Atrial fibrillation (AF) is the most common sustained arrhythmia, and its prevalence in the population is increasing. Diastolic dysfunction shares many common risk factors with AF, including age, hypertension, obesity, and diabetes. Like AF, diastolic dysfunction increases with age, and patients given the diagnosis of diastolic dysfunction are more likely to have AF at the time. Diastolic dysfunction has significant pathological effects on atrial structure and function, many of which are proarrhythmic. However, much remains to be learned about the specific mechanisms through which diastolic dysfunction ultimately promotes AF.

Previous reviews have examined the broad association of diastolic dysfunction and AF. In this review, we attempt to examine this association on a mechanistic level. We begin with a basic review of the physiology of diastolic function, with particular attention to the complex interaction between the atrium and the ventricle during diastole. We then provide an overview of some of the most common clinical methods to quantify diastolic function and highlight the strengths and weaknesses of these methods with regard to providing an accurate picture of this physiology. We describe how these methods are applied to diagnose diastolic dysfunction, including the development of a widely adopted classification scheme of diastolic dysfunction. We then review the limited clinical data available connecting diastolic dysfunction with the risk of incident, nonvalvular AF, with a focus on studies examining diastolic dysfunction in populations without structural heart disease—ie, with preserved systolic function in the absence of hypertrophic cardiomyopathic disease or congenital heart disease. Finally, we attempt to reconcile the results of these clinical studies with experimental data in both human, animal, and cellular models, to create a mechanistic link between diastolic dysfunction and pathological changes that increase the likelihood of AF.

Atrial and Ventricular Diastolic Dynamics

A number of excellent resources are available for more detailed review of the dynamics of ventricular diastole, including invasive and noninvasive descriptions. Ventricular diastole is the period of the cardiac cycle that begins with the closure of the aortic valve and ends with mitral valve closure, during which the ventricle is filling with blood. It can be further divided into 4 sequential components: (1) isovolumic relaxation, (2) early rapid filling, (3) diastasis, and (4) atrial systole (late filling). Dynamically, none of the components is completely independent of each other, or the systolic function of the heart, and changes in one can influence the others in predictable and unpredictable ways.

Essentially, there are 2 characteristics of ventricular function that contribute to diastolic function: relaxation (lusitropy) and compliance. Relaxation refers to the process by which the ventricular pressure drops after contraction to a level below that of the atrium, causing blood to flow down its pressure gradient and fill the ventricle. Compliance refers to the pressure–volume relationship as blood fills the ventricle, with a decrease in compliance causing an increase in the pressure per given amount of volume filling the chamber. Conceptually, relaxation and compliance might be described as independent factors in diastolic function. In reality, the 2 are intimately connected, and most measures of diastolic function are unable to distinguish them from each other.

During ventricular diastole, the atrium also cycles through a series of phases—passively, as a result of ventricular dynamics, and actively, through atrial systole. In early ventricular diastole, immediately after opening of the mitral valve, the atrial pressure decreases as a result of ventricular relaxation. During this early phase, blood flows from the pulmonary veins (PVs) into the left atrium (LA), and from the LA into the left ventricle (LV), and accounts for the first of 2 atrial filling phases (y descent). As the ventricle fills, and its pressure rises to match the atrium, filling slows and the atrium reaches its end-diastolic volume (or pre-A volume), which occurs just before atrial contraction. In late ventricular diastole, the LA then contracts, ejecting blood across the mitral valve and into the LV. This point, at the end of atrial systole when the mitral valve has closed before isovolumic contraction, is when the atrial volume is the lowest of the cardiac cycle (minimum atrial volume). After atrial systole, atrial pressure decreases owing to relaxation, and ventricular contraction, as well. The latter occurs because, when the ventricle contracts, the base of the heart (containing the mitral valve) descends toward the apex, essentially pulling the atrium with it. This drop in atrial pressure (x descent)
facilitates the second filling phase from the PVs up to the point at which ventricular systole has completed and relaxation begins. This causes the relative atrial pressure to rise above the ventricular pressure, the mitral valve to open, and passive ventricular filling to begin anew. At the period just before the mitral valve opening, the atrial size is at its largest (maximum atrial volume). From these measures an atrial emptying fraction, or atrial reservoir function, can be calculated by the use of minimum atrial volume as (maximum atrial volume/minimum atrial volume)/maximum atrial volume (18–20) (Figure 1). Atrial systolic function, or atrial ejection fraction, can also be calculated as it is in the ventricle by the use of preatrial volume and minimum atrial volume.

