are recruited to maintain cardiac output at rest or during mild to moderate cardiac stress (*e.g.*, exercise) in the presence of atrial fibrillation, but declines in cardiovascular performance occur with the loss of atrial systole during more profound stress or concomitant LV dysfunction. A reduction in LA compliance and an increase in the LA pressure peak v wave have been observed with onset of atrial fibrillation.[18,109] The increase in LA pressure enhances the LA–LV pressure gradient during early LV filling to maintain stroke volume in the absence of atrial booster pump function.[110] Administration of dobutamine reduces LA chamber stiffness and LA size assessed with LA pressure–area relations in humans with atrial fibrillation (fig. 6), presumably by

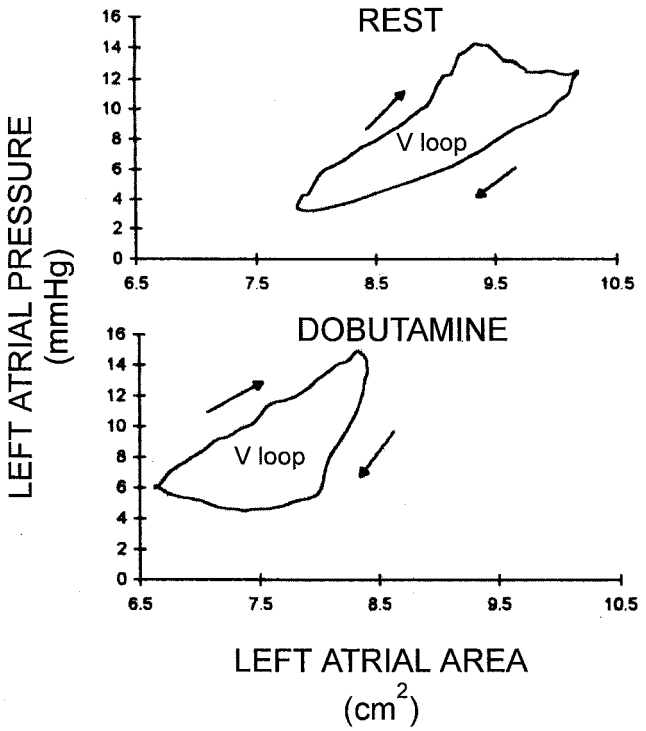

Fig. 6. Typical left atrial (LA) pressure–area diagrams under resting conditions (*top*) and during administration of dobutamine (*bottom*) in a patient with atrial fibrillation. The arrows indicate the temporal movement of the diagram. Note that no active work is performed during atrial fibrillation. The clockwise movement of each diagram indicates that forces external to the LA determine the observed changes in pressure and volume over time. Dobutamine produced a decrease in LA minimum and maximum volumes consistent with enhanced left ventricular (LV) contractility and reduced LA afterload. Reprinted with permission.[18]

indirectly improving LA afterload.[18] Left atrial reservoir function and early LV filling are maintained by increased LA compliance during infusion of dobutamine despite the reduction in LA preload, and LV stroke volume increases as a result of direct positive inotropic effects on LV myocardium.[18] The S wave of pulmonary venous blood flow velocity may be attenuated in patients with atrial fibrillation because LA relaxation after active contraction does not occur.[111] Nevertheless, the S wave and its corresponding velocity–time integral provide effective indices of LA filling, and LA reservoir function has been shown to be preserved to a greater extent in patients with isolated atrial fibrillation than in those with dilated cardiomyopathy using this technique.[111]

Atrial fibrillation most often results from sustained increases in LA afterload that cause enlargement of the LA chamber.[112] Conversely, progressive LA dilatation also occurs in patients with atrial fibrillation independent of alterations in LV function or geometry.[113] As a result, the presence of atrial fibrillation may establish a positive feedback loop that precipitates further LA enlargement, reduces the likelihood that chemical or electrical cardioversion will be successful, and increases the probability of thrombus formation. Atrial fibrillation increases LA myocardial oxygen consumption and coronary blood flow and reduces the peak reactive hyperemic response.[114] Coronary vasodilator reserve is not completely exhausted during atrial fibrillation, but limitations in coronary flow reserve may also contribute to development of LA ischemia, fibrosis, and further perpetuation of the arrhythmia.[115] Atrial fibrillation and other atrial tachyarrhythmias[116] also produce a characteristic biatrial myopathy[117] that is very similar to experimental tachycardia-induced cardiomyopathy.[118] The presence of this dysfunctional atrial myocardium also contributes to continuation of the atrial fibrillation.[118] Thus, preservation of normal sinus rhythm and atrial contraction may eliminate the detrimental effects of LA dilatation, avert the potentially adverse reductions in atrial perfusion, and prevent the development of atrial cardiomyopathy that sustain atrial fibrillation once it has been established.[115,117,119] Advanced age has been identified as the major risk factor for the development of postoperative atrial fibrillation that is associated with increased morbidity and prolonged hospitalization.[120]

Atrial stunning occurs after defibrillation from or spontaneous conversion to sinus rhythm after brief or prolonged periods of atrial fibrillation that reduce the active contribution of the LA to LV filling and increases thromboembolic risk.[121,122] The degree of contractile dysfunction observed during atrial stunning after cardioversion is inversely related to LA chamber size.[123] Reduced LA emptying fraction has been observed after 30 min of atrial fibrillation in dogs.[124] Treatment with verapamil attenuated but the calcium channel agonist Bay K 8644 exacerbated the development of atrial stunning, suggesting that this process is mediated in part by intracellular calcium overload.[125] As few as several minutes of atrial fibrillation may be sufficient to produce stunned atrial myocardium after cardioversion in humans.[126] Verapamil also improved the recovery of LA emptying fraction in this setting.[126] However, inhibition of Na^+–H^+ exchange more effectively reduced the severity of LA stunning in a canine rapid pacing model of atrial fibrillation than nifedipine.[127] These data are similar to those observed in stunned ventricular myocardium[128] and implicate a role for intracellular acid–base balance and its indirect action on the Na^+–Ca^{2+} exchanger in the pathophysiology of atrial stunning.

Left atrial stunning was demonstrated after spontaneous conversion of atrial fibrillation of only 60 min duration to sinus rhythm in normal canine hearts.[129] Interestingly, LA appendage stunning was more prolonged than contractile dysfunction of the LA body,[129] suggesting potential mechanisms by which overall LA emptying fraction remains depressed[130] and thrombosis may occur in the appendage after cardioversion.[129] The LA appendage displays a characteristic pattern of emptying that may be assessed by Doppler echocardiographic measure-

ment of peak outflow blood flow velocity.[122,131] Thrombus formation has been shown to be associated with appendage dilatation and contractile dysfunction in patients during sinus rhythm.[132] Thus, it is not surprising that LA appendage dysfunction before cardioversion predisposes to thrombosis.[122] Left atrial appendage stunning also occurs in patients with atrial flutter, but the risk of thromboembolic events after cardioversion appears to be less in these patients as compared to those with atrial fibrillation, presumably because LA appendage systolic function is maintained to a greater extent.[133]

Electrical cardioversion of atrial fibrillation produces LA pump dysfunction that is more severe and persists for a greater duration than either spontaneous conversion to or pharmacologically induced restoration of normal sinus rhythm.[134] For example, cardioversion using amiodarone produces relatively rapid restoration of LA emptying fraction in the vast majority of patients with new-onset atrial fibrillation.[135] In contrast, endocardial defibrillation or external cardioversion may produce LA chamber and appendage stunning in these patients.[136–138]

Internal atrial defibrillation in particular results in depressed LA emptying fraction and may cause accumulation of spontaneous echocardiographic contrast (an indicator of blood stasis and a risk factor for thromboembolism) or the development of thrombosis after cardioversion,[136] but the severity of stunned atrial myocardium appears to be independent of the electrical energy used for cardioversion in this setting.[137] Atrial stunning and transient spontaneous echocardiographic contrast have also been observed after a 15-min episode of atrial fibrillation followed by internal defibrillation in patients with documented cardiac disease.[138] Atrial stunning persisted but spontaneous echo contrast resolved rapidly after defibrillation in this study, suggesting that thromboembolic risk may be remain relatively low after restoration of sinus rhythm despite a continued reduction in LA emptying fraction.[138] In contrast to atrial stunning observed after defibrillation following a short episode of atrial fibrillation, cardioversion-induced restoration of sinus rhythm in patients with chronic atrial fibrillation is associated with a gradual increase in LA emptying fraction and cardiac output over 4 weeks in the majority of patients. However, cardiac output may decrease initially in some patients. This initial depression of cardiac output may persist for up to a week after cardioversion and contributes to an increased incidence of pulmonary edema and thromboembolic complications.[139] Another study demonstrated that LA emptying fraction and reservoir function gradually improve over 3 months after cardioversion of chronic atrial fibrillation.[140]

Dilated and Infiltrative Cardiomyopathy. Reductions in LA emptying fraction occur in patients with idiopathic dilated cardiomyopathy concomitant with LA dilatation consistent with the presence of a primary atrial myopathy.[141] These findings contrast with those observed in patients with pressure-overload hypertrophy or ischemic cardiomyopathy in which declines in LA emptying fraction occur primarily as a consequence of increases in LA afterload.[141,142] Histologic evidence of atrial fibrosis is more apparent in patients with dilated cardiomyopathy as compared to those with remote myocardial infarction, suggesting that a primary atrial disease process occurs in dilated cardiomyopathy that cannot be attributed solely to LA mechanical overload.[143] Exercise capacity is directly related to LA emptying fraction and inversely related to LA volume in dilated cardiomyopathy, observations that emphasize the critical importance of LA pump performance to functional capacity in patients with this disease.[144] Marked reductions in LA systolic function and kinetic energy transfer to the LV have also been observed in patients with AL (amyloid light chain) amyloidosis (formerly known as primary amyloidosis) that occur as a consequence of amyloid infiltration into atrial myocardium[92,145] and are associated with a grave prognosis.[146] However, LA emptying fraction remains relatively normal before amyloid infiltration becomes echocardiographically apparent.[145] Declines in LA compliance also occur in both dilated and infiltrative cardiomyopathy that attenuate LA reservoir function, increase pulmonary arterial pressures, and contribute to the development of right ventricular failure.

Experimental models of atrial myopathy provide additional insight into the mechanical consequences of LA contractile dysfunction that mimic many of the features observed in dilated and infiltrative cardiomyopathy. Rapid atrial pacing (400 beats/min) for 1 week in dogs produces an atrial myopathy characterized by impaired global and regional LA systolic shortening with relative preservation of LV function.[147] An increase in the transmitral E-to-A ratio and a decrease in the pulmonary venous S-to-D ratio were observed consistent with reduced LA emptying fraction and increased conduit function, respectively.[147] Rapid atrial pacing of longer duration (6 weeks) also produces decreases in LA compliance, LA systolic dysfunction, impaired reservoir function, and enhanced conduit function as assessed with LA pressure–volume relations.[148] Interestingly, LA failure induced by rapid atrial pacing has little or no effect on cardiac output and right ventricular function if LV function remains normal because increases in conduit function offset reductions in emptying fraction and reservoir capability.[148,149] However, augmented conduit function is unable to compensate for impaired LA systolic performance and reservoir function in the presence of concomitant LV diastolic dysfunction.[149] This experimental finding may be especially important in dilated and infiltrative cardiomyopathy during which profound abnormalities in LV systolic and diastolic function are observed.

