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Journal of Atrial Fibrillation
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Role of Left Ventricular Diastolic Dysfunction in Predicting Atrial Fibrillation Recurrence after Successful Electrical Cardioversion

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Abstract

The role of left ventricular (LV) diastolic dysfunction in predicting atrial fibrillation (AF) recurrence after successful electrical cardioversion is largely unknown. Studies suggest that there may be a link between abnormal LV compliance and the initial development, and recurrence of AF after electrical cardioversion. Although direct-current cardioversion (DCCV) is a well-established and highly effective method to convert AF to sinus rhythm, it offers little else beyond immediate rate control because it does not address the underlying cause of AF. Preservation of sinus rhythm after successful cardioversion still remains a challenge for clinicians. Despite the use of antiarrhythmic drugs and serial cardioversions, the rate of AF recurrence remains high in the first year. Current evidence suggests that diastolic dysfunction, which is associated with atrial volume and pressure overload, may be a mechanism underlying the perpetuating cycle of AF recurrence following successful electrical cardioversion. Diastolic dysfunction is considered to be a defect in the ability of the myofibrils, which have shortened against a load in systole to eject blood into the high-pressure aorta, to rapidly or completely return to their resting length. Consequently, LV filling is impaired and the non-compliant left ventricle is unable to fill at low pressures. As a result, left atrial and pulmonary vein pressure rises, and electrical and structural remodeling of the atrial myocardium ensues, creating a vulnerable substrate for AF. In this article, we review the current evidence highlighting the association of LV diastolic dysfunction with AF recurrence after successful electrical cardioversion and provide an approach to the management of LV diastolic dysfunction to prevent AF recurrence.

Introduction

AF is a highly prevalent condition and is associated with substantial morbidity and mortality. Currently, AF affects approximately 2.3 million individuals in the United States,[1] and if current trends continue, the number of individuals with prevalent AF in the US is projected to increase to 5.6 million by 2050.[1] Similar increase in AF prevalence rates has also been projected in northern Europe. In a large community-based study from Reykjavik, Iceland, the prevalence of AF was estimated to increase from 2.0% in 2008 to 4.3% by 2050, assuming that the incidence of AF remains constant.[2] The prevalence of AF is strongly related to age, affecting approximately 4% of persons older than 60 years and up to 8% of individuals older than 80 years.[3] Approximately 70% of individuals with AF are between 65 and 85 years of age. [1] AF is an independent predictor of mortality and a major risk factor for ischemic stroke.[4,5] The attributable risk of all new stroke from AF is estimated to be 15%, and 30% for those over the age of 80 years.[6] The precise mechanisms of AF are poorly understood.

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Several lines of evidence indicate that a trigger arising from the pulmonary veins and a substrate broadly related to abnormal LV compliance, increased left atrial pressure, stretch and fibrosis are key players in the pathogenesis of AF. Over the years, a body of evidence has been accumulated suggesting that LV diastolic dysfunction may be a common denominator underlying a permissive profibrillatory environment that promotes the initiation and recurrence of AF.[7-14] Assessment of diastolic function therefore carries paramount importance in patients with AF. Although electrical cardioversion restores sinus rhythm in a substantial proportion of patients with AF, particularly those of shorter duration, the rate of AF recurrence is excessively high. This review intends to summarize the role of LV diastolic dysfunction as a major risk factor for AF recurrence after successful electrical cardioversion.

Assessment of Diastolic Function

Evaluation of diastolic function by echocardiogrphy is essential in the risk stratification of arrhythmia recurrence after electrical cardioversion.[15] Assessment of diastolic function involves integration of multiple echocardiographic parameters for estimation of LV filling pressure.[16] Clinically useful mitral inflow parameters, reflecting the pressure gradient between the left atrium (LA) and LV, include mitral inflow Doppler patterns of early filling peak velocity (E), atrial peak velocity (A), E/A ratio, and deceleration time (DT). These transmitral flow parameters are load dependent and are generally used in combination with tissue Doppler imaging (TDI), which are less hindered by preload dependency, along with pulmonary vein flow pattern and the response of E/A to Valsalva maneuver. Diastolic dysfunction is characterized by progressive reduction in LV compliance with corresponding impairment in myocardial relaxation, resulting in elevated LV end diastolic pressure despite normal end diastolic volume. As diastolic dysfunction progresses, the pressure gradient between the left atrium and left ventricle increases. The transmitral inflow pattern (E/A ratio and E wave deceleration time) in turn takes a parabolic distribution dependent upon loading conditions. Patients with an abnormal mitral inflow pattern on Doppler echocardiography, such that the A-wave velocity exceeds the E-wave velocity and the deceleration time of the E-wave prolongs, demonstrate a pattern consistent with abnormal left ventricular relaxation. As left ventricular filling pressures rise, the deceleration time of the E-wave shortens, the ratio of peak E-wave to A-wave velocities increases, and mitral annulus e' velocity, as assessed by tissue Doppler imaging, decreases. The physiology of left ventricular filling progresses from a pattern of abnormal relaxation to a pattern of restrictive filling. This shift results in significant derangement of the normal left ventricular pressure-volume relationships.[17,18] Table 1 summarizes the echocardiograhic crite-