**Measurement of Ventricular Diastolic Function**

No current modality perfectly measures all aspects of ventricular diastole, and very few measures have been able to specifically evaluate effects on atrial function. The earliest attempts to measure diastolic function were invasive and focused on the relationship of LV pressure and volume during diastolic filling and essentially measured ventricular compliance.13 Because these measures failed to describe the early phase of diastole, and thus failed to describe the lusitropic properties of the heart, other measures were introduced. Among the more robust was tau, the time constant of relaxation,21,22 which measures the decay in ventricular pressure during ventricular relaxation. In addition to being invasive, and thus difficult to apply to large populations, the clinical application of tau has been shown to be limited.23

With the development of 2-dimensional echocardiography, pulse-wave Doppler, tissue Doppler, and speckled tracking, echocardiography has become the primary modality for clinical assessment of diastolic function. Among the earliest echocardiographic measures of diastolic function was transmitral Doppler, through which the early (E wave) and late (A
wave) filling can be measured (Figure 2). In 1988, Van Dam and colleagues proposed using the combined index, the peak E/peak A ratio, because they determined that it allowed adjustment for differences in mitral annular size. This metric has since become the most broadly used clinical measure of diastolic function. Other measures of transmirtal flow, including the E-wave deceleration time and velocity-time integral of the E and A wave, have also been used to describe LV diastolic function. However, there are drawbacks to the use of the transmirtal inflow alone in the assessment of diastolic function, and particularly in the description of diastolic ventricular filling pertaining to the atra and the development of AF. Mitral inflow patterns are determined primarily by loading conditions, and thus can change with Valsalva, volume shifts, or preload-reducing agents. This shortcoming frequently requires incorporation of other measures to more accurately describe diastolic function.

Other methods have been developed to improve the estimates of diastolic function, including pulse-wave Doppler at the PV ostia (PV velocity measurements), tissue Doppler measurement of ventricular relaxation, color Doppler M-mode across the mitral valve (propagation velocity), and speckled tracking analysis (strain rates). In addition, other groups have used more indirect measures, such as plasma brain natriuretic peptide levels or LA size, to enhance the picture of diastolic function. Each of these modalities, alone or combined with others, has shown promise in the study of diastolic function, although in many cases, reproducibility and ease of measurement are ongoing issues.

**Mechanisms and Classification of LV Diastolic Dysfunction**

One can never truly separate a classification scheme from the modality used in its study, and diastolic dysfunction is a very good example of this principle. Much of the current classification scheme used in the study of diastolic dysfunction was created through categorization of echocardiography metrics, which have shaped much of the thinking surrounding analysis of diastolic dysfunction. A full assessment of the conceptual basis for measures of diastolic dysfunction is beyond the scope of this review, and the reader is referred to one of several excellent reviews and texts.

From the ventricular perspective, diastolic dysfunction encompasses 3 basic problems that occur during ventricular diastole: (1) impaired ventricular relaxation, (2) decreased ventricular compliance, and (3) increased atrial filling pressures. Although longitudinal studies demonstrating progression through various phases of diastolic function have been limited, a study by Aljaroudi and colleagues did demonstrate that individuals who demonstrated worsening of diastolic dysfunction on follow-up study had an increased mortality risk. A classification scheme based on echocardiographic patterns observed in patients with diastolic dysfunction has been developed and includes class I (impaired relaxation), class II (pseudonormalization), class III (restrictive filling, reversible), and class IV (irreversible restrictive filling pattern) (Figure 3).