Hypertrophic Obstructive Cardiomyopathy. Substantial increases in LA chamber stiffness and reductions in reservoir function that may influence cardiac output have been reported in patients with hypertrophic obstructive cardiomyopathy.[150] These declines in LA compliance are proportionally greater in hypertrophic obstructive cardiomyopathy as compared to other forms of pressure-overload LV hypertrophy.[82] Declines in LA emptying fraction may also occur earlier in the natural history of hypertrophic obstructive cardiomyopathy.[151] Increases in LA afterload produced by hypertrophied LV myocardium and elevations in LV end-diastolic pressure contribute to a reduction in LA emptying fraction and increase retrograde pulmonary venous blood flow during atrial systole.[152] Mitral regurgitation during middle and late LV systole also markedly attenuates LA reservoir function by dramatically increasing LA pressure. Patients with hypertrophic obstructive cardiomyopathy demonstrate abnormal echocardiographic indices of LA relaxation and filling.[93] These findings support the contention that hypertrophic obstructive cardiomyopathy is a disease that directly affects both atrial and ventricular myocardium[153] regardless of the distribution of LV hypertrophy or the severity of LV outflow tract obstruction.[93] Nonsurgical septal reduction[154] in patients with hypertrophic obstructive cardiomyopathy reduces LA size and improves LA ejection force and kinetic energy expenditure in conjunction with a decline in the LV outflow tract pressure gradient, resolution of mitral insufficiency, and improved LA diastolic function.[155,156] These findings are associated with concomitant increases in passive LV filling and exercise capacity.[156]

Heart Transplantation. Passive emptying of the LA is impaired in patients after heart transplantation because of alterations in LV diastolic function in the donor organ.[157] As a consequence, LA preload is greater in these patients, and LA stroke volume may be maintained or even augmented by activation of the Frank-Starling mechanism. This effect plays an important role in preserving LV stroke volume despite reductions in intrinsic LA myocardial contractility.[157,158] The contractile elements of the donor heart dominate overall LA booster pump function after heart transplantation. Nevertheless, overall LA emptying fraction may be reduced in the transplanted as compared to the normal heart because some dysfunctional LA myocardium remains intact in the recipient.[159] Left atrial emptying fraction may also be depressed after heart transplantation as a result of atrial contractile asynchrony because recipient atrial remnants are electrically isolated and contract independent of donor atrial and ventricular myocardium.[160] Heart transplantation using selective bicaval and pulmonary venous anastomoses is associated with relative preservation of active and passive LA function as compared to conventional biatrial techniques.[161]

Left Atrial Adaptation to Left Ventricular Dysfunction

Myocardial Ischemia and Infarction. Acute myocardial ischemia or infarction resulting from brief or prolonged occlusion of the left anterior descending coronary artery (LAD) produces LA dilation, enhances LA preload, and increases LA emptying fraction[162] by the Frank-Starling effect[37,40] that serves to maintain LV stroke volume despite the reduction in LV systolic function.[163] These compensatory alterations in LA size and emptying fraction are often manifested by electrocardiographic evidence of LA stress during and after the acute ischemic event.[164] Left atrial pressure–area relations derived using a micromanometer and echocardiographic automated boundary detection in patients with isolated LAD stenoses indicate that LV supply or demand ischemia produced by balloon occlusion or rapid pacing, respectively, is associated with enhanced LA stroke work (*i.e.*, A-loop area) and reservoir function (*i.e.*, V-loop area) concomitant with increases in LA preload (fig. 7).[42] These findings confirmed the well-established role of augmented atrial booster pump function for the maintenance of cardiovascular performance in patients with acute myocardial infarction.[12] In contrast, patients with left circumflex coronary artery (LCCA) stenoses of similar severity failed to display enhanced LA emptying fraction but instead demonstrated increases in LA static compliance and conduit function during supply or demand ischemia.[42] These observations were attributed to the presence of LA ischemia because coronary arterial blood supply to the LA is derived from branches of the LCCA.[165,166] Thus, LA systolic compensation for LV ischemia is adversely affected by the presence of simultaneous LA ischemia. Pressure–volume analysis of adaptation to increases in mechanical load associated with remote myocardial infarction and ventricular hypertrophy also indicated that augmented LA emptying fraction contributes to the preservation of LV filling, but adverse reductions in static LA compliance (fig. 8) and reservoir function were also observed that may limit further compensatory responses,[41] especially during exercise.

Left atrial afterload mismatch and impaired LA–LV coupling have been observed in dogs during acute myocardial infarction produced by prolonged LAD occlusion despite simultaneous increases in LA emptying fraction.[167] This afterload mismatch may be attributed to elevations in LV end-diastolic pressure resulting from LV diastolic dysfunction. Administration of dobutamine reversed these detrimental effects by further enhancing LA emptying fraction and indirectly reducing LV chamber stiffness *via* declines in arterial load.[167] Thus, administration of positive inotropic drugs or arterial vasodilators may facilitate more efficient transfer of LA stroke volume to the LV in the presence of ischemic injury. The importance of efficient mechanical matching between the LA and LV after myocardial infarction is further emphasized

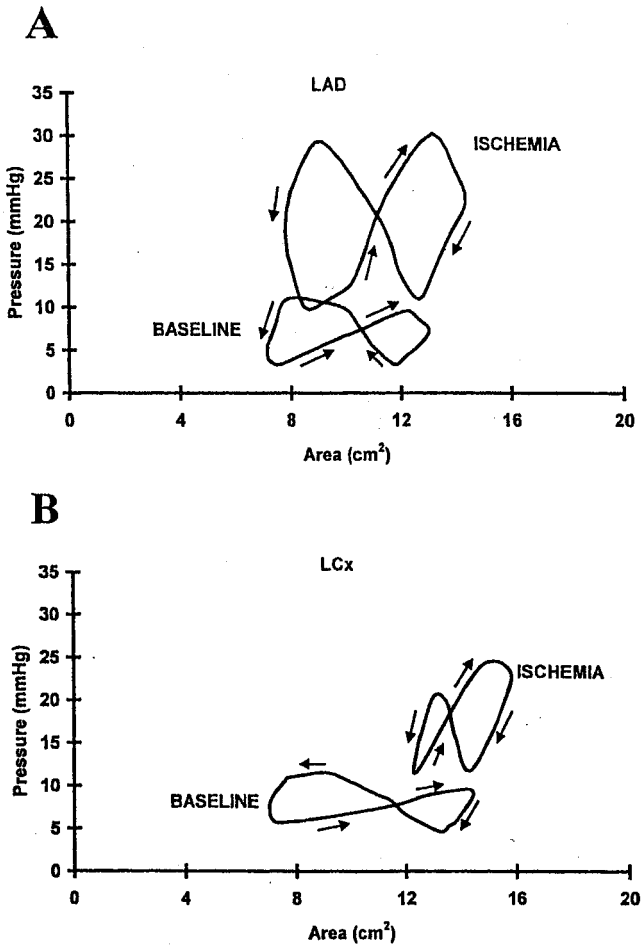

Fig. 7. Typical left atrial (LA) pressure–area diagrams under control conditions and immediately after pacing-induced ischemia obtained from a patient with a left anterior descending coronary artery (LAD) stenosis (*A*, *top*) and a patient with a left circumflex coronary artery (LCx) stenosis (*B*, *bottom*). An upward shift of the LA pressure–area diagram was observed in the patient with the LAD stenosis. In contrast, an upward and rightward shift in the diagram was observed in the patient with the LCx stenosis. The area of the A loop of the LA pressure–area diagram increased in the patient with the LAD stenosis but not in the patient with the LCx stenosis. Reprinted with permission.[42]

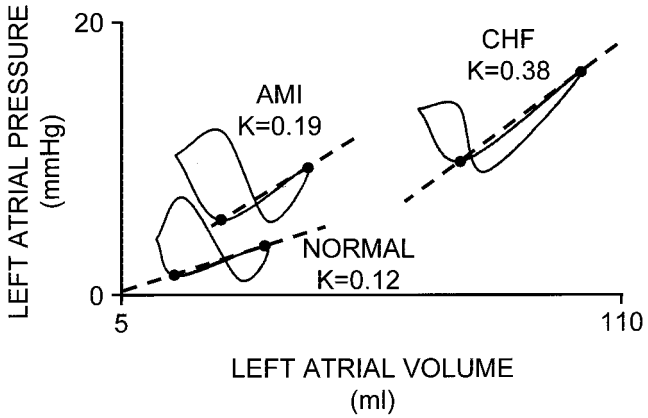

Fig. 8. Steady state left atrial (LA) pressure–volume diagrams in typical patients with normal cardiac function (*bottom left*) and those with acute myocardial infarction (AMI; *top left*) and congestive heart failure (CHF; *top right*). Linear regression lines (dashed lines) indicate LA stiffness (K) measured from the bottom of the A loop and the top of the V loop (solid dots). Note that both acute myocardial infarction and congestive heart failure increase LA stiffness. Adapted with permission.[41]

by the observations that LV dilatation and increased LV end-diastolic pressure also may lead to progressive reductions in LA stroke volume index in patients with remote myocardial infarction.[168] Such an inverse correlation between LA stroke volume and LV end-diastolic pressure has also been described in patients with symptomatic coronary artery disease using Doppler echocardiography.[169] Left atrial systolic dysfunction associated with afterload mismatch contributes to the development of pulmonary edema and right ventricular failure[170] and has been shown to be closely related to secretion of atrial natriuretic peptide as a compensatory response to perceived volume overload.[171] Nevertheless, LA emptying fraction may be relatively preserved even in patients with severe ischemic cardiomyopathy,[142] in contrast to the findings in those with idiopathic dilated[141] or hypertrophic obstructive cardiomyopathy.[151] Interestingly, the extent of LA emptying fraction at rest has been shown to predict LV diastolic filling and cardiac output during exercise in patients with recent myocardial infarction.[172] These latter findings emphasize the critical role of enhanced LA emptying fraction and relatively normal LA–LV coupling in determining the functional capacity of these patients.

Pressure-Overload Hypertrophy. Left ventricular pressure-overload hypertrophy caused by pathologic conditions, such as essential hypertension and aortic stenosis, delays LV isovolumic relaxation, impairs early LV filling, increases LV chamber stiffness, and elevates LV filling pressures.[173] These factors combine to increase LA afterload and produce compensatory LA dilatation.[174] In the absence of other demonstrable causes, this enlargement of the LA in patients with hypertension appears to be most highly correlated with elevated nocturnal arterial blood pressure[175] and may represent an early clinical sign of hypertensive heart disease detected using two-dimensional echocardiography before any electrocardiographic changes become evident.[176] Increases in LA reservoir and reductions in conduit function have been observed in patients with long-standing hypertension that occur as a consequence of LV diastolic dysfunction and elevations in LA afterload.[87,174,177] Impaired LA–LV coupling resulting from this afterload mismatch has also been quantified in patients with pressure-overload hypertrophy.[72] The increase in LA preload associated with LA dilatation contributes to enhanced LA emptying fraction by activation of the Frank-Starling mechanism that is partially responsible for maintenance of LV stroke volume in hypertensive patients.[174] Sympathetic nervous system stimulation also appears to play a role in augmented LA inotropic state in patients with

essential hypertension, in contrast to the findings in patients with remote myocardial infarction.[40] However, chronic increases in active LA workload and energy expenditure may produce LA hypertrophy, reduce LA compliance, compromise reservoir function, and contribute to an eventual reduction in LA pump performance.[87] Such a reduction in LA systolic function may eventually contribute to the development of heart failure in patients with pressure-overload hypertrophy. Nevertheless, LA emptying fraction appears to be relatively well-preserved in the vast majority of patients with essential hypertension, in contrast to those with idiopathic dilated[141] or hypertrophic obstructive cardiomyopathy[151] in whom evidence of atrial myopathy has been demonstrated. Left atrial dilatation may contribute to the development of atrial arrhythmias in patients with hypertension and may be associated with paroxysmal atrial fibrillation and subsequent atrial stunning that significantly impair LV filling.[178] Antihypertensive therapy with a diuretic or an angiotensin-converting enzyme inhibitor normalizes alterations in indices of active and passive LA function concomitant with regression of LV hypertrophy.[87] Nifedipine has also been shown to reverse hypertension-induced alterations in LA function concomitant with improvements in LV diastolic function in humans.[179]

The contribution of atrial systole to LV filling and performance in patients with severe aortic stenosis is well-known[180] as the loss of LA pump function with the onset of atrial fibrillation is often poorly tolerated in these patients.[181] Left atrial dilatation in aortic stenosis is directly related to LV mass.[182] Frank-Starling–induced increases in LA emptying fraction serve to counterbalance the depressed reservoir function that occurs as a result of decreases in LV compliance. Thus, LA dilation and augmented LA systolic function are important compensatory mechanisms that serve to maintain LV stroke volume and cardiac output in these patients.[182]

Mitral Valve Disease. The mitral valve does not contribute substantially to resistance of blood flow from the LA to the LV under normal circumstances. However, restricted motion of the mitral apparatus becomes the predominant factor affecting LA afterload in mitral stenosis. Left atrial pressure and volume increase in direct proportion to the severity of the stenosis. Despite the increase in LA preload, the contribution of atrial systole to total LV filling in patients with mitral stenosis is reduced during sinus rhythm in comparison to normal subjects because LA contractile force cannot overcome the mechanical obstruction.[180] Intrinsic myocardial contractility of the LA is depressed in long-standing mitral stenosis as a result of chronic elevations in workload and wall stress,[183] and the contribution of the LA appendage to overall LA emptying fraction is also reduced.[184] As a result, loss of LA contractile function with the onset of atrial fibrillation may be less responsible for hemodynamic decompensation in patients with mitral stenosis than a rapid ventricular response and limited LV diastolic filling time.[25,185]

Left atrial compliance is an important determinant of LA pressure in patients with mitral stenosis during normal sinus rhythm in addition to the pressure gradient across the mitral valve.[186] Declines in LA compliance have been shown to correlate with increases in LA pressure and progressive narrowing of the mitral valve orifice.[187] These reductions of LA compliance and elevations in LA pressure are associated with compromised reservoir function. Left atrial pressure–area relations have been recorded in patients with mitral stenosis before and after retrograde balloon valvuloplasty that provide important insights into the mechanical consequences of this disease.[188] Significant increases in A-loop area were observed after valvuloplasty in the presence of sinus rhythm consistent with enhanced emptying fraction and stroke work (fig. 9). In contrast, V-loop area increased after the procedure in patients with atrial fibrillation, indicating that reservoir function had been improved. Increases in LA static compliance also occurred concomitant with reductions in pressure and volume in both groups.[188] These data confirm that mitral stenosis produces profound alterations in LA function that may be acutely reversed in large part with valve repair.

