

The Influence of Type 2 Diabetes on Left Atrial Remodeling

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ABSTRACT

The influence of type 2 diabetes mellitus on cardiac remodeling has been evaluated for decades; however, the majority of investigations were focused only on the left ventricle. The impact of diabetes on the left atrial (LA) function is less researched. LA enlargement has been shown as an independent predictor of cardiovascular morbidity and mortality in the general and diabetic population; however, LA dysfunction has been proven to be an independent predictor only in the general population. There are not much follow-up data about the influence of diabetes on LA function. New echocardiographic techniques, such as 2-dimensional speckle tracking imaging, provide more accurate, sensitive, and reliable information about LA function than traditional, volumetric methods. The aim of this review was to summarize the most recent reports about the influence of diabetes on LA function, as well as to discuss the possible mechanisms and potential clinical implications of the relationship between diabetes and LA remodeling.

Introduction

Type 2 diabetes mellitus represents a frequent cardiovascular risk factors whose prevalence constantly increases over the years, predominantly due to epidemic obesity, sedentary lifestyle, and long-term exposure to stress. The effect of diabetes on cardiac remodeling has been extensively investigated in the last several decades. However, the research has been mainly focused on the left ventricle^{1–4} and more recently on the right ventricle.^{5–7} The impact of diabetes on left atrial (LA) function is significantly less studied. The importance of LA function on left ventricular diastolic dysfunction^{8–10} and overall morbidity and mortality in the general population^{11,12} and in patients with diabetes,¹³ as well as the significance of left atrial–ventricular coupling,¹⁴ increase the interest in LA remodeling in different conditions such as ischemic heart disease, cardiac valve disease, hypertension, and diabetes.¹⁵

The aim of this review article is to summarize current knowledge about the influence of diabetes on LA remodeling using echocardiographic, computed tomography (CT), and cardiac magnetic resonance (CMR) studies that evaluated LA volume, function, and mechanics in diabetic patients.

Left Atrial Structure and Function in Diabetes

Left Atrial Size

Determination of LA size represents a challenging echocardiography task. Namely, the enlargement of the LA is often

asymmetrical, which is why LA volume reflects LA size more accurately than LA anteroposterior diameter, which is still widely used in clinical practice.¹⁶ Therefore, LA volume represents a better predictor of cardiovascular outcome than LA diameter.¹⁷

The recently published CARDIA (Coronary Artery Risk Development in Young Adults) study investigated the influence of modifiable cardiovascular risk factors on LA size in 2903 young adults (age 23–35 years) over a 20-year follow-up period.¹⁸ After a 5-year period, investigators showed that diabetes was not associated with unindexed LA diameter and LA diameter indexed for body surface area or height. Whereas, after a 20-year follow-up period, diabetes was associated with the increased unindexed and indexed LA diameters.¹⁸ The TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth) trial, which included 455 adolescents with type 2 diabetes (average age 18 years), showed that LA diameter, even after indexing for height, did not correlate with hemoglobin (Hb) A1c level or inability to maintain normal glycemic control.¹⁹ These results raise the question of the usefulness of LA diameters in diabetic population.

On the other hand, the usage of LA volumes in detection of subclinical cardiac damage in diabetic patients is more convincing. Namely, the majority of studies published in the last 10 years that investigated LA remodeling in diabetes confirmed enlargement of LA size assessed by LA volumes and corresponding indexes.^{9,20,21} Not all of the investigations confirmed an enlarged LA in the diabetic patients²²; however, the main reason for these results is a small sample size that was the main obstacle in reaching statistical significance.