Among the earliest changes in diastolic function is impaired relaxation, which can be due to abnormal active relaxation, such as from impaired calcium handling and contractile fiber cycling, or abnormal passive recoil due to...
poor ventricular systole or deficient structural proteins, such as titin. Regardless, if ventricular relaxation is impaired, less ventricular filling occurs in early diastole, leading to more ventricular filling occurring later in diastole, as a result of atrial contraction (hence, a smaller transmitral E wave and larger A wave). The impact of this change on atrial function is less predictable, although based on studies of PV velocities, it appears that the atrium encounters a situation of an increased preload (preatrial volume) and a likely increase in the atrial ejection fraction. In this state, the amount of work done by the atrium is increased, which in theory would increase the energy demands of the atrial myocytes and could have important ramifications for future remodeling. One interesting issue is whether this state is considered normal in elderly patients, in whom a peak E/A ratio of <1 is common, or whether impaired relaxation is a part of natural cardiac aging, and thus represents an important risk factor for the development of AF. The implication of this dilemma concerning clinical studies remains to be determined.

At some point after relaxation has become impaired, LA pressure increases and LV compliance decreases. These changes could occur as a result of the impaired relaxation itself, although it is also likely that they occur as a result of progression of the underlying condition (eg, hypertension) leading to LV hypertrophy and fibrosis. With the use of invasive methods, these 2 changes can be measured through direct measurement of the LA pressure, and through evaluation of the end-diastolic pressure–volume relationship, as well. Noninvasively, these measurements are more difficult to make.

In terms of mitral inflow, an increase in LA pressure relative to the ventricle will increase the transmitral E wave (early filling velocity) and, in theory, the transmitral A wave (although more often a decrease in ventricular compliance that accompanies the increase in LA pressure causes higher ventricular pressure at end of diastole, and with it a decrease in the pressure gradient at the time of atrial contraction resulting in a smaller A wave). Because the resultant peak E/A ratio normalizes, this state is referred to as pseudonormalization, or stage II diastolic dysfunction. As compliance decreases further and atrial filling pressures increase even more, a state of restrictive filling occurs, in which nearly all of the LV filling occurs rapidly, with little atrial contribution (stage III). With this pattern, LV filling becomes limited to a brief period at the very beginning of diastole, with a resultant large transmitral E wave, short deceleration time, and minimal transmitral A wave. This state is associated with very high filling pressures and often symptoms of heart failure. A final state (stage IV), in which the restrictive filling pattern becomes irreversible despite maneuvers to decrease filling pressure, such as Valsalva, has also been described. Its relevance with regard to risk of AF is unknown.

One consistent observation with progressive diastolic dysfunction has been that LA dilation occurs concurrently, and LA pressures described in stages II to IV of diastolic dysfunction creates a highly unfavorable situation for the LA. Unlike the LV, the LA is a thin-walled structure and thus primarily responds to increased pressure through dilation rather than hypertrophy (wall thickening). As a result, LA dilation is a major manifestation of diastolic dysfunction, which has important implications with regard to AF.

**Clinical Studies of AF and Diastolic Dysfunction**

Despite what would appear to be a well-defined link, clinical data connecting diastolic dysfunction and risk of nonvalvular AF in populations without structural heart disease are limited, particularly on a mechanistic level. Moreover, owing to the effects of prevalent AF on LA size and function, studies of paroxysmal or persistent AF and diastolic dysfunction will tend to be more complex and challenging than those of incident AF. Among these studies, the most robust association has been that of increased LA size, with a number of studies demonstrating an association with AF. As far as incident AF, several studies have attempted to examine the different patterns and individual measures of diastolic dysfunction with mixed results.

Small studies in patients with myocardial infarction or diabetes mellitus have detected an increase in the risk of incident AF in patients with diastolic dysfunction, especially in patients with pseudonormal or restrictive filling patterns. Although they did not include other parameters that might distinguish pseudonormal from normal filling, Vasan et al examined data from the longitudinally followed Framingham Heart Study and found a trend toward increased incident AF in patients with transmitral peak E/A greater than median (1.23). Overall, these studies were too small to adjust for common risk factors of AF and many did not include LA size as a variable, which makes broad application difficult in terms of understanding the mechanisms of risk of AF.