The effects of chronic mitral regurgitation on LA function have been examined using LA pressure–dimension relations.[189] Left atrial size and mass increase during chronic mitral regurgitation, and the LA contribution to LV filling is augmented in sinus rhythm as a result of activation of the Frank-Starling mechanism. The LA also becomes more compliant, and reservoir function may be enhanced. Thus, enlargement of the LA is an important compensatory mechanism in chronic mitral regurgitation by attenuating increases in LA pressure while simultaneously maintaining adequate LV filling volume.[189] However, LA volume overload and pronounced dilatation of the chamber may eventually lead to reductions in LA emptying fraction because optimal myocardial fiber length is exceeded. This concept is emphasized by the observation that LA size alone predicts outcome after mitral valve replacement in patients with symptomatic chronic mitral regurgitation because LA size reflects the severity and duration of the disease process.[190] The v-wave magnitude of the LA pressure waveform has been shown to be inversely related to LA compliance, and increases in the amplitude of the v wave indicate increasing severity of acute mitral regurgitation and decreased LA compliance during incremental balloon commissurotomy.[191]

Regurgitant blood flow during LV systole attenuates, abolishes, or reverses early LA expansion and forward flow from the pulmonary veins dependent upon the degree of the regurgitation.[25] This process contributes to the development of pulmonary hypertension and

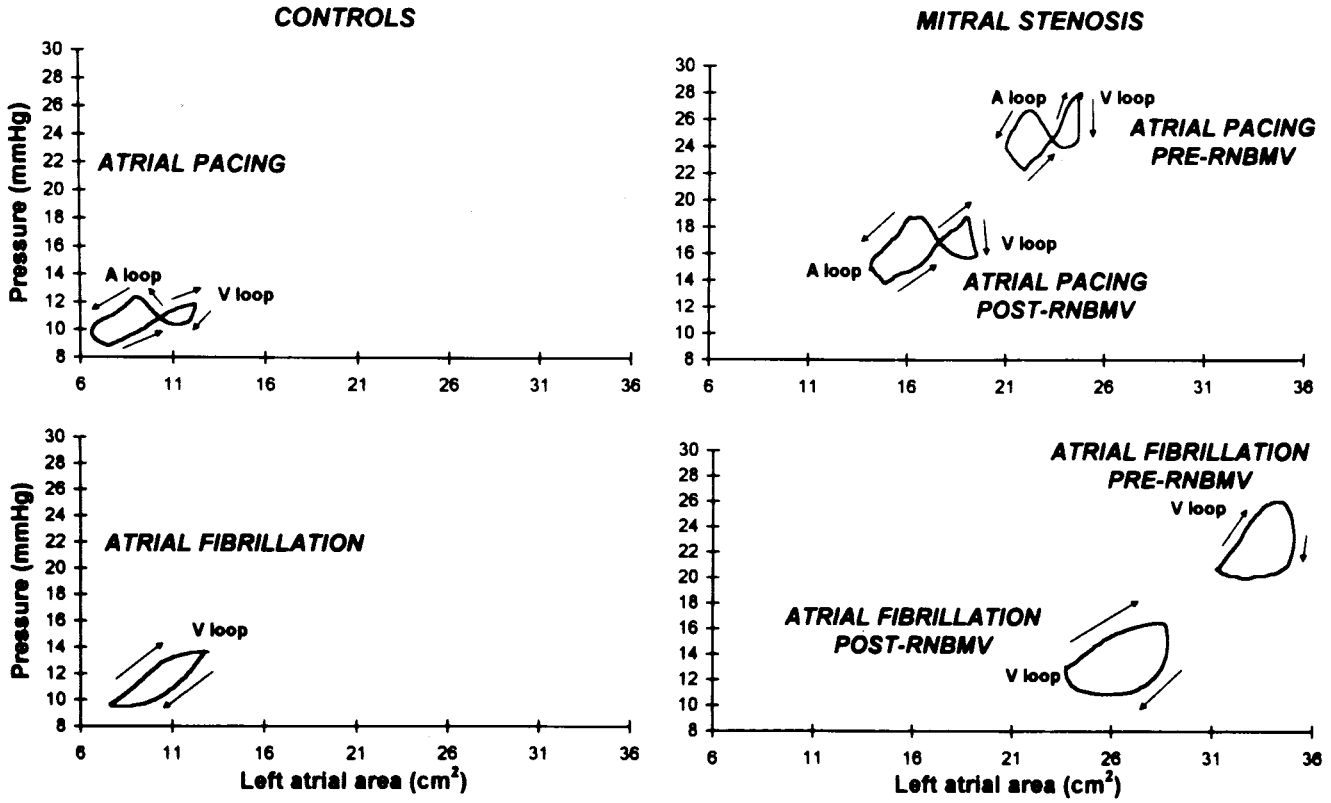

Fig. 9. Representative left atrial (LA) pressure–area diagrams from a normal subject (*top left*), a patient with atrial fibrillation (*bottom left*), and two patients, one with sinus rhythm (*top right*) and the other with atrial fibrillation (*bottom right*), with mitral stenosis before and after balloon mitral valvuloplasty. RNBMV = retrograde nontransseptal balloon mitral valvuloplasty. Reprinted with permission.[188]

right ventricular dysfunction. The pulmonary venous blood flow velocity pattern assessed with Doppler echocardiography has been shown to be a very sensitive index of the severity of mitral regurgitation that is highly correlated with angiographic grade of valve disease.[54,55] Acute mitral regurgitation of increasing severity is initially associated with augmented LA emptying fraction as a result of LA dilatation. However, the LA contribution to LV filling rapidly declines as the regurgitant fraction increases because LA volume overload occurs. Treatment with sodium nitroprusside improves LA emptying fraction during severe acute mitral regurgitation by decreasing excessive LA stretch, restoring LA geometry, and reestablishing more optimal Frank-Starling relations.[192] Enhanced LA emptying fraction occurring as a consequence of vasoactive drugs in acute mitral regurgitation most likely results from reductions in LV afterload, decreases in LV volume overload, and improvements in mitral valve geometry and competence.[193]

Heart Failure. Left atrial pressure–volume analysis of LA adaptation to evolving LV failure produced by rapid ventricular pacing has been examined in a canine model of dilated cardiomyopathy.[47] The development of heart failure over 3 weeks of pacing was associated with progressive increases in LA volume, stroke volume, and A-loop area (LA stroke work). Myocardial contractility evaluated with end-systolic pressure–volume relations was unchanged, but LA mean circumferential fiber shortening was reduced in a time-dependent manner. An up-regulation of the β myosin heavy chain was also observed concomitant with decreased velocity of LA contraction and increased mechanical work.[47] These latter findings indicate that compensatory increases in LA emptying fraction initially occur during developing LV failure. Temporal improvements in LV systolic function were observed after cessation of rapid ventricular pacing in this canine model, but LA systolic ejection rate was persistently depressed as a result of continued LV diastolic dysfunction, LA hypertrophy, and alterations in myosin heavy chain isoforms.[194] Intrinsic LA dysfunction quantified using a variety of invasive and noninvasive techniques eventually occurs in heart failure because persistent increases in LA afterload and energy expenditure resulting from reduced LV compliance and elevated LV diastolic wall stress are present.[41,86,183,195–197] Interestingly, contractile function of the LA appendage may be an accurate predictor of LV end-diastolic pressure in patients with heart failure.[198] Left atrial emptying fraction is inversely and LA maximal volume is directly related to plasma renin activity, aldosterone concentration, and atrial natriuretic peptide concentration in patients with heart failure resulting from idiopathic dilated car-

diomyopathy,[199] suggesting that hormonal compensatory responses are correlated closely with LA function under these conditions. Primary LA systolic failure may be observed even during normal sinus rhythm in the presence of severe, long-standing LV dysfunction because of complete exhaustion of contractile reserve.[200] Nevertheless, treatment of heart failure may be associated with improvements in LA emptying fraction as LV stiffness declines, LA afterload mismatch is reduced, and LA–LV coupling is normalized.[41,86] For example, afterload reduction acutely enhances LA emptying fraction in the failing heart.[86] This finding supports the hypothesis that declines in LA performance occur principally as a result of LA afterload mismatch during LV failure and not as a consequence of primary LA pathology.

Profound alterations in the passive mechanical properties of the LA are also observed during the development of heart failure. Left atrial reservoir function was augmented and conduit function was reduced in patients with a minor derangement in LV diastolic function as indicated by an impaired relaxation transmitral blood flow velocity pattern.[69] In contrast, patients with a restrictive LV filling pattern indicative of severe LV diastolic dysfunction and elevated LV diastolic pressure demonstrated a predominance of LA conduit function and a marked reduction in reservoir function concomitant with contractile dysfunction (fig. 8).[69] These findings indicate that evolving heart failure is associated with the progressive conversion of the LA from a storage and contractile chamber to a simple conduit. This concept was dramatically emphasized by the report of a patient with amyloidosis and end-stage heart failure in whom complete LA akinesis was observed throughout the cardiac cycle despite the continued presence of an electrocardiographically demonstrable normal sinus rhythm.[92] The ratio of conduit to active LA emptying volume has also been shown to be greater in patients with normal as compared to pseudonormal transmitral LV filling patterns.[201] These data suggest that analysis of active and passive LA function provides an alternative means of distinguishing between normal and pseudonormal filling patterns that may be used instead of standard analysis of pulmonary venous blood flow.[53]

Left atrial pressure–area relations also demonstrate that LA compliance is reduced in patients with congestive heart failure and normal sinus rhythm or atrial fibrillation.[18,41,202] Improvements in LA distensibility have been observed with the administration of positive inotropic drugs[18] or arterial vasodilators[203] in congestive heart failure and, conversely, abnormal LA compliance is further exacerbated by β-adrenoceptor antagonists or additional LA preload in this setting.[202] Effects of dobutamine and sodium nitroprusside on LA function were examined in patients with severe congestive heart failure using Doppler echocardiographic evaluation of transmitral and pulmonary venous blood flow velocity.[204] Dobutamine increased LA reservoir and conduit volumes but did not substantially affect pump function, alter pulmonary arterial pressures, or influence the restrictive pattern of LV filling that was observed under baseline conditions in these patients. In contrast, sodium nitroprusside did not alter reservoir or conduit volume but did enhance LA contractile performance and improve the pattern of LV filling from a restrictive to a normal morphology. These findings suggest that an arterial vasodilator may acutely provide more consistent improvements in LA and LV function than a β_1-adrenoceptor agonist by reducing LV afterload, improving LV compliance, decreasing ventricular interaction,[205] restoring LA preload reserve, and enhancing LA emptying fraction.[204]

Anesthetics and Left Atrial Function

The negative inotropic effects of halothane and methoxyflurane were initially described by Paradise *et al.*[206–208] in rat atrial myocardium *in vitro*. Volatile anesthetics also depress the contractile function of atrial myocardium obtained from guinea pigs,[209] rabbits,[210] and humans.[211–213] These actions have been attributed to reductions in transsarcolemmal calcium (Ca^{2+}) influx through voltage-dependent Ca^{2+} channels and decreases in Ca^{2+} availability from the sarcoplasmic reticulum,[210] mechanisms that are very similar to those responsible for anesthetic-induced depression of LV myocardium.[214] The negative inotropic effects of volatile agents in the intact LA were recently quantified using pressure–volume analysis.[33] Desflurane, sevoflurane, and isoflurane reduced LA contractility (*i.e.*, E_{es}) by approximately 50% at an end-tidal concentration of 1.2 minimum alveolar concentration (MAC; fig. 4). The magnitude of this effect in LA myocardium was similar to the degree of LV contractile depression produced by these agents as quantified with LV end-systolic pressure–volume relations.[215] Desflurane, sevoflurane, and isoflurane also impaired LA and LV relaxation to similar degrees. These data indicate that volatile anesthetics produce equivalent alterations in contractility and relaxation in LA compared to LV myocardium.[33] The magnitude of reductions in LA inotropic and lusitropic state produced by the volatile anesthetics was also similar in the intact LA, supporting the results obtained in isolated human atrial myocardium.[213]