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The studies that investigated LA volume in the diabetic population with other imaging techniques such as CT and CMR are scarce.²³ Mahabadi et al showed that diabetes correlated with LA enlargement²³; however, in multivariable regression, only body mass index, blood pressure, antihypertensive medication, and smoking remained associated with LA size.²³ The same group of authors recently reported that CT-derived LA size is associated with major cardiovascular events (coronary event, stroke, cardiovascular death) independently of cardiovascular risk factors and coronary artery calcium in a large population of subjects, age 45 to 75 years old, without prevalent cardiovascular disease.²⁴

Graca et al showed that CMR-derived LA volumes were similar between the controls and the diabetic subjects. However, they found significant difference in LA function between these 2 groups.²⁵

The number of studies that compare different cardiovascular imaging modalities for determination of LA volumes is constantly increasing. The investigations showed a good correlation between 2-dimensional echocardiography (2DE)-derived and CT-obtained LA volumes.²⁶ Kataoka et al reported that CT-derived LA volumes correlated well with 2DE- and 3-dimensional echocardiography (3DE)-derived LA volumes²⁷; whereas Rohner et al obtained similar findings comparing 3DE and CT LA volumes.²⁸ However, both techniques—2DE and 3DE—significantly and equally underestimated LA volumes in comparison with CT. On the other hand, studies that used CMR showed that 3DE-derived LA volumes are more accurate than 2DE-based analysis, compared with CMR-obtained LA volumes, even if 3DE measurements still underestimate real LA volumes.^{29,30}

The advantages of CMR and CT over the echocardiographic technique are independence of quality of acoustic window, accurate delineation of endocardial border, and precise determination of all parts of the LA, including the

LA appendage.³¹ This could partly explain the difference between 3DE- and CT/CMR-calculated LA volumes. However, only 3DE and CT could obtain a true 3-dimensional dataset, whereas CMR could provide only 1 in selected sequences. Additionally, CT is related with usage of iodine contrast and radiation, whereas CMR could be used in patients with pacemakers or defibrillators only with caution.

Studies showed that reproducibility of 3DE, CT, and CMR is very high. Intraclass correlation for 3DE- and CT-derived LA volumes is 0.99, and interclass correlation for 3DE and CT LA volumes is 0.97–0.99.²⁸ Interobserver and intraobserver variability for LA volume were $7\% \pm 4\%$ and $6\% \pm 4\%$, for 2DE, $6\% \pm 4\%$ and $5\% \pm 3\%$ for 3DE, and $6\% \pm 4\%$ and $4\% \pm 3\%$ for CT, respectively.³² Artang et al reported that intraobserver and interobserver variability for CMR-derived LA maximum volume were 1.8% and 6.4%, respectively, and 2% and 5.1% for 3DE-derived LA volume.³³

Left Atrial Phasic Function

Traditional determination of LA phasic function means evaluation of LA volumes in a different phase of the cardiac cycle (maximum, minimum, and pre-atrial contraction volumes), as well as the assessment of various emptying fractions (total, passive, and active emptying fraction).¹⁵ Traditional 2DE volumetric methods of the LA assessment are presented in Figure 1.

Total emptying volume corresponds with the LA reservoir function, and it is calculated as the difference between maximum and minimum LA volume. Passive emptying volume resembles LA conduit function, and it is computed as the difference between LA maximum and pre-atrial contraction volume; whereas active emptying volume describes LA booster function and is calculated as the difference between pre-atrial contraction and minimum LA volume.