An early study to examine diastolic dysfunction and incident AF was performed by Tsang and colleagues, who followed 840 elderly men and women, of whom 80 (9.5%) developed AF over a mean follow-up of 4.1 years. With the use of a derived classification system for diastolic dysfunction based on transmitral Doppler patterns and LA volume index, they found that more severe diastolic dysfunction was associated with an increased risk of incident AF. The strongest predictor of AF in their study was LA volume index, with none of the other individual Doppler diastolic parameters reaching significance. In a follow-up study, these authors examined only patients with impaired relaxation based on transmitral peak E/A (<0.75) and deceleration time (>240 ms) and found an increased risk of the combined end point of AF and heart failure with impaired relaxation, although this effect was not significant in the absence of an increased LA volume index (>27 mL/m²), again suggesting that it was LA size, rather than any particular diastolic parameter, that increases risk of AF.
In what is, to date, the largest study examining diastolic dysfunction and AF, 4480 participants of the Cardiovascular Health Study were followed for a mean of 12.1 years, with 1219 cases (27.2%) of incident AF. Limited to only a few measures of diastolic function, this study found that the transmitral E-wave velocity, the LA dimension, and the transmitral A-wave velocity-time integral were significantly associated with the development of AF independent of each other and other AF risk factors after nonlinear modeling. Among the findings with potential mechanistic implications for AF, the transmitral A-wave velocity-time integral was found to display a U-shaped relationship with AF risk, a finding that others have noted as well. This finding implies that at either end of the spectrum—a heart with a large proportion of LA filling and one in which the LA contributes very little to filling—there is an increased risk of development of AF. Another finding was that, after hierarchical clustering of the diastolic variables, those clusters with an increased peak transmitral E-wave velocity, rather than increased LA diameter, were at increased risk of AF. Because, as mentioned above, an increase in the transmitral E wave tends to occur with pseudonormal or restrictive filling patterns, this finding suggested that these participants were developing increased filling pressures and that this was the most important factor in developing AF.

Interestingly, in the Cardiovascular Health Study population, a separate study also found that an increase in N-terminal pro-B-type natriuretic peptide was associated with incident AF. Because both pseudonormal and restrictive filling patterns have also been associated with elevated natriuretic peptide levels, as opposed to that of impaired filling patterns, this finding suggested that these participants were developing increased filling pressures and that this was the most important factor in developing AF.

AF after myocardial infarction, and AF recurrence after PV isolation, noted that LA enlargement in the setting of mitral regurgitation tends to be more spherical than that occurring with diastolic dysfunction, which tends to be more eccentric, suggesting that the more spherical modeling is more relevant to the development of AF. However, a study by Gertz et al found that mitral regurgitation tended to improve with restoration of sinus rhythm, implying that AF itself can exacerbate mitral regurgitation. Because of the heterogeneity of mitral regurgitation in terms of causes and characteristics, the challenges with accurate quantification, and the impact of mitral regurgitation on passive filling parameters (transmitral E wave), the assessment and adjustment for mitral regurgitation in clinical studies to date has likely been inadequate to fully separate effects due to mitral regurgitation from those due to diastolic dysfunction.

Mechanistic Connections Between Diastolic Dysfunction and AF

Based on the clinical studies discussed above, a number of mechanistic links can be made between diastolic dysfunction and AF. Broadly, the effects of LV diastolic dysfunction on the LA can be grouped into 3 mechanisms that can promote AF (Figure 4): (1) increased atrial afterload, (2) increased atrial stretch (preload), and (3) increased atrial wall stress as a result of dilation.