Table 1 | **Doppler Criteria For Classification of Diastolic Function and Estimation of LV Filling Pressure**

	Normal Diastolic Function	**Grade I (Impaired Relaxation)**	Grade **II**(pseudo-normal)	**Grade III(reversible/Fixed Restrictive)**
Mitral Inflow	E/A 0.75-1.5 DT 150-240ms	E/A< 0.75 DT >240ms	E/A 0.75-1.5 DT 160-240ms	E/A >1.5 DT<160ms
Mitral Inflow at Peak Valsalva	ΔE/A<0.5	ΔE/A<0.5	ΔE/A≥0.5	ΔE/A≥0.5/<0.5
Septal è	≥8	<8	<8	<8
TDI at Mitral Annular Motion	E/è <8	E/è≤8	E/è9-12	E/è≥13
Pulmonary Venous Flow	S >D ARdur<Adur	S ≥D ARdur<Adur	S <D or ARdur-Adur≥ 30ms	S <D or ARdur-Adur≥30ms
LA Volume	<34mL/m2	≥34mL/m2	≥34mL/m2	≥34mL/m2
LA Compliance	Normal	Normal to ↓	↓↓	↓↓↓
LV Filling Pressure	Normal	Normal to↑	↑↑	↑↑↑

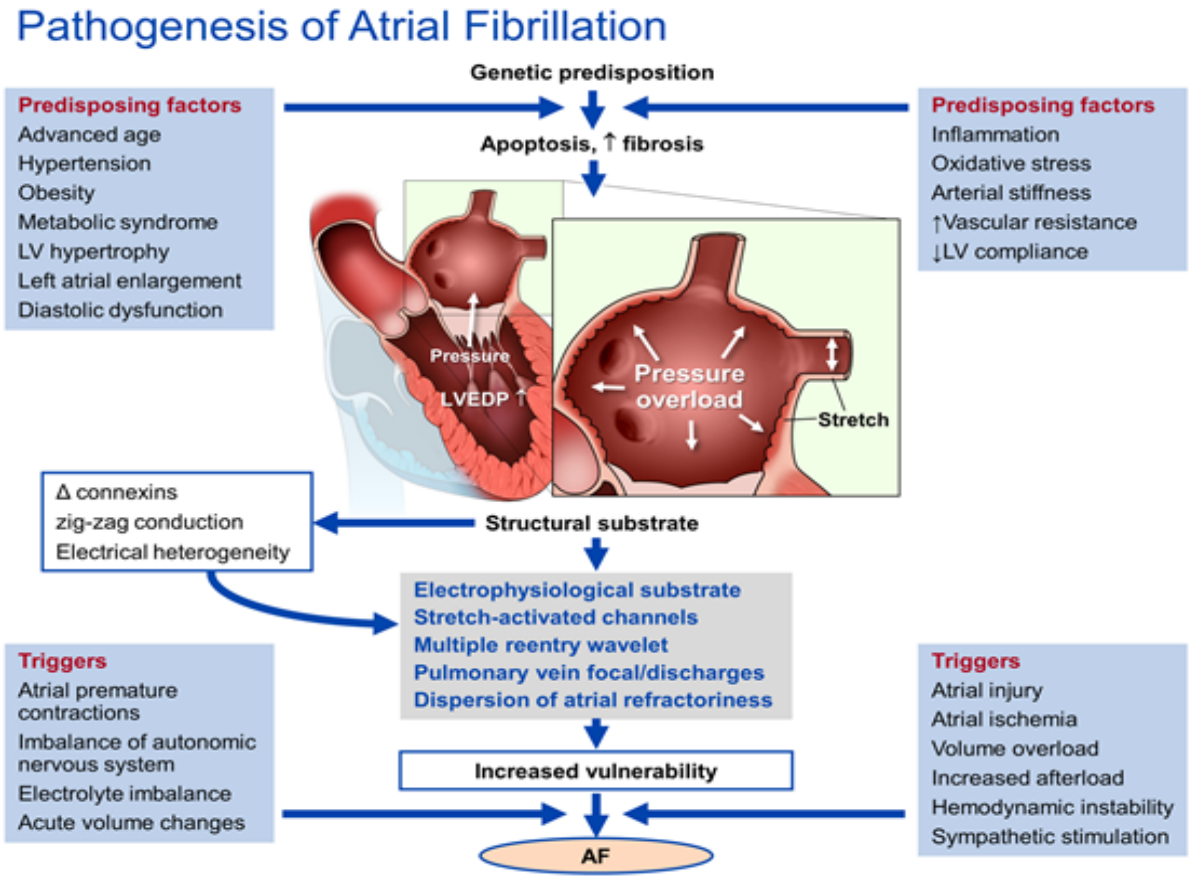
Doppler Criteria for Classification of Diastolic Function and Estimation of LV Filling Pressure E= peak mitral early filling velocity; A= mitral a-wave velocity at atrial contraction; DT= mitral E-wave deceleration time; e'= velocity of mitral annulus early diastolic motion; S= pulmonary vein systolic forward flow; D= pulmonary vein diastolic forward flow; ARdur= pulmonary vein atrial reversal flow duration; Adur= mitral a-wave duration, LA= left atrial, LV=left ventricle, TDI= Tissue Doppler imaging.