Desflurane, sevoflurane, and isoflurane altered LA passive mechanical behavior.[33] Left atrial reservoir function (V-loop area and reservoir volume) was maintained during the administration of anesthetic concentrations of less than 1.0 MAC (fig. 10). This preservation of reservoir function contributed to the relative maintenance of LV stroke volume[215] by compensating for decreases in LV filling associated with a reduced contribution of LA contraction. The volatile anesthetics also reduced dynamic LA chamber stiffness, an action that most likely contributed to the preservation of reservoir function because

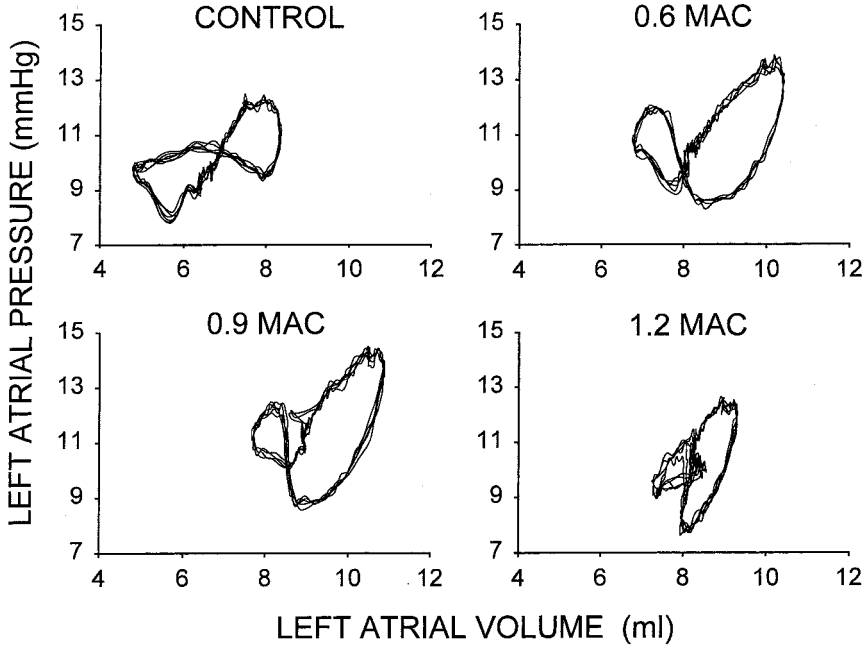

Fig. 10. Steady state left atrial (LA) pressure–volume diagrams obtained during control conditions (*top left*) and during the administration of 0.6, 0.9, and 1.2 MAC desflurane (*top right*, *bottom left*, and *bottom right*) in a typical experiment. A decrease in LA stroke work (A-loop area) and compensatory increases in LA reservoir volume and V-loop area occur during 0.6 and 0.9 MAC desflurane anesthesia. However, V-loop area decreases at 1.2 MAC consistent with a subsequent impairment of the passive component of the LA contribution to left ventricular (LV) filling. Reprinted with permission.[33]

the delays in LA relaxation and declines in LV systolic function that also occurred would be expected to decrease reservoir function.[20] However, LA reservoir function was reduced during administration of higher concentrations of the volatile anesthetics because further impairment of LA relaxation and LV contractility occurred. Decreases in the ratio of LA stroke work to total pressure–volume diagram area and the increases in the ratio of LA conduit to total reservoir volume (fig. 11) were also produced by desflurane, sevoflurane, and isoflurane. These data indicated that the LA contribution to LV filling becomes less active and more passive during the administration of the volatile agents.

Desflurane, sevoflurane, and isoflurane decreased the ratio of LA to LV elastance (E_{es}/E_{LV}), consistent with impaired mechanical matching between these chambers. Volatile anesthetics have been shown to produce LV diastolic dysfunction by delaying LV isovolumic relaxation and impairing early LV filling in association with direct negative inotropic effects.[216] Thus, the attenuation of transfer of kinetic energy from the LA to the LV probably resulted from the combination of LA contractile depression and LV systolic and diastolic dysfunction. Volatile anesthetic-induced abnormalities in LA–LV matching were greater than analogous impairment of LV–arterial coupling evaluated using a similar series of elastic chamber models in a previous investigation[215] because these agents produced beneficial alterations in the determinants of LV afterload[217,218] that partially compensate for simultaneous depression of LV myocardial contractility.

Propofol depresses the contractile function of isolated atrial myocardium obtained from guinea pigs[219] and humans[220] at concentrations higher than those typically achieved during intravenous infusions in a clinical setting. These findings are similar to those observed in normal ventricular myocardium *in vitro*,[221,222] *in situ*,[223] and *in vivo*.[224,225] The negative inotropic actions of propofol in ventricular myocardium have been attributed to inhibition of transsarcolemmal calcium (Ca^{2+}) current[226,227] and L-type Ca^{2+} channel function,[228] and it is likely that similar mechanisms are responsible for depression of contractility in atrial myocardium. The effects of propofol on LA myocardial contractility *in vivo* were recently quantified using pressure–volume analysis.[52] The magnitude of the negative inotropic effect of several doses of propofol in LA myocardium was nearly identical to the degree of LV contractile depression.[225] Dose-related declines in E_{es}/E_{LV} were observed during administration of propofol consistent with impaired mechanical matching between these elastic chambers. In contrast to the findings with volatile anesthetics, previous investigations[229,230] have demonstrated that propofol does not affect LV relaxation and compliance. Thus, the impairment of LA–LV coupling observed during the administration of propofol most likely resulted from the depression of LA contractile function and not because of LV diastolic dysfunction.

Propofol also affected LA passive filling and emptying properties.[52] Increases in V-loop area occurred during administration of larger doses of propofol, and total LA reservoir volume was unchanged. These findings suggested that LA reservoir function is maintained during propofol anesthesia. This preservation of reservoir function may partially compensate for reductions in the active contribution of LA contraction to LV filling and serves to maintain stroke volume.[225] Left atrial chamber stiffness decreased during administration of propofol

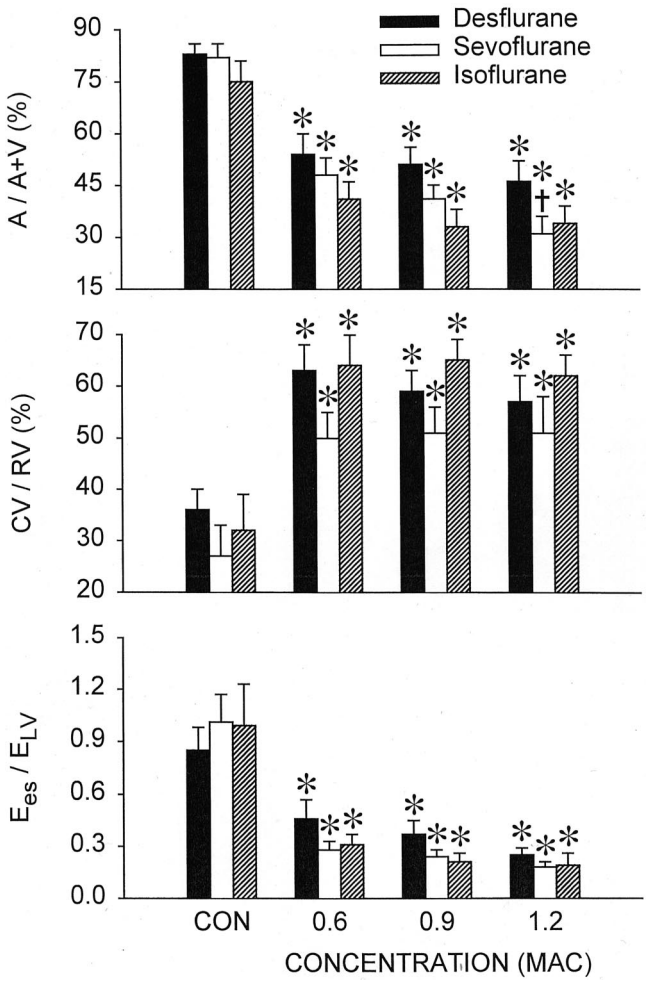

Fig. 11. Histograms depicting the ratio of the left atrial (LA) A loop to total pressure–volume diagram area (A/A + V; *top*), the ratio of LA conduit to total reservoir volume (CV/RV; *middle*), and LA–left ventricular (LV) coupling (E_{es}/E_{LV}; *bottom*) under baseline conditions and during the administration of 0.6, 0.9, and 1.2 MAC desflurane (solid bars), sevoflurane (open bars), or isoflurane (hatched bars). *Significantly ($P < 0.05$) different from CON; †significantly ($P < 0.05$) different from 0.6 MAC. Reprinted with permission.[33]

despite modest increases in LA pressure, suggesting that LA compliance is improved by this intravenous agent. The preservation of reservoir function that occurred during administration of propofol was probably related to these decreases in LA chamber stiffness, because decreases in LV systolic function were observed that would be expected to reduce reservoir function.[20] A delay in LA relaxation has also been shown to contribute to a reduction in reservoir function,[20] but an LA relaxation constant was unchanged during administration of propofol. These latter data support previous observations indicating that this drug does not alter LV relaxation.[229,230]

Summary

Insights obtained from the analysis of LA pressure–volume relations and Doppler echocardiography have substantially advanced our understanding of LA function in the normal and diseased heart. The active and passive mechanical actions of the LA play critical roles in determining overall cardiovascular performance by unloading the pulmonary venous circulation and by facilitating LV filling. Compensatory LA enlargement and enhanced LA emptying fraction produce an increase in the active LA contribution to LV filling in a variety of pathologic conditions that serve to maintain stroke volume and cardiac output. However, LA dilatation may eventually adversely affect LA emptying fraction if optimal Frank-Starling relations are exceeded or atrial tachyarrhythmias occur. In addition, declines in LA compliance adversely affect LA reservoir function, impede pulmonary venous blood flow into the LA, and impair LV filling. Left atrial failure may occur as a consequence of primary atrial disease or chronic elevations in LA afterload and contribute to the development of clinical signs and symptoms of congestive heart failure. Pharmacological management of heart failure not only enhances LV function, but also improves the interaction between the LA and LV. Volatile and intravenous anesthetics have recently been shown to profoundly affect LA function in the normal heart. How these agents influence LA mechanical behavior in the presence of LV dysfunction remains an important goal of future research.