Increased Atrial Afterload

As previously mentioned, clinical studies have suggested a U-shaped relationship between the transmitral peak A wave and the risk of AF. Although the increased A wave of this U-shaped relationship might reflect larger filling volumes (see below), the smaller transmitral A wave reflects a higher LV pressure against which the LA must contract, or an increased atrial afterload.
There is evidence that an increased atrial afterload is proarhythmic, at least in the short term, based on studies in which the atrioventricular interval is manipulated through pacing. Calkins et al.\(^5\) found that with simultaneous LA and LV pacing there was a decrease in the LA refractory period, whereas with a gradual increase in AV interval there was no effect on the LA refractory period or inducibility of arrhythmias.\(^6\) Other groups have also described the effects of acute changes in atrial afterload on LA repolarization.\(^7\)–\(^9\) and similar experiments in animal models have suggested that these changes in refractory periods were mediated, at least in part, via changes in autonomic tone.\(^90\) Because shortening of atrial refractory periods has been shown to promote the maintenance and development of AF,\(^91\)–\(^93\) these results suggest a potential mechanism by which increased atrial afterload might promote AF.

Another potential effect of atrial afterload can be inferred with what is seen with increased LV afterload. In the LV, the response to chronic afterload is cellular hypertrophy, which can over time lead to failure and dilation.\(^94\) In models of atrial pathology, investigators have detected a different response that suggests that the atria may be more likely to develop fibrosis than hypertrophy when faced with increased afterload.\(^95\)–\(^96\) Whether these changes occur clinically and are predictive of arrhythmic events remains to be determined. Furthermore, most clinical models of atrial afterload, such as mitral stenosis, are also associated with impaired passive ventricular filling, which also increases atrial preload, the impact of which is discussed below.

**Atrial Preload/Stretch**

Among the echocardiographic patterns of diastolic dysfunction associated with AF, the pseudonormal and restrictive filling patterns,\(^46,65,69,71\) including an increased transmitral peak E wave,\(^68,72\) appear to be consistently associated with an increased risk of AF. Physiologically, when the increased filling pressure (preload) associated with these states is transmitted back to the atrium during the early filling phase, or when blood is returned to the LA from the LV with mitral regurgitation, the amount of stretch imposed on the atrial cells is also increased, an effect that can be proarhythmic.

Tsai et al.\(^97\) examined the cellular effects of atrial stretch by using mouse atrial cells that were stretched and then rapidly electrically stimulated, and observed spatial and temporal alternans of the atrial action potential duration, a possible precursor to AF. These changes were attributed to downregulation of sarcoplasmic adenosine triphosphatase 2 owing to the ability to reverse these electric changes through overexpression of this protein in the cells. In another study, Saygili et al.\(^98\) examined protein and gene expression in stretched neonatal rat atrial cells and found that stretch induced expression of ion channels, Kir2.1, Kir2.3 (IK1), and Kv1.5 (Ikur), resulting in the shortening of the atrial action potential duration, an effect that favors the maintenance of AF.\(^92\) All of these effects were reversible with losartan administration,\(^98\) suggesting that they may occur downstream of the angiotensin-signaling pathway, which may have important clinical implications.

Based on the multiple-wavelet hypothesis proposed by Moe et al.\(^99\) in 1964, any increase in LA size increases the probability of AF because of an increased ability to accommodate multiple wavelets of reentry. Beyond increasing atrial wall stress long term (discussed below), an increase in atrial size as a result of stretch alone would, by this mechanism, increase the likelihood of developing AF. Studies attempting to distinguish this effect from the fibrosis due to wall stress are limited.