ria for classifying LV diastolic dysfunction. The individual non-invasive echocardiographic parameters for evaluation diastolic function have generally demonstrated adequate correlation with invasively obtained filling pressures from the cardiac catheterization laboratory.[16,19] For example, in a study of patients with coronary artery disease, a difference of 0 between the duration of the pulmonary venous A-wave and the mitral inflow A-wave demonstrated a sensitivity of 82% and a specificity of 92% for left-ventricular end-diastolic pressures >20 mmHg.[20] In patients with low ejection fraction, E/A ratio ≥2 demonstrated a 52% sensitivity and 100% specificity for left atrial pressures ≥20 mmHg.[21] Similarly, a deceleration time of the mitral inflow E-wave of <180 msec demonstrated 100% sensitivity and specificty for left atrial pressures ≥20 mmHg.[21] In patients with normal left ventricular ejection fraction, the ratio of the early diastolic mitral inflow velocity vs. the tissue Doppler velocity of the medial mitral annulus in early diastole (i.e. E/e') has demonstrated excellent correlation with elevated filling pressures.[16] When incorporated into a comprehensive algorithm, careful non-invasive assessment using echocardiographic parameters can provide an accurate estimation of left ventricular diastolic function.

Pathophysiology of Atrial Fibrillation: Role of Diastolic Dysfunction

The pathophysiology of AF is complex and is incompletely understood. However, the development of AF appears to require both a trigger and an atrial substrate. Figure 1 illustrates our current understanding of the pathophysiology of atrial fibrillation. During diastole, the left atrium is directly exposed to pressures in the left ventricle that increase with abnormal relaxation and decreased compliance. LA pressure increases to

Figure 1: The Pathogenesis of AF is Multifactorial and is Thought to Involve an Interaction between Initiating Triggers and an Atrial Tissue Substrate Capable of Maintaining the Arrhythmia. The Interrelations between the Different Predisposing Factors and Triggers are Illustrated, Demonstrating the Multi-Causal and Complex Nature of AF



maintain adequate filling, and the increased atrial wall tension leads to atrial electrical and structural remodeling including stretching, dilatation and fibrosis of the atrial myocardium, providing a vulnerable substrate for AF. Normally, the left atrium is a highly compliant structure that maintains relatively low pressures despite mild volume shifts. Thus, atrial volume overload with low intraatrial pressure is benign. In this circumstance, the atria can be enlarged and AF may not occur if the atrial pressure is low. For instance, LA enlargement in athletes, which represents a physiologic cardiac remodeling due to systematic exercise training, appears to be benign and is rarely associated with AF. In a large population of highly trained athletes,[22] Pelliccia and colleagues showed that the prevalence of AF among trained athletes was similar to that in the general population (<1%),[23] despite a high frequency (20%) of LA enlargement. However, under conditions of physiologic stress when LV compliance is reduced, LA pressure rises causing atrial pressure overload that later leads atrial stretch, myolysis, and fibrosis. [24,25] This form of LA enlargement is pathological and has been shown to be independently associated with incident AF.[26]