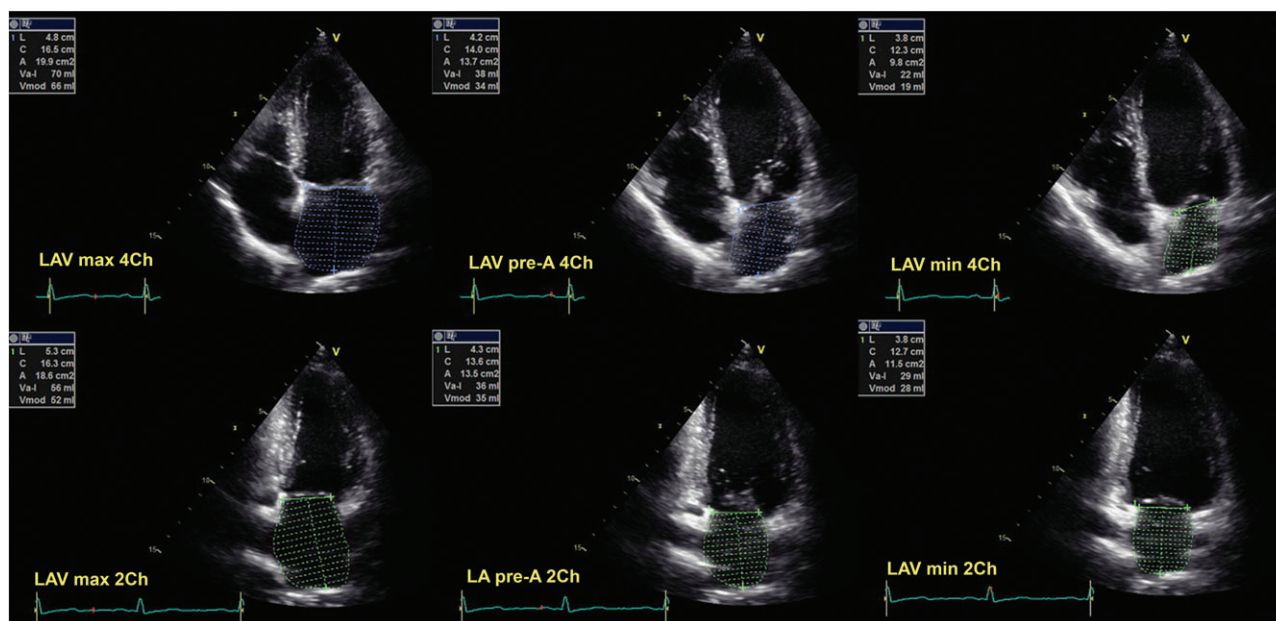


Figure 1. Traditional 2-dimensional echocardiographic volumetric methods of evaluation of the left atrium in 2-chamber (2Ch) and 4-chamber (4Ch) apical views. Abbreviations: LAV, left atrial volume; LV, left ventricle; max, maximum; min, minimum.

Recent studies have shown that LA minimal volume is associated with the worsening diastolic dysfunction, even more than LA maximal volume.³⁴ Furthermore, minimal LA volume increases even in mild left ventricular diastolic dysfunction, whereas maximal LA volume increases in later stages of diastolic dysfunction. These findings are very interesting considering the fact that a majority of investigations are focused on maximal LA volume as a surrogate marker of left ventricular diastolic dysfunction and a predictor of cardiovascular outcomes. This suggests that minimal LA volume could be a more sensitive marker of left ventricular dysfunction than maximal LA volume, and also underlines the necessity of comprehensive evaluation of LA phasic function, and not simplification to only 1 parameter—maximal LA volume. The same analysis showed that LA reservoir function correlated well with left ventricular longitudinal

function and ejection fraction.³⁴ Additionally, Murata et al demonstrated that LA reservoir function is associated with worsening of left ventricular diastolic function.⁸ These findings could be very important for diabetic patients, because early detection of an impaired LA reservoir function in diabetic patients could prevent the development of left ventricular systolic and diastolic dysfunction and consequent heart failure. Mirza et al also showed that LA reservoir function represents an independent predictor of atrial fibrillation occurrence,³⁵ which might explain the predisposition to this arrhythmia in diabetic patients.

According to some authors, LA reservoir function assessed by volumetric method, is not different between diabetics and healthy controls.^{20,36} Difficulties exist in evaluation of LA conduit and pump function. Huang et al showed that LA passive emptying volume and fraction are lower in

Table 1. The Strengths and Limitation in Left Atrial Assessment Using 2DE and 3DE Volumetric Methods and 2DE Speckle Tracking Imaging