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References

1. Nolan SP, Dixon SH Jr, Fisher RD, Morrow AG: The influence of atrial contraction and mitral valve mechanics on ventricular filling: A study of instantaneous mitral valve flow *in vivo*. Am Heart J 1969; 77:784–91
2. Ruskin J, McHale PA, Harley A, Greenfield JC Jr: Pressure-flow studies in man: Effect of atrial systole on left ventricular function. J Clin Invest 1970; 49:472–8
3. Grant C, Bunnell IL, Greene DG: The reservoir function of the left atrium during ventricular systole: An angiocardiographic study of atrial stroke volume and work. Am J Med 1964; 37:36–43
4. Ishida Y, Meisner JS, Tsujioka K, Gallo JI, Yoran C, Frater RWM, Yellin EL: Left ventricular filling dynamics: Influence of left ventricular relaxation and left atrial pressure. Circulation 1986; 74:187–96
5. Suga H: Importance of atrial compliance in cardiac performance. Circ Res 1974; 35:39–43
6. Keynes G: The anatomical exercises of Dr. William Harvey. De motu cordis 1628; De circulatione sanguinis 1649: The first English text of 1653. London, Nonesuch, 1928, p 202
7. Gesell RA: Auricular systole and its relation to ventricular output. Am J Physiol 1911; 29:32–63
8. Mitchell JH, Gilmore JP, Sarnoff SJ: The transport function of the atrium: Factors influencing the relation between mean left atrial pressure and left ventricular end diastolic pressure. Am J Cardiol 1962; 9:237–47
9. Braunwald E, Frahm CJ: Studies on Starling's law of the heart: IV. Observations on the hemodynamic functions of the left atrium in man. Circulation 1964; 24:633–42
10. Mitchell JH, Gupta DN, Payne RM: Influence of atrial systole on effective ventricular stroke volume. Circ Res 1965; 17:11–8
11. Mitchell JH, Shapiro W: Atrial function and the hemodynamic consequences of atrial fibrillation in man. Am J Cardiol 1969; 23:556–67
12. Rahimtoola SH, Ehsani A, Sinno MZ, Loeb HS, Rosen KM, Gunnar RM: Left atrial transport function in myocardial infarction: Importance of its booster pump function. Am J Med 1975; 59:686–94

13. Appleton CP, Hatle LK, Popp RL: Relation of transmitral flow velocity patterns to left ventricular diastolic function: New insights from a combined hemodynamic and Doppler echocardiographic study. J Am Coll Cardiol 1988; 12:426–40

14. Lo HM, Lin FY, Lin JL, Hsu KL, Chiang FT, Tseng CD, Tseng YZ: Impaired cardiac performance relating to delayed left atrial activation after atrial compartment operation for chronic atrial fibrillation. Pacing Clin Electrophysiol 1999; 22:379–81

15. Rossi R, Muia N Jr, Modena MG: Relationship between atrial function, left ventricular isovolumic relaxation time, and early filling in dual chamber-paced patients. J Am Soc Echocardiogr 1997; 10:300–9

16. Hettrick DA, Euler DE, Pagel PS, Musley S, Warman W, Ziegler PD, Mehra R: Effects of atrial pacing lead location and atrial-ventricular delay on atrial and ventricular hemodynamics in dogs. Pacing Clin Electrophysiol 2002; 25:888–96

17. Henderson Y, Scarbrough MM, Chillingworth FP: The volume curve of the ventricles of the mammalian heart, and the significance of this curve in respect to the mechanics of the heart beat and the filling of the ventricles. Am J Physiol 1906; 16:325–67

18. Stefanadis C, Dernellis J, Stratos C, Tsiamis E, Tsioufis C, Toutouzas K, Vlachopoulos C, Pitsavos C, Toutouzas P: Assessment of left atrial pressure-area relation in humans by means of retrograde left atrial catheterization and echocardiographic automatic boundary detection: Effect of dobutamine. J Am Coll Cardiol 1998; 31:426–36

19. Hitch DC, Nolan SP: Descriptive analysis of instantaneous left atrial volume with special reference to left atrial function. J Surg Res 1981; 30:110–20

20. Barbier P, Solomon SB, Schiller NB, Glantz SA: Left atrial relaxation and left ventricular systolic function determine left atrial reservoir function. Circulation 1999; 100:427–36

21. Mehta S, Charbonneau F, Fitchett DH, Marpole DG, Patton R, Sniderman AD: The clinical consequences of a stiff left atrium. Am Heart J 1991; 122: 1184–91

22. Hoit BD, Shao Y, Tsai LM, Patel R, Gabel M, Walsh RA: Altered left atrial compliance after atrial appendectomy: Influence on left atrial and ventricular filling. Circ Res 1993; 72:167–75

23. Hoit BD, Shao Y, McMannis K, Gabel M, Walsh RA: Determination of left atrial volume using sonomicrometry: A cast validation study. Am J Physiol 1993; 264:H1011–6

24. Poutanen T, Ikonen A, Vainio P, Jokinen E, Tikanoja T: Left atrial volume assessed by transthoracic three dimensional echocardiography and magnetic resonance imaging: Dynamic changes during the heart cycle in children. Heart 2000; 83:537–42

25. Waggoner AD, Barzilai B, Miller JG, Perez JE: On-line assessment of left atrial area and function by echocardiographic automatic boundary detection. Circulation 1993; 88:1142–9

26. Clarkson PBM, Wheeldon NM, Lim PO, Pringle SD, MacDonald TM: Left atrial size and function: Assessment using echocardiographic automated boundary detection. Br Heart J 1995; 74:664–70

27. Abe M, Oki T, Tabata T, Yamada H, Onose Y, Matsuoka M, Mishiro Y, Wakatsuki T, Ito S: Evaluation of the hemodynamic relationship between the left atrium and left ventricle during atrial systole by pulsed tissue Doppler imaging in patients with left heart failure. Jpn Circ J 1999; 63:763–9

28. Bough EW, Gandsman EJ, Shulman RS: Measurement of normal left atrial function with gated radionuclide angiography. Am J Cardiol 1981; 48:473–8

29. Fujii K, Ozaki M, Yamagishi T, Ishine K, Furutani Y, Nagano H, Yamamoto K, Saiki A, Matsuzaki M: Effect of left ventricular contractile performance on passive left atrial filling: Clinical study using radionuclide angiography. Clin Cardiol 1994; 17:258–62

30. Kircher B, Abbott JA, Pau S, Gould RG, Himelman RB, Higgins CB, Lipton MJ, Schiller NB: Left atrial volume determination by biplane two-dimensional echocardiography: Validation by cine computed tomography. Am Heart J 1991; 121:864–71

31. Jarvinen VM, Kupari MM, Poutanen VP, Hekali PE: A simplified method for the determination of left atrial size and function using cine magnetic resonance imaging. Magn Reson Imaging 1996; 14:215–26

32. Hoit BD, Walsh RA: Regional atrial distensibility. Am J Physiol 1992; 262:H1356–60

33. Gare M, Schwabe DA, Hettrick DA, Kersten JR, Warltier DC, Pagel PS: Desflurane, sevoflurane, and isoflurane affect left atrial active and passive mechanical properties and impair left atrial–left ventricular coupling *in vivo*: Analysis using pressure–volume relations. ANESTHESIOLOGY 2001; 95:689–98

34. Alexander J Jr, Sunagawa K, Chang N, Sagawa K: Instantaneous pressure-volume relation of the ejecting canine left atrium. Circ Res 1987; 61:209–19

35. Suga H, Sagawa K, Shoukas AA: Load-independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. Circ Res 1973; 32:314–22

36. Sagawa K: The end-systolic pressure-volume relation of the ventricle: Definition, modifications and clinical use. Circulation 1981; 63:1223–7

37. Matsuda Y, Toma Y, Ogawa H, Matsuzaki M, Katayama K, Fujii T, Yoshino F, Moritani K, Kumada T, Kusukawa R: Importance of left atrial function in patients with myocardial infarction. Circulation 1983; 67:566–71

38. Glower DD, Spratt JA, Snow ND, Kabas JS, Davis JW, Olsen CO, Tyson GS, Sabiston DC Jr, Rankin JS: Linearity of the Frank-Starling relationship in the intact heart: The concept of preload recruitable stroke work. Circulation 1985; 71:994–1009

39. Little RC: Volume pressure relationships of the pulmonary-left heart vascular segment: Evidence for a "valve-like" closure of the pulmonary veins. Circ Res 1960; 8:594–9

40. Matsuzaki M, Tamitani M, Toma Y, Ogawa H, Katayama K, Matsuda Y, Kusukawa R: Mechanism of augmented left atrial pump function in myocardial infarction and essential hypertension evaluated by left atrial pressure dimension relation. Am J Cardiol 1991; 67:1121–6

41. Dernellis JM, Stefanadis CI, Zacharoulis AA, Toutouzas PK: Left atrial mechanical adaptation to long-standing hemodynamic loads based on pressure-volume relations. Am J Cardiol 1998; 81:1138–43

42. Stefanadis C, Dernellis J, Tsiamis E, Toutouzas P: Effects of pacing-induced and balloon coronary occlusion ischemia on left atrial function in patients with coronary artery disease. J Am Coll Cardiol 1999; 33:687–96

43. Lau VK, Sagawa K, Suga H: Instantaneous pressure-volume relationship of right atrium during isovolumic contraction in canine heart. Am J Physiol 1979; 236:H672–9

44. Hoit BD, Shao Y, Gabel M, Walsh RA: In vivo assessment of left atrial contractile performance in normal and pathological conditions using a time-varying elastance model. Circulation 1994; 89:1829–38

45. Kass DA, Maughan WL: From "Emax" to pressure-volume relations: A broader view. Circulation 1988; 77:1203–12

46. Pagel PS, Warltier DC: Mechanical function of the left ventricle, Anesthesia: Biologic Foundations. Edited by Yaksh TL, Lynch C III, Zapol WM, Maze M, Biebuyck JF, Saidman LJ. Philadelphia, Lippincott–Raven, 1998, pp 1081–133

47. Hoit BD, Shao Y, Gabel M, Walsh RA: Left atrial mechanical and biochemical adaptation to pacing induced heart failure. Cardiovasc Res 1995; 29:469–74

48. Sunagawa K, Maughan WL, Burkhoff D, Sagawa K: Left ventricular interaction with arterial load studied in isolated canine ventricle. Am J Physiol 1983; 245:H773–80

49. Sunagawa K, Maughan WL, Sagawa K: Optimal arterial resistance for the maximal stroke work studied in isolated canine left ventricle. Circ Res 1985; 56:586–95

50. Hoit BD, Shao Y, Gabel M, Walsh RA: Influence of pericardium on left atrial compliance and pulmonary venous flow. Am J Physiol 1993; 264:H1781–7

51. Gilbert JC, Glantz SA: Determinants of left ventricular filling and of the diastolic pressure-volume relation. Circ Res 1989; 64:827–52

52. Kehl F, Kress TT, Mraovic B, Hettrick DA, Kersten JR, Warltier DC, Pagel PS: Propofol alters left atrial function evaluated using pressure-volume relations *in vivo*. Anesth Analg 2002; 94:1421–6

53. Rakowski H, Appleton C, Chan KL, Dumesnil JG, Honos G, Jue J, Koilpillai C, Lepage S, Martin RP, Mercier LA, O'Kelly B, Prieur T, Sanfilippo A, Sasson Z, Alvarez N, Pruitt R, Thompson C, Tomlinson C: Canadian consensus recommendations for the measurement and reporting of diastolic dysfunction by echocardiography: From the Investigators of Consensus on Diastolic Dysfunction by Echocardiography. J Am Soc Echocardiogr 1996; 9:736–60

54. Klein AL, Obarski TP, Stewart WJ, Casale PN, Pearce GL, Husbands K, Cosgrove DM, Salcedo EE: Transesophageal Doppler echocardiography of pulmonary venous flow: A new marker of mitral regurgitation severity. J Am Coll Cardiol 1991; 18:518–26

55. Castello R, Pearson AC, Lenzen P, Labovitz AJ: Effect of mitral regurgitation on pulmonary venous velocities derived from transesophageal echocardiography color-guided pulsed Doppler imaging. J Am Coll Cardiol 1991; 17:1499–506

56. Rossi A, Golia G, Gasparini G, Prioli MA, Anselmi M, Zardini P: Left atrial filling volume can be used to reliably estimate the regurgitant volume in mitral regurgitation. J Am Coll Cardiol 1999; 33:212–7

57. Kuecherer HF, Kusumoto F, Muhiudeen IA, Cahalan MK, Schiller NB: Pulmonary venous flow patterns by transesophageal pulsed Doppler echocardiography: Relation to parameters of left ventricular systolic and diastolic function. Am Heart J 1991; 122:1683–93

58. Kuecherer HF, Muhiudeen IA, Kusumoto FM, Lee E, Moulinier LE, Cahalan MK, Schiller NB: Estimation of mean left atrial pressure from transesophageal pulsed Doppler echocardiography of pulmonary venous flow. Circulation 1990; 82:1127–39

59. Oki T, Kageji Y, Fukuda N, Iuchi A, Tabata T, Manabe K, Yamada H, Fukuda K, Ito S: Assessment of left atrial pressure and volume changes during atrial systole with transesophageal pulsed Doppler echocardiography of transmitral and pulmonary venous flow velocities. Jpn Heart J 1996; 37:333–42

60. Gorcsan J III, Snow FR, Paulsen W, Nixon JV: Noninvasive estimation of left atrial pressure in patients with congestive heart failure and mitral regurgitation by Doppler echocardiography. Am Heart J 1991; 121:858–63

61. Hoit BD, Shao Y, Gabel M, Walsh RA: Influence of loading conditions and contractile state on pulmonary venous flow. Validation of Doppler velocimetry. Circulation 1992; 86:651–9

62. Hofman T, Keck A, Van Ingen G, Simic O, Ostermeyer J, Meinertz T: Simultaneous measurement of pulmonary venous flow by intravascular catheter Doppler velocimetry and transesophageal Doppler echocardiography: Relation to left atrial pressure and left atrial and left ventricular function. J Am Coll Cardiol 1995; 26:239–49

63. Castello R, Pearson AC, Lenzen P, Labovitz AJ: Evaluation of pulmonary venous flow by transesophageal echocardiography in subjects with a normal

heart: Comparison with transthoracic echocardiography. J Am Coll Cardiol 1991; 18:65–71