**Atrial Wall Stress**

The clinical significance of LA enlargement on the risk of AF has been well documented.\(^46,65–68\) According to the Law of Laplace, an increase in diameter increases the wall tension in a linear fashion; thus, as LA diameter increases, so increases atrial wall stress. One mechanism by which the LA can compensate for these new demands is through generation of increased extracellular matrix, with expression of proteins such as collagen. With increasing wall stress, atrial fibrosis progressively increases, creating an AF substrate.\(^100,101\) Increased LA size has been shown to correlate with the amount of atrial fibrosis,\(^102\) and it has been suggested that the pathway from atrial dilation to AF involves the development of fibrosis.\(^100\) Electrophysiologically, atrial fibrosis impairs intermyocyte coupling via gap junctions,\(^103\) resulting in fragmented conduction that promotes arrhythmias.\(^104\)

Angiotensin II has been shown to increase fibroblast proliferation in the atria,\(^105\) and animal models of AF using angiotensin-converting enzyme inhibitors have shown decreased fibrosis and AF.\(^106,107\) For prevention of new AF, initial studies suggested a clinical benefit to the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers,\(^108,109\) although, in many of these cases, the effect may have been due to prevention or treatment of the underlying risk factor (eg, hypertension) than to any intrinsic effect on atrial remodeling.\(^110\) This finding may also explain why studies of angiotensin receptor blockers/angiotensin-converting enzyme inhibitors on prevalent AF have failed to detect an effect on atrial remodeling and the risk of AF.\(^111–113\) Whether these results reflect a different mechanism of remodeling in the atria in comparison with the ventricles\(^96,114\) or the remodeling changes in the atria are irreversible by the time AF occurs is unclear.

Of note, in a follow-up study to the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico (GISSI)-AF study, valsartan (an angiotensin receptor blocker) failed to affect echocardiographic parameters of diastolic function.\(^113\) Other studies of diastolic function have suggested otherwise, with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers improving diastolic parameters, although the effect appeared to occur primarily through effects on blood pressure alone.\(^115,116\) Other agents directed at aldosterone, transforming growth factor β, and inflammation have shown promise at reducing fibrosis; however, results on prevention of AF have been limited.\(^100\)

**Limitations and Future Directions**

A key limitation to assessment of the risk of diastolic dysfunction on the development of AF is the lack of effective therapy for diastolic dysfunction itself.\(^117\) Although this
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limitation may in part reflect finding the appropriate timing for therapy as suggested above, newer therapies are clearly needed. Cyclic GMP–enhancing agents,119 phosphodiesterase 5 inhibitors,119 and uncoupling of nitric oxide synthase120 are currently being tested in the treatment of diastolic dysfunction. Future studies are needed to determine whether these agents are also effective in the prevention of AF.

Another key limitation not to be overlooked in clinical studies is the degree and effect of subclinical AF on diastolic function. Once AF has developed, objective assessment of diastolic function on the risk of AF becomes more complex because of the effects on atrial size and function,62–64,121 and structural and electric properties of atrial cells, as well.92,106 A review of the studies of diastolic dysfunction as a result of AF is beyond the scope of this review,12,122 but 1 issue that must be examined in any study of diastolic dysfunction and AF is the method of electric monitoring of atrial arrhythmias. This issue is especially important in lieu of recent studies finding that even short amounts of AF have clinical relevance with an increased risk of adverse outcomes.123

As technology advances, exciting novel methods for assessing diastolic function and, in particular, for quantifying LA function124 are emerging. With more accurate noninvasive methods of measuring LA volume using 3-dimensional echocardiography,125 and novel approaches to quantifying LA mechanics such as speckle-based strain42 and velocity vector imaging, as well,41 a more complete characterization of diastolic dysfunction on the LA will become available. As these novel techniques are applied across large study cohorts, new paradigms will likely emerge for both treatment of diastolic dysfunction and prevention of AF.

Conclusions

Diastolic dysfunction presents a potentially important link between many common risk factors, such as hypertension, age, obesity, and diabetes mellitus, and the development of AF. Clinical studies of diastolic dysfunction and the risk of nonvalvular AF in populations without structural heart disease suggest that increased filling pressures and LA dilation may represent important mechanisms of disease. Among the mechanisms through which diastolic dysfunction may increase the risk of AF, increased atrial afterload, atrial myocyte stretching, and atrial wall stress are important potential connections. Further research into both treatment of diastolic dysfunction and methods for noninvasive assessment are needed to further clarify this likely connection.

Disclosures

None.

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