Under conditions of pathophysiological stress or aging, the myocardium becomes progressively stiff and fibrotic.[24,25] This leads to abnormalities in ventricular relaxation and increased filling pressures characteristic of diastolic dysfunction.[27] The increased in atrial pressure with subsequent left atrial and pulmonary veins dilation and activation of stretch-sensitive signaling pathways, may induce ectopic firing from the pulmonary veins and contribute to the development and maintenance of atrial fibrillation.[28-31] The muscular wall of the left atrium may extend up to a few centimeters around the pulmonary veins.[32] In the setting of an additional substrate in the atria, the atrial tissue in the pulmonary veins is often the initiating focus for AF,[33] and has relatively short refractory periods compared to other parts of the atria.[34] This heterogeneity of conduction facilitate the development of a substrate for reentry, favoring initiation, recurrence and maintenance of AF.[35] Accurate non-invasive measurement of filling pressures therefore carries paramount importance in the assessment of patients with AF. Tissue Doppler imaging (TDI) techniques have significantly enhanced the ability of echocardiography to detect abnormalities in left-sided cardiac filling pressures. In a study of patients undergoing simultaneous hemodynamic cardiac catheterization and echocardiography, the ratio of mitral valve diastolic inflow velocity over the diastolic inflow TDI velocity of the medial mitral annulus (i.e. E/e') provided the most accurate assessment of left ventricular filling pressures when compared to other measures of diastolic dysfunction.[16] The correlation of E/e' with elevated filling pressures has also been demonstrated in patients with AF with sensitivities >70% and specificities >90%.[36] Tissue Doppler imaging can therefore provide significant insight into the pathophysiological derangements in patients with AF.

Role of Cardioversion in the Management of Atrial Fibrillation

Direct-current cardioversion is an effective and useful technique frequently used to restore sinus rhythm and has been a mainstay of therapy for nearly 4 decades in patients with AF.[37,38] Despite the high initial success rates (>90%) of this procedure, there is an excessively high rate of AF recurrence after an initially successful cardioversion to sinus rhythm with or without the concomitant use of an anti-arrhythmic agent.[39] Success of rate or rhythm control by any means is related to AF duration[40] electrical, morphologic, and ultrastructural remodeling,[41] and atrial size,[42,43] and global function.[44,45] The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study randomized 4060 patients with AF to a strategy of rate vs. rhythm control.[46] A subgroup study analyzed data in 1293 patients with AF >48 hours who underwent a successful pharmacological or electrical cardioversion.[47] Among all 1293 patients in the subgroup study, 503 (39%) experience recurrence of AF within 2 months of successful cardioversion. In another study, in which one hundred consecutive patients admitted for DCCV of chronic AF were followed, in the absence of antiarrhythmic medication, only 23% and 16% of patients remained in sinus rhythm after 1 year and 2 years, respectively.[48] Duration of AF, which reflects the degree of atrial remodeling and myocyte death over time, has been shown to be a strong predictor of the success of cardioversion. Elhendy and colleagues[49] found that among patients with AF of short duration (<48 hours), 95% successfully con-

verted to sinus rhythm with direct-current shock. However, among those with AF of long duration (>1 year), success rates dropped to 72%. Other factors associated with an unsuccessful cardioversion included clinical factors known to influence filling dynamics, including a higher body mass index, a history of a dilated cardiomyopathy, and lower LV ejection fraction. A prospective study of 246 patients undergoing DCCV also found that factors associated with atrial remodeling and diastolic dysfunction such as advanced age, and longer arrhythmia duration, negatively impacted the success rate of DCCV.[50]

Implications of Left Ventricular Diastolic Dysfunction in Atrial Fibrillation

Diastolic dysfunction has been associated with the development of nonvalvular AF (NVAF). A population-based study of 840 elderly patients from Olmsted County, MN with no prior history of atrial arrhythmias demonstrated a strong and independent association of the presence and severity of diastolic dysfunction with higher risk of developing NVAF. Kaplan-Meier five-year age-adjusted cumulative risks of NVAF were 1%, 12%, 14%, and 21% for patients with normal, abnormal relaxation, pseudonormal, and restrictive LV diastolic filling, respectively. [51] Similarly, in another recent population-based study of Olmsted County, Minnesota patients undergoing cardiac surgery between 2000 and 2005, we showed that the rate of new-onset postoperative AF increased exponentially with the severity diastolic dysfunction. After adjusting for clinical and surgical risk factors, abnormal LV diastolic function grade (DFG) (DFG 1, OR: 5.12 [p = 0.006]; DFG 2, OR: 9.87 [p < 0.001]; and DFG 3, OR: 28.52 [p < 0.001]) independently predicted the development of new-onset AF after cardiac surgery.[8]