64. Appleton CP: Hemodynamic determinants of Doppler pulmonary venous flow velocity components: New insights from studies in lightly sedated normal dogs. J Am Coll Cardiol 1997; 30:1562–74

65. Morkin E, Collins JA, Goldman HS, Fishman AP: Pattern of blood flow in the pulmonary veins of the dog. J Appl Physiol 1965; 20:1118–28

66. Nakao T, Shimizu M, Kita Y, Yoshio H, Arai Y, Ino H, Takeda R: Noninvasive measurement of left atrial functions using transesophageal echocardiography. Jpn Heart J 1996; 37:227–38

67. Smiseth OA, Thompson CR, Lohavanichbutr K, Ling H, Abel JG, Miyagishima RT, Lichtenstein SV, Bowering J: The pulmonary venous systolic flow pulse: Its origin and relationship to left atrial pressure. J Am Coll Cardiol 1999; 34:802–9

68. Appleton CP, Gonzalez MS, Basnight MA: Relationship of left atrial pressure and pulmonary venous flow velocities: Importance of baseline mitral and pulmonary venous flow velocity patterns in lightly sedated dogs. J Am Soc Echocardiogr 1994; 7:264–75

69. Prioli A, Marino P, Lanzoni L, Zardini P: Increasing degrees of left ventricular filling impairment modulate left atrial function in humans. Am J Cardiol 1998; 82:756–61

70. Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA: Recommendations for quantification of Doppler echocardiography: A report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr 2002; 15:167–84

71. Chen YT, Kan MN, Lee AYS, Chen JS, Chiang BN: Pulmonary venous flow: Its relationship to left atrial and mitral valve motion. J Am Soc Echocardiogr 1993; 6:387–94

72. Oki T, Iuchi A, Tabata T, Yamada H, Manabe K, Kageji Y, Abe M, Fukuda N, Ito S: Transesophageal pulsed Doppler echocardiographic evaluation of left atrial systolic performance in hypertrophic cardiomyopathy: Combined analysis of transmitral and pulmonary venous flow velocities. Clin Cardiol 1997; 20:47–54

73. Oki T, Fukuda N, Iuchi A, Tabata T, Tanimoto M, Manabe K, Kageji Y, Sasaki M, Yamada H, Ito S: Left atrial systolic performance in patients with elevated left ventricular end-diastolic pressure: Evaluation by transesophageal pulsed Doppler echocardiography of left ventricular inflow and pulmonary venous flow velocities. Echocardiography 1997; 14:23–32

74. Nakatani S, Garcia MJ, Firstenberg MS, Rodriguez L, Grimm RA, Greenberg NL, McCarthy PM, Vandervoort PM, Thomas JD: Noninvasive assessment of left atrial maximum dP/dt by a combination of transmitral and pulmonary venous flow. J Am Coll Cardiol 1999; 34:795–801

75. Goldman S, Olajos M, Morkin E: Comparison of left atrial and left ventricular performance in conscious dogs. Cardiovasc Res 1984; 18:604–12

76. Urthaler F, Walker AA, Hefner LL, James TN: Comparison of contractile performance of canine atrial and ventricular muscles. Circ Res 1975; 37:762–71

77. Wikman-Coffelt J, Refsum H, Hollosi G, Rouleau L, Chuck L, Parmley WW: Comparative force-velocity relation and analyses of myosin of dog atria and ventricles. Am J Physiol 1982; 243:H391–7

78. Stone HL: Effect of heart rate on left atrial systolic shortening in the dog. J Appl Physiol 1975; 38:1110–6

79. Payne RM, Stone HL, Engelken EJ: Atrial function during volume loading. J Appl Physiol 1971; 31:326–31

80. Williams JF Jr, Sonnenblick EH, Braunwald E: Determinants of atrial contractile force in the intact heart. Am J Physiol 1965; 209:1061–8

81. Trikas A, Triposkiadis F, Androulakis A, Toutouzas K, Tentolouris K, Nihoyannopoulos P, Gialafos J, Toutouzas P: Response of left atrial systolic function to handgrip in normal subjects. Am Heart J 1995; 130:1303–5

82. Dernellis J, Tsiamis E, Stefanadis C, Pitsavos C, Toutouzas P: Effects of postural changes on left atrial function in patients with hypertrophic cardiomyopathy. Am Heart J 1998; 136:982–7

83. Hondo T, Okamoto M, Kawagoe T, Karakawa S, Yamane T, Yamagata T, Matsuura H, Kajiyama G: Effects of heart rate on left atrial contractile performance and left ventricular filling during atrial systole in dogs. Jpn Heart J 1995; 36:367–75

84. Buttrick PM, Malhotra A, Brodman R, McDermott L, Lam L: Myosin isoenzyme distribution in overloaded human atrial tissue. Circulation 1986; 74:477–83

85. Ritter O, Luther HP, Haase H, Baltas LG, Baumann G, Schulte HD, Morano I: Expression of atrial myosin light chains but not alpha-myosin heavy chains is correlated in vivo with increased ventricular function in patients with hypertrophic obstructive cardiomyopathy. J Mol Med 1999; 77:677–85

86. Ito T, Suwa M, Kobashi A, Yagi H, Hirota Y, Kawamura K: Reversible left atrial dysfunction possibly due to afterload mismatch in patients with left ventricular dysfunction. J Am Soc Echocardiogr 1998; 11:274–9

87. Dernellis JM, Vyssoulis GP, Zacharoulis AA, Toutouzas PK: Effects of antihypertensive therapy on left atrial function. J Hum Hypertens 1996; 10: 789–94

88. Keren G, Bier A, Sherez J, Miura D, Keefe D, LeJemtel T: Atrial contraction is an important determinant of pulmonary venous flow. J Am Coll Cardiol 1986; 7:693–5

89. Toma Y, Matsuda Y, Moritani K, Ogawa H, Matsuzaki K, Kusukawa R: Left atrial filling in normal human subjects: Relation between left atrial contraction and left atrial early filling. Cardiovasc Res 1987; 21:255–9

90. Keren G, Sonnenblick EH, LeJemtel TH: Mitral anulus motion: Relation to pulmonary venous and transmitral flows in normal subjects and in patients with dilated cardiomyopathy. Circulation 1988; 78:621–9

91. Guntheroth WG, Gould R, Butler J, Kinnen E: Pulsatile flow in pulmonary artery, capillary, and vein in the dog. Cardiovasc Res 1974; 8:330–7

92. Plehn JF, Southworth J, Cornwell GG III: Brief report: Atrial systolic failure in primary amyloidosis. N Engl J Med 1992; 327:1570–3

93. Dardas PS, Fillippatos GS, Tsikaderis DD, Michalis LK, Goudevenos IA, Sideris DA, Shapiro LM: Noninvasive indexes of left atrial diastolic function in hypertrophic cardiomyopathy. J Am Soc Echocardiogr 2000; 13:809–17

94. Davis CA III, Rembert JC, Greenfield JC Jr: Compliance of the left atrium with and without left atrial appendage. Am J Physiol 1990; 259:H1006–8

95. Tabata T, Oki T, Yamada H, Iuchi A, Ito S, Hori T, Kitagawa T, Kato I, Kitahata H, Oshita S: Role of left atrial appendage in left atrial reservoir function as evaluated by left atrial appendage clamping during cardiac surgery. Am J Cardiol 1998; 81:327–32

96. Benchimol A: Significance of the contribution of atrial systole to cardiac function in man. Am J Cardiol 1969; 23:568–71

97. Nishikawa Y, Roberts JP, Tan P, Klopfenstein CE, Klopfenstein HS: Effect of dynamic exercise on left atrial function in conscious dogs. J Physiol 1994; 481:457–68

98. Cheng C-P, Noda T, Nozawa T, Little WC: Effect of heart failure on the mechanism of exercise-induced augmentation of mitral valve flow. Circ Res 1993; 72:795–806

99. Toutouzas K, Trikas A, Pitsavos C, Barbetseas J, Androulakis A, Stefanadis C, Toutouzas P: Echocardiographic features of left atrium in elite male athletes. Am J Cardiol 1996; 78:1314–7

100. Triposkiadis F, Tentolouris K, Androulakis A, Trikas A, Toutouzas K, Kyriakidis M, Gialafos J, Toutouzas P: Left atrial mechanical function in the healthy elderly: New insights from a combined assessment of changes in atrial volume and transmitral flow velocity. J Am Soc Echocardiogr 1995; 8:801–9

101. Manning WJ, Silverman DI, Katz SE, Douglas PS: Atrial ejection force: A noninvasive assessment of atrial systolic function. J Am Coll Cardiol 1993; 22:221–5

102. Spencer KT, Mor-Avi V, Gorcsan J III, DeMaria AN, Kimball TR, Monaghan MJ, Perez JE, Weinert L, Bednarz J, Edelman K, Kwan OL, Glascock B, Hancock J, Baumann C, Lang RM: Effects of aging on left atrial reservoir, conduit, and booster pump function: A multi-institution acoustic quantification study. Heart 2001; 85:272–7

103. Kuo LC, Quinones MA, Rokey R, Sartori M, Abinader EG, Zoghbi WA: Quantification of atrial contribution to left ventricular filling by pulsed Doppler echocardiography and the effect of age in normal and diseased hearts. Am J Cardiol 1987; 59:1174–8

104. Nishigaki K, Arakawa M, Miwa H, Kagawa K, Noda T, Ito Y: A study of left atrial transport function. Effect of age or left ventricular ejection fraction on left atrial storage function. Angiology 1994; 45:953–62

105. Zuccala G, Cocchi A, Lattanzio F, Bernabei R, Carbonin PU: Effect of age on left atrial function in patients with coronary artery disease. Cardiology 1994; 85:8–13

106. Pilote L, Huttner I, Marpole D, Sniderman A: Stiff left atrial syndrome. Can J Cardiol 1988; 4:255–7

107. Mehta A, Sniderman A: Stiff LA syndrome: Reply. Am Heart J 1993; 125:1814–5

108. Fitchett DH: Time varying loading of the pulmonary circulation: A model to describe hemodynamic observations in the stiff left atrial syndrome. Can J Cardiol 1995; 11:23–9

109. Leistad E, Christensen G, Ilebekk A: Effects of atrial fibrillation on left and right atrial dimensions, pressures, and compliances. Am J Physiol 1993; 264:H1093–7

110. Leistad E, Christensen G, Ilebekk A: Significance of increased atrial pressure on stroke volume during atrial fibrillation in anaesthetized pigs. Acta Physiol Scand 1993; 149:157–61

111. Oki T, Tabata T, Yamada H, Wakatsuki T, Fukuda K, Abe M, Onose Y, Iuchi A, Fukuda N, Ito S: Evaluation of left atrial filling using systolic pulmonary venous flow velocity measurements in patients with atrial fibrillation. Clin Cardiol 1998; 21:169–74

112. Henry WL, Morganroth J, Pearlman AS, Clark CE, Redwood DR, Itscoitz SB, Epstein SE: Relation between echocardiographically determined left atrial size and atrial fibrillation. Circulation 1976; 53:273–9

113. Suarez GS, Lampert S, Ravid S, Lown B: Changes in left atrial size in patients with lone atrial fibrillation. Clin Cardiol 1991; 14:652–6

114. White CW, Holida MD, Marcus ML: Effects of acute atrial fibrillation on the vasodilator reserve of canine atrium. Cardiovasc Res 1986; 20:683–9

115. White CW, Kerber RE, Weiss HR, Marcus ML: The effects of atrial fibrillation on atrial pressure-volume and flow relationships. Circ Res 1982; 51:205–15

116. Tokushima T, Utsunomiya T, Yoshida K, Kido K, Ogawa T, Ryu T, Ogata T, Tsuji S, Matsuo S: Left atrial systolic function assessed by left atrial ejection force in patients with sick sinus syndrome and paroxysmal atrial fibrillation. Jpn Heart J 2000; 41:723–31

117. Zipes DP: Atrial fibrillation: A tachycardia-induced atrial cardiomyopathy. Circulation 1997; 95:562–4

118. Morillo CA, Klein GJ, Jones DL, Guiraudon CM: Chronic rapid atrial pacing: Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. Circulation 1995; 91:1588–95

119. Sanfilippo AJ, Abascal VM, Sheehan M, Oertel LB, Harrigan P, Hughes RA, Weyman AE: Atrial enlargement as a consequence of atrial fibrillation: A prospective echocardiographic study. Circulation 1990; 82:792–7