	Volumetric Assessment		Speckle Tracking Assessment
	2DE	3DE	LA Strain/Strain Rates
Technical consideration			
Availability	High	Moderate	Moderate/high
Cost	Low	Moderate	Low
Typical scan duration (min)*	3–5	1	3–5
Typical time for analysis (min)	4–6	5–7	2–3
Problem with imaging window	Present	Present	Present
Temporal resolution	+++	+	++/+++
Spatial resolution	+++	++	+++
Authentic 3-dimensional imaging	No	Yes	No
Assessment of LA structure	+	++	No
Assessment of LA volumes			
Static	+	++	No
Phasic	+	++	No
Assessment of LA function	+	++	++
Major advantages			
	Low cost	No geometric assumptions	Short time of analysis
	High availability	High reproducibility	High reproducibility
	LA appendage could be evaluated		
Major limitations			
	Measurements are made only in 2-chamber, 4-chamber, and apical long-axis views	Cost	
	Geometric assumptions	Stable cardiac rhythm	Relatively low availability
	Long time for analysis	Acquisition of LA full-volume	Higher cost than for volumetric method
	LA appendage is not measured	Visualization of LA endocardial border	Stable cardiac rhythm is preferred
Abbreviations: 2DE, 2-dimensional echocardiography; 3DE, 3-dimensional echocardiography; LA, left atrium. += low, ++ = moderate, +++ = high, ++++ = very high major limitation of the modality. *Time only for scanning.			

diabetic patients, whereas LA active volume and emptying fraction are higher in this group.²⁰ We obtained similar results in diabetic subjects, whereas Mondillo et al did not find any difference in conduit and booster pump function between the diabetic subjects and the controls.³⁶ However, Mondillo et al investigated only diabetic patients with normal LA size and included a small number of subjects, which could explain the results of this investigation. Table 1 shows all characteristics of 2DE and 3DE assessment of LA function, and Table 2 summarizes the most important studies that investigated LA remodeling in diabetic patients.

CT and CMR studies that researched LA phasic function in the diabetic population are not common. Graca et al have recently shown that CMR successfully detects subtle LA dysfunction in asymptomatic DM patients: reduced

LA reservoir and conduit functions.²⁵ The authors demonstrated that diabetes was independently associated with LA reservoir function, but not with LA conduit function.²⁵

Buechel et al found high correlations between 3DE and CMR for total LA emptying fraction ($r = 0.92$, $P < 0.001$), and active LA emptying fraction ($r = 0.87$, $P < 0.001$). Similarly, Bland-Altman analysis revealed narrow limits of agreement for total LA emptying fraction (-11.2% – 14.9%), and active LA emptying fraction (-10.6% – 6.8%).³⁷ There was no difference in LA reservoir function assessed by 3DE and CMR. However, LA active function obtained by CMR was slightly higher than calculated by 3DE.³⁷

Kataoka et al revealed that CT-derived LA reservoir function was similar to 3DE-obtained, but significantly lower than 2DE-derived LA total emptying fraction

Table 2. The Studies That Investigated LA Volumes and Mechanics in Diabetic Population

Reference	Imaging Techniques	Patients/ Controls, No.	Age, y	Main Findings
CARDIA study ¹⁸	2DE	2903	23–35	After a 5-year period diabetes was not associated with LA diameter, and LA diameter indexed for body surface area or height. After a 20-year follow-up period, diabetes was associated with the increased unindexed and indexed LA diameters.
TODAY study ¹⁹	2DE	455	~18	LA diameter, even after indexation for height, did not correlate with hemoglobin A1c level.
Kadappu et al ⁹	2DE	73/73	43 ± 10	LA enlargement in diabetes is independent of hypertension and diastolic function, and it is associated with LA dysfunction evaluated by 2DE strain.
Poulsen et al ¹³	2DE	305	58.6 ± 11.3	Increased LA volume index was an independent predictor of cardiovascular morbidity and mortality in diabetic patients free of cardiovascular disease.
Huang et al ²⁰	2DE	58/40	32–78	Maximal, minimal, and pre-atrial contraction LA volumes were higher in diabetic patients than in controls. LA reservoir and conduit function were reduced, whereas LA pump function was increased in diabetic patients.
Muranaka et al ²²	2DE strain	39/16	62 ± 9	2DE strain imaging detected impairment of LA reservoir and conduit functions in diabetic patients, even in the absence of left ventricular hypertrophy and LA dilatation.
Graca et al ²⁵	CMR	45/24	45–75	CMR detection of LA dysfunction in asymptomatic diabetic patients: reduced LA reservoir and conduit functions. LA pump function did not differ.
Mondillo et al ³⁶	2DE strain	155/36	65 ± 11	LA deformation is impaired in diabetic patients, even if LA volumes were similar between groups.
Jarnert et al ⁴³	2DE VVI strain	87	60 ± 7	LA strain by VVI is impaired in patients with type 2 diabetes mellitus. LA strain distinguished normal from abnormal diastolic function.
Liu et al ⁴⁴	2DE strain	164/26	51 ± 11	Hypertension leads to abnormal LA reservoir and conduit functions, and coexisting diabetes can further impair conduit function.