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Left atrial (LA) enlargement, which reflects the cumulative effects of LV filling pressures over time, and severity of diastolic dysfunction, represents a quantifiable surrogate of the arrhythmogenic substrate for the development and AF recurrence. Therefore, recurrent AF following cardioversion is related to the preexistence and continuation of increased LV filling pressure and LA remodeling. Previous studies have shown that the measurable increase in LA volume precedes the onset of non–surgery-related AF.[52,53] Marchese and colleagues[43] prospectively studied 411 patients (mean age 64.1 +/- 11.4 years, 34.5% women) with AF who underwent successful cardioversion and showed that, after a median follow-up of 11.5 months, 60.8% of patients develop AF recurrence. Left atrial volume index (LAVI) was a significant and independent predictor of AF recurrence. Each mL/m2 increase in LAVI was independently associated with a 21% increase in the risk of AF recurrence (adjusted OR 1.21, CI 1.11–1.30, P <0.001). When LAVI was categorized according to the American Society of Echocardiography and European Association of Echocardiography (ASE/EAE) recommendation for chamber quantification cut-offs, there was a progressive increase in the cumulative risk of AF recurrence from normal to severely increased LAVI, suggesting causality in terms of a dose response. By ROC curves, the best discriminating value of LAVI to predict AF recurrence was 33.5 mL/m2, with 83% sensitivity and 76% specificity.

Diastolic dyfunction appears to be a consistent predictor of AF recurrence after cardioversion. We prospectively studied 59 consecutive patients with AF undergoing transesophageal echocardio-

graphically guided electrical cardioversion. The overall arrhythmia recurrence rates at 1, 2, and 3 years were 57%, 67%, and 78%, respectively, irrespective of antiarrhythmic therapy at discharge. Patients with echocardiographic evidence of high LV filling pressures, defined as having a short deceleration time (restrictive filling) prior to cardioversion, trended toward a higher rate of arrhythmia recurrence compared to those with lower filling pressures (86% vs. 53%; P = .06).[7] Others have found LA enlargement, a marker of chronically elevated LV filling pressure, to be an independent predictor of AF recurrence.[54]

Prevention of AF Recurrence After Successful Electrical Cardioversion

After cardioversion of AF, long-term maintenance of sinus rhythm remains a challenging task. Most patients ultimately relapse despite the use of antiarrhythmic therapy. Studies suggest that preventive therapy may be most effective if aimed at modifying the substrate and controlling the mechanism of the arrhythmia. There is strong evidence that the renin–angiotensin–aldosterone system (RAS) is involved in the genesis of AF.[55]A meta-analysis of all published randomized controlled trials reporting the effects of treatment with angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) in the primary or secondary prevention of AF demonstrated overall, a significant reduction in the risk for AF recurrence after cardioversion with the use of ACE-Is or ARBs, reducing the odds for secondary AF by 33% ($p < 0.00001$).[56] This suggests that blockade of the renin–angiotensin–aldosterone system may prevent AF, possibly by promoting the regression of atrial fibrosis, modifying the substrate for AF. Similarly data from animal and human studies suggest that inhibition of aldosterone may reduce AF recurrence.[57,58] A recent substudy in EMPHASIS-HF of patients with mild systolic heart failure, addition of eplerenone to recommended therapy reduced the incidence of new AF by 42% compared to placebo,[59] confirming previous observations that mineralocorticoid receptor antagonists may attenuate structural remodeling of the atria and improve electrical remodeling by reducing atrial fibrosis,[58,60,61] thereby preventing recurrence of AF after cardioversion.

Conclusions and Future Directions

In summary, AF is the most common sustained arrhythmia in adults and prevalence increases substantially with age. Diastolic dysfunction appears to play a central role in the pathogenesis of AF. Direct-current cardioversion is an effective tool frequently used to restore sinus rhythm and has been a mainstay of therapy in patients with AF for decades. However, AF is frequently recurrent in the first year and beyond after electrical cardioversion. Studies have shown that antiarrhythmic drug therapy for prevention of AF after cardioversion is ineffective and may have limited use due to significant side effects. New approaches for the prevention and treatment of AF are needed. Studies suggest that interventions should be aimed at preventing or modifying the electrical and structural remodeling associated with AF to prevent AF recurrence after cardioversion. There may be a potential role for RAS inhibition for secondary prevention of AF by reversing the atrial remodeling that is required to provide the substrate for atrial fibrillation.

Disclosures

No disclosures relevant to this article were made by the authors.

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