120. Amar D, Zhang H, Leung DHY, Roistacher N, Kadish AH: Older age is the strongest predictor of postoperative atrial fibrillation. ANESTHESIOLOGY 2002; 96:352–6

121. Fatkin D, Kuchar DL, Thorburn CW, Feneley MP: Transesophageal echocardiography before and during direct current cardioversion of atrial fibrillation: Evidence for "atrial stunning" as a mechanism of thromboembolic complications. J Am Coll Cardiol 1994; 23:307–16

122. Fatkin D, Feneley M: Stratification of thromboembolic risk of atrial fibrillation by transthoracic echocardiography and transesophageal echocardiography: The relative role of left atrial appendage function, mitral valve disease, and spontaneous echocardiographic contrast. Prog Cardiovasc Dis 1996; 39:57–68

123. Mattioli AV, Sansoni S, Lucchi GR, Mattioli G: Serial evaluation of left atrial dimension after cardioversion for atrial fibrillation and relation to atrial function. Am J Cardiol 2000; 85:832–6

124. Leistad E, Christensen G, Ilebekk A: Atrial contractile performance after cessation of atrial fibrillation. Am J Physiol 1993; 264:H104–9

125. Leistad E, Aksnes G, Verburg E, Christensen G: Atrial contractile dysfunction after short-term atrial fibrillation is reduced by verapamil but increased by BAY K8644. Circulation 1996; 93:1747–54

126. Daoud EG, Marcovitz P, Knight BP, Goyal R, Man KC, Strickberger SA, Armstrong WF, Morady F: Short-term effect of atrial fibrillation on atrial contractile function in humans. Circulation 1999; 99:3024–7

127. Altemose GT, Zipes DP, Weksler J, Miller JM, Olgin JE: Inhibition of the Na^+/H^+ exchanger delays the development of rapid pacing-induced atrial contractile dysfunction. Circulation 2001; 103:762–8

128. du Toit EF, Opie LH: Role for the Na^+/H^+ exchanger in reperfusion stunning in isolated perfused rat heart. J Cardiovasc Pharmacol 1993; 22:877–83

129. Louie EK, Liu D, Reynertson SI, Loeb HS, McKiernan TL, Scanlon PJ, Hariman RJ: "Stunning" of the left atrium after spontaneous conversion of atrial fibrillation to sinus rhythm: Demonstration by transesophageal Doppler techniques in a canine model. J Am Coll Cardiol 1998; 32:2081–6

130. Ito T, Suwa M, Otake Y, Kobahi A, Hirota Y, Ando H, Kawamura K: Assessment of left atrial appendage function after cardioversion of atrial fibrillation: Relation to left atrial mechanical function. Am Heart J 1998; 135:1020–6

131. Hoit BD, Shao Y, Gabel M: Influence of acutely altered loading conditions on left atrial appendage flow velocities. J Am Coll Cardiol 1994; 24:1117–23

132. Pollick C, Taylor D: Assessment of left atrial appendage function by transesophageal echocardiography: Implications for the development of thrombus. Circulation 1991; 84:223–31

133. Grimm RA, Stewart WJ, Arheart K, Thomas JD, Klein AL: Left atrial appendage "stunning" after electrical cardioversion of atrial flutter: An attenuated response compared with atrial fibrillation as the mechanism for lower susceptibility to thromboembolic events. J Am Coll Cardiol 1997; 29:582–9

134. Harjai KJ, Mobarek SK, Cheiref J, Boulos LM, Murgo JP, Abi-Samra F: Clinical variables affecting recovery of left atrial mechanical function after cardioversion from atrial fibrillation. J Am Coll Cardiol 1997; 30:481–6

135. Escudero EM, San Mauro M, Laugle C: Bilateral atrial function after chemical cardioversion of atrial fibrillation with amiodarone: An echo-Doppler study. J Am Soc Echocardiogr 1998; 11:365–71

136. Omran H, Jung W, Rabahieh R, Schimpf R, Wolpert C, Hagendorff A, Fehske W, Luderitz B: Left atrial chamber and appendage function after internal atrial defibrillation: A prospective and serial transesophageal echocardiographic study. J Am Coll Cardiol 1997; 29:131–8

137. Harjai K, Mobarek S, Abi-Samra F, Gilliland Y, Davison N, Drake K, Revall S, Cheiref J: Mechanical dysfunction of the left atrium and left atrial appendage following cardioversion of atrial fibrillation and its relation to total electrical energy used for cardioversion. Am J Cardiol 1998; 81:1125–9

138. Sparks PB, Jayaprakash S, Mond HG, Vohra JK, Grigg LE, Kalman JM: Left atrial mechanical function after brief duration atrial fibrillation. J Am Coll Cardiol 1999; 33:342–9

139. Upshaw CB Jr: Hemodynamic changes after cardioversion of chronic atrial fibrillation. Arch Intern Med 1997; 157:1070–6

140. Ito Y, Arakawa M, Noda T, Miwa H, Kagawa K, Nishigaki K, Fujiwara H: Atrial reservoir and active transport function after cardioversion of chronic atrial fibrillation. Heart Vessels 1996; 11:30–8

141. Triposkiadis F, Pitsavos C, Boudoulas H, Trikas A, Toutouzas P: Left atrial myopathy in idiopathic dilated cardiomyopathy. Am Heart J 1994; 128:308–15

142. Triposkiadis F, Moyssakis I, Hadjinikolaou L, Makris T, Zioris H, Hatzizaharias A, Kyriakidis M: Left atrial systolic function is depressed in idiopathic and preserved in ischemic dilated cardiomyopathy. Eur J Clin Invest 1999; 29:905–12

143. Ohtani K, Yutani C, Nagata S, Koretsune Y, Hori M, Kamada T: High prevalence of atrial fibrosis in patients with dilated cardiomyopathy. J Am Coll Cardiol 1995; 25:1162–9

144. Triposkiadis F, Trikas A, Pitsavos C, Papadopoulos P, Toutouzas P: Relation of exercise capacity in dilated cardiomyopathy to left atrial size and systolic function. Am J Cardiol 1992; 70:825–7

145. Murphy L, Falk RH: Left atrial kinetic energy in AL amyloidosis: Can it detect early dysfunction? Am J Cardiol 2000; 86:244–6

146. Klein AL, Hatle LK, Taliercio CP, Oh JK, Kyle RA, Gertz MA, Bailey KR, Seward JB, Tajik AJ: Prognostic significance of Doppler measures of diastolic function in cardiac amyloidosis: A Doppler echocardiography study. Circulation 1991; 83:808–16

147. Hoit BD, Shao Y, Gabel M: Global and regional atrial function after rapid atrial pacing: An echo Doppler study. J Am Soc Echocardiogr 1997; 10:805–10

148. Hoit BD, Shao Y, Gabel M: Left atrial systolic and diastolic function accompanying chronic rapid pacing-induced atrial failure. Am J Physiol 1998; 275:H183–9

149. Hoit BD, Gabel M: Influence of left ventricular dysfunction on the role of atrial contraction: An echocardiographic-hemodynamic study in dogs. J Am Coll Cardiol 2000; 36:1713–9

150. Sanada H, Shimizu M, Sugihara N, Shimizu K, Ino H, Takeda R: Increased left atrial chamber stiffness in hypertrophic cardiomyopathy. Br Heart J 1993; 69:31–5

151. Sanada H, Shimizu M, Shimizu K, Kita Y, Sugihara N, Takeda R: Left atrial afterload mismatch in hypertrophic cardiomyopathy. Am J Cardiol 1991; 68: 1049–54

152. Takeuchi Y, Yokota Y, Yokoyama M: Left atrial backward ejection in symptomatic hypertrophic cardiomyopathy: Assessment by transthoracic and transesophageal Doppler echocardiography. Jpn Circ J 1994; 58:809–20

153. Bouvagnet P, Leger J, Pons F, Dechesne C, Leger JJ: Fiber types and myosin types in human atrial and ventricular myocardium: An anatomical description. Circ Res 1984; 55:794–804

154. Knight C, Kurbaan AS, Seggewiss H, Henein M, Gunning M, Harrington D, Fassbender D, Gleichmann U, Sigwart U: Nonsurgical septal reduction for hypertrophic obstructive cardiomyopathy: Outcome in the first series of patients. Circulation 1997; 95:2075–81

155. Nagueh SF, Lakkis NM, Middleton KJ, Killip D, Zoghbi WA, Quinones MA, Spencer WH III: Changes in left ventricular diastolic function 6 months after nonsurgical septal reduction therapy for hypertrophic obstructive cardiomyopathy. Circulation 1999; 99:344–7

156. Nagueh SF, Lakkis NM, Middleton KJ, Killip D, Zoghbi WA, Quinones MA, Spencer WH III: Changes in left ventricular filling and left atrial function six months after nonsurgical septal reduction therapy for hypertrophic obstructive cardiomyopathy. J Am Coll Cardiol 1999; 34:1123–8

157. Boudoulas H, Starling RC, Vavuranakis M, Haas GJ, Sparks E, Myerowitz PD, Wooley CF: Left atrial volumes and function in orthotopic cardiac transplantation. Am Heart J 1995; 129:774–82

158. Starling RC, Boudoulas H: Left atrial dysfunction after orthotopic heart transplantation. J Heart Lung Transplant 1996; 15:431–2

159. Cresci S, Goldstein JA, Cardona H, Waggoner AD, Perez JE: Impaired left atrial function after heart transplantation: Disparate contribution of donor and recipient atrial components studied on-line with quantitative echocardiography. J Heart Lung Transplant 1995; 14:647–53

160. Geny B, Piquard F, Petit H, Trinh A, Mettauer B, Epailly E, Charpentier A, Chakfe N, Popescu S, Kretz JG, Eisenmann B, Haberey P: Atrial systolic function after heart transplantation. Transplant Proc 1998; 30:2835–6

161. Freimark D, Czer LSC, Aleksic I, Barthold C, Admon D, Trento A, Blanche C, Valenza M, Siegel RJ: Improved left atrial transport and function with orthotopic heart transplantation by bicaval and pulmonary venous anastomoses. Am Heart J 1995; 130:121–6

162. Stewart JT, Grbic M, Sigwart U: Left atrial and left ventricular diastolic function during acute myocardial ischaemia. Br Heart J 1992; 68:377–81

163. Sigwart U, Grbic M, Goy JJ, Kappenberger L: Left atrial function in acute transient left ventricular ischemia produced during percutaneous transluminal coronary angioplasty of the left anterior descending coronary artery. Am J Cardiol 1990; 65:282–6

164. Mehta A, Jain AC, Mehta M, Billie M: Left atrial abnormality in acute myocardial infarction. Am J Cardiol 1997; 79:807–11

165. Porter WT: The influence of the heart-beat on the flow of blood through the walls of the heart. Am J Physiol 1898; 1:145–63

166. James TN, Burch GE: The atrial coronary arteries in man. Circulation 1958; 17:90–8

167. Sakai H, Kunichika H, Murata K, Seki K, Katayama K, Hiro T, Miura T, Matsuzaki M: Improvement of afterload mismatch of left atrial booster pump function with positive inotropic agent. J Am Coll Cardiol 2001; 37:270–7

168. Maezawa H, Muroi IM, Ooida A, Ogawa K, Iizuka M: Effects of left ventricular chamber size and left ventricular diastolic pressure on left atrial booster pump function in patients with old myocardial infarction. Jpn Heart J 1997; 38:651–62

169. Appleton CP, Galloway JM, Gonzalez MS, Gaballa M, Basnight MA: Estimation of left ventricular filling pressures using two-dimensional and Doppler echocardiography in adult patients with cardiac disease: Additional value of analyzing left atrial size, left atrial ejection fraction and the difference in duration of pulmonary venous and mitral flow velocity at atrial contraction. J Am Coll Cardiol 1993; 22:1972–82

170. Takeichi N, Fukuda N, Tamura Y, Oki T, Ito S: Relationship between left atrial function and plasma level of atrial natriuretic peptide in patients with heart disease. Cardiology 1998; 90:13–9

171. Kawakami H, Sumimoto T, Matsuoka H, Kobayashi T, Ohtani T, Abe M, Shigematsu Y, Hamada M, Hiwada K: Atrial natriuretic peptide and left atrial systolic function in normal subjects. Angiology 1993; 44:903–7

172. Jikuhara T, Sumimoto T, Tarumi N, Yuasa F, Hattori T, Sugiura T, Iwasaka

T: Left atrial function as a reliable predictor of exercise capacity in patients with recent myocardial infarction. Chest 1997; 111:922–8

173. Grossman W, Jones D, McLaurin LP: Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 1975; 56:56–64

174. Matsuda Y, Toma Y, Moritani K, Ogawa H, Kohno M, Miura T, Matsuda M, Matsuzaki M, Fujii H, Kusukawa R: Assessment of left atrial function in patients with hypertensive heart disease. Hypertension 1986; 8:779–85

175. Galderisi M, Petrocelli A, Fakher A, Izzo A, Alfieri A, de Divitiis O: Influence of night-time blood pressure on left atrial size in uncomplicated arterial systemic hypertension. Am J Hypertens 1997; 10:836–42

176. Miller JT, O'Rourke RA, Crawford MH: Left atrial enlargement: An early sign of hypertensive heart disease. Am Heart J 1988; 116:1048–51

177. Lip GYH: The left atrium in hypertension, an appendage often forgotten. J Hum Hypertens 1997; 11:145–7

178. Barbier P, Alioto G, Guazzi MD: Left atrial function and ventricular filling in hypertensive patients with paroxysmal atrial fibrillation. J Am Coll Cardiol 1994; 24:165–70

179. Nagano R, Masuyama T, Naka M, Hori M, Kamada T: Contribution of atrial reservoir function to ventricular filling in hypertensive patients: Effects of nifedipine administration. Hypertension 1995; 26:815–9

180. Stott DK, Marpole DGF, Bristow JD, Kloster FE, Griswold HE: The role of left atrial transport in aortic and mitral stenosis. Circulation 1970; 41:1031–41

181. Jackson JM, Thomas SJ: Valvular heart disease, Cardiac Anesthesia, 4th edition. Edited by Kaplan JA, Reich DL, Konstadt SN. Philadelphia, WB Saunders, 1999, pp 727–84

182. Triposkiadis F, Pitsavos C, Boudoulas H, Trikas A, Kallikazaros I, Stefanadis C, Toutouzas P: Left atrial volume and function in valvular aortic stenosis. J Heart Valve Dis 1993; 2:104–13

183. Stefanadis C, Dernellis J, Lambrou S, Toutouzas P: Left atrial energy in normal subjects, in patients with symptomatic mitral stenosis, and in patients with advanced heart failure. Am J Cardiol 1998; 82:1220–3

184. Tukek T, Atilgan D, Akkaya V, Kudat H, Demirel S, Ozcan M, Korkut F: Assessment of left atrial appendage function and its relationship to pulmonary venous flow pattern by transesophageal echocardiography. Int J Cardiol 2001; 78:121–6

185. Boudoulas H, Boudoulas D, Sparks EA, Pearson AC, Nagaraja HN, Wooley CF: Left atrial performance indices in chronic mitral valve disease. J Heart Valve Dis 1995; 4(suppl 2):S242–7

186. Ko YG, Ha JW, Chung N, Shim WH, Kang SM, Rim SJ, Jang Y, Cho SY, Kim SS: Effects of left atrial compliance on left atrial pressure in pure mitral stenosis. Catheter Cardiovasc Interv 2001; 52:328–33

187. Sato S, Kawashima Y, Hirose H, Nakano S, Matsuda H, Shimasaki Y: Clinical study of left atrial compliance and left atrial volume in mitral stenosis. Jpn Circ J 1991; 55:481–6

188. Stefanadis C, Dernellis J, Stratos C, Tsiamis E, Vlachopoulos C, Toutouzas K, Lambrou S, Pitsavos C, Toutouzas P: Effects of balloon valvuloplasty on left atrial function in mitral stenosis as assessed by pressure-area relation. J Am Coll Cardiol 1998; 32:159–68

189. Kihara Y, Sasayama S, Miyazaki S, Onodera T, Susawa T, Nakamura Y, Fujiwara H, Kawai C: Role of the left atrium in adaptation of the heart to chronic mitral regurgitation in conscious dogs. Circ Res 1988; 62:543–53

190. Reed D, Abbott RD, Smucker ML, Kaul S: Prediction of outcome after mitral valve replacement in patients with symptomatic chronic mitral regurgitation: The importance of left atrial size. Circulation 1991; 84:23–34

191. Wang A, Harrison JK, Pieper KS, Kisslo KB, Bashore TM: What does the left atrial v wave signify during balloon commissurotomy of mitral stenosis? Am J Cardiol 1998; 82:1388–93

192. Sasayama S, Takahashi M, Osakada G, Hirose K, Hamashima H, Nishimura E, Kawai C: Dynamic geometry of the left atrium and left ventricle in acute mitral regurgitation. Circulation 1979; 60:177–86

193. Sasayama S, Takahashi M, Kawai C: Left atrial function in acute mitral regurgitation: Factors which modify the regurgitant volume. Herz 1981; 6:156–65

194. Hoit BD, Shao Y, Gabel M, Pawloski-Dahm C, Walsh RA: Left atrial systolic and diastolic function after cessation of pacing in tachycardia-induced heart failure. Am J Physiol 1997; 273:H921–7

195. Kono T, Sabbah HN, Rosman H, Alam M, Stein PD, Goldstein S: Left atrial contribution to ventricular filling during the course of evolving heart failure. Circulation 1992; 86:1317–22

196. Miyaguchi K, Iwase M, Matsui H, Kitano T, Hattori R, Yokota M, Hayashi H: Role of left atrial booster pump function in a worsening course of congestive heart failure. Jpn Circ J 1992; 56:509–17

197. Greenberg B, Chatterjee K, Parmley WW, Werner JA, Holly AN: The influence of left ventricular filling pressure on atrial contribution to cardiac output. Am Heart J 1979; 98:742–51

198. Li YH, Tsai LM, Tsai WC, Chao TH, Lin LJ, Chen JH: Decreased left atrial appendage function is an important predictor of elevated left ventricular filling pressure in patients with congestive heart failure. Int J Cardiol 1999; 68:39–45

199. Trikas A, Triposkiadis F, Pitsavos C, Tentolouris K, Kyriakidis M, Gialafos J, Toutouzas P: Relation of left atrial volume and systolic function to the hormonal response in idiopathic dilated cardiomyopathy. Int J Cardiol 1994; 47:139–43

200. Wang K, Gibson DG: Non-invasive detection of left atrial mechanical failure in patients with left ventricular disease. Br Heart J 1995; 74:536–40

201. Zhang G, Yasumura Y, Uematsu M, Nakatani S, Nagaya N, Miyatake K, Yamagishi M: Echocardiographic determination of left atrial function and its application for assessment of mitral flow velocity pattern. Int J Cardiol 1999; 72:19–25

202. Dernellis JM, Vyssoulis GP, Zacharoulis AA, Toutouzas PK: Acute changes of left atrial distensibility in congestive heart failure. Clin Cardiol 1998; 21:28–32

203. Xie GY, Berk MR, Fiedler AJ, Sapin PM, Smith MD: Left atrial function in congestive heart failure: Assessment by transmitral and pulmonary vein Doppler. Int J Card Imaging 1998; 14:47–53

204. Capomolla S, Pozzoli M, Opasich C, Febo O, Riccardi G, Salvucci F, Maestri R, Sisti M, Cobelli F, Tavazzi L: Dobutamine and nitroprusside infusion in patients with severe congestive heart failure: Hemodynamic improvement by discordant effects on mitral regurgitation, left atrial function, and ventricular function. Am Heart J 1997; 134:1089–98

205. Atherton JJ, Moore TD, Thomson HL, Frenneaux MP: Restrictive left ventricular filling patterns are predictive of diastolic ventricular interaction in chronic heart failure. J Am Coll Cardiol 1998; 31:413–8

206. Paradise RR, Griffith LK: Influence of halothane, chloroform and methoxyflurane on potassium content of rat atria. ANESTHESIOLOGY 1965; 26:195–8

207. Ko KC, Paradise RR: The effects of substrates on contractility of rat atria depressed with halothane. ANESTHESIOLOGY 1969; 31:532–9

208. Ko KC, Paradise RR: Multiple mechanisms of action of halothane and methoxyflurane on force of contraction of isolated rat atria. ANESTHESIOLOGY 1973; 39:278–84

209. Seifen AB, Kennedy RH, Seifen E: Effects of volatile anesthetics on response to norepinephrine and acetylcholine in guinea pig atria. Anesth Analg 1991; 73:304–9

210. Komai H, Rusy BF: Direct effect of halothane and isoflurane on the function of the sarcoplasmic reticulum in intact rabbit atria. ANESTHESIOLOGY 1990; 72:694–8

211. Ko KC, Paradise RR: The effects of substrates on halothane-depressed isolated human atria. ANESTHESIOLOGY 1970; 33:508–14

212. Luk HN, Lin CI, Wei J, Chang CL: Depressant effects of isoflurane and halothane on isolated human atrial fibers. ANESTHESIOLOGY 1988; 69:667–76

213. Hanouz JL, Massetti M, Guesne G, Chanel S, Babatasi G, Rouet R, Ducouret P, Khayat A, Galateau F, Bricard H, Gerard JL: *In vitro* effects of desflurane, sevoflurane, isoflurane, and halothane in isolated human right atria. ANESTHESIOLOGY 2000; 92:116–24

214. Pagel PS, Farber NE, Warltier DC: Cardiovascular pharmacology, Anesthesia, 5th edition. Edited by Miller RD. Philadelphia, Churchill Livingstone, 2000, pp 96–124

215. Hettrick DA, Pagel PS, Warltier DC: Desflurane, sevoflurane, and isoflurane impair canine left ventricular–arterial coupling and mechanical efficiency. ANESTHESIOLOGY 1996; 85:403–13

216. Pagel PS, Warltier DC: Anesthetics and left ventricular function, Ventricular Function. Edited by Warltier DC. Baltimore, Williams and Wilkins, 1995, pp 213–52

217. Hettrick DA, Pagel PS, Warltier DC: Differential effects of isoflurane and halothane on aortic input impedance quantified using a three-element Windkessel model. ANESTHESIOLOGY 1995; 83:361–73

218. Lowe D, Hettrick DA, Pagel PS, Warltier DC: Influence of volatile anesthetics on left ventricular afterload *in vivo*: Differences between desflurane and sevoflurane. ANESTHESIOLOGY 1996; 85:112–20

219. Azari DM, Cork RC: Comparative myocardial depressive effects of propofol and thiopental. Anesth Analg 1993; 77:324–9

220. Gelissen HP, Epema AH, Henning RH, Krijnen HJ, Hennis PJ, den Hertog A: Inotropic effects of propofol, thiopental, midazolam, etomidate, and ketamine on isolated human atrial muscle. ANESTHESIOLOGY 1996; 84:397–403

221. Riou B, Besse S, Lecarpentier Y, Viars P: *In vitro* effects of propofol on rat myocardium. ANESTHESIOLOGY 1992; 76:609–16

222. Park WK, Lynch C III: Propofol and thiopental depression of myocardial contractility: A comparative study of mechanical and electrophysiologic effects in isolated guinea pig ventricular muscle. Anesth Analg 1992; 74:395–405

223. Ismail EF, Kim SJ, Salem MR, Crystal GJ: Direct effects of propofol on myocardial contractility in *in situ* canine hearts. ANESTHESIOLOGY 1992; 77:964–72

224. Pagel PS, Warltier DC: Negative inotropic effects of propofol as evaluated by the regional preload recruitable stroke work relationship in chronically instrumented dogs. ANESTHESIOLOGY 1993; 78:100–8

225. Hettrick DA, Pagel PS, Warltier DC: Alterations in canine left ventricular–arterial coupling and mechanical efficiency produced by propofol. ANESTHESIOLOGY 1997; 86:1088–93

226. Yang CY, Wong CS, Yu CC, Luk HN, Lin CI: Propofol inhibits cardiac L-type calcium current in guinea pig ventricular myocytes. ANESTHESIOLOGY 1996; 84:626–35

227. Buljubasic N, Marijic J, Berczi V, Supan DF, Kampine JP, Bosnjak ZJ: vkDifferential effects of etomidate, propofol, and midazolam on calcium and potassium channel currents in canine myocardial cells. ANESTHESIOLOGY 1996; 85:1092–9

228. Zhou W, Fontenot HJ, Liu S, Kennedy RH: Modulation of cardiac calcium channels by propofol. ANESTHESIOLOGY 1997; 86:670–5

229. Pagel PS, Schmeling WT, Kampine JP, Warltier DC: Alteration of canine left ventricular diastolic function by intravenous anesthetics *in vivo*: Ketamine and propofol. ANESTHESIOLOGY 1992; 76:419–25

230. Belo SE, Kolesar R, Mazer CD: Intracoronary propofol does not decrease myocardial contractile function in the dog. Can J Anaesth 1994; 41:43–9