Abbreviations: 2DE, 2-dimensional echocardiography; CMR, cardiac magnetic resonance; LA, left atrium; LV, left ventricle; VVI, vector velocity imaging.

(25.3% ± 13.1%, 30.2% ± 6.8%, and 33.9% ± 8.9%, respectively). The correlation coefficients for LA total emptying fraction of interobserver variation were 0.64, 0.77, and 0.34, respectively for CT, 3DE, and 2DE.²⁷

Left Atrial Mechanics in Diabetes

Determination of LA volumes during the whole cardiac cycle has long been the only method of LA mechanics assessment. Development of new echocardiographic tools, initially speckle tracking imaging, enables the usage of strain and strain rates as a feasible, sensitive, rather simple, and reliable method for evaluation of LA deformation.³⁸ More important is that investigations revealed that global LA strain is a strong and independent predictor of cardiovascular events, even superior to LA conventional parameters (indexed LA volume, LA total emptying fraction, LA area, and LA diameter).³⁹ Cameli et al showed that overall predictive value of cardiovascular events was the highest for global longitudinal LA strain (area under receiver operator characteristic curve: global LA strain 0.83, indexed LA volume 0.71, LA total emptying fraction 0.69, LA area 0.64, and LA diameter 0.59).³⁹ Additionally, Hirose et al demonstrated the relationship between LA strain and new onset of atrial fibrillation⁴⁰ and stroke.⁴¹ It was also reported that LA strain and strain rates correlate with the level of left ventricular diastolic dysfunction.⁴² All of these findings suggest that LA dysfunction has significant prognostic implications, and that LA strain could detect LA dysfunction earlier than volumetric measurements, and emphasize the need for inclusion of LA strain in a routine echocardiographic examination and report.

LA strain/strain rate during systole correspond with LA reservoir function, LA strain/strain rate during early diastole describe LA conduit function, and LA strain/strain rate during late diastole represent the measure of LA booster pump function. The evaluation of LA mechanics by 2DE speckle tracking is presented in Figure 2.

Mondillo et al showed that LA deformation is impaired in patients with hypertension or diabetes with normal LA size.³⁶ They also reported that coexistence of both

conditions further impairs LA performance in an additive fashion, which is very important for clinical practice where these conditions are usually met together. The authors demonstrated a good correlation between LA global longitudinal strain and left ventricular diastolic function assessed by pulsed and tissue Doppler.

Kadappu et al revealed that longitudinal strain in all 6 segments of the LA is lower in the diabetic patients compared with the controls.⁹ However, LA global strain was similar between the patients with diabetes and hypertension. LA reservoir, conduit, and pump function, evaluated by systolic, early, and late diastolic strain rates, were reduced in the diabetic subjects.⁹ Considering the fact that transmitral velocities during late diastole obtained by pulsed and tissue Doppler were increased in the subjects with diabetes, one would expect that pump function, assessed by late diastolic strain rate, is also increased due to a compensatory increase in late diastolic blood flow as a consequence of left ventricular diastolic dysfunction. However, this was not observed, implying changed intrinsic LA function with a reduction in atrial deformation even during its contractile phase.

Velocity vector imaging of the LA showed that LA strain is reduced in the diabetic patients with mild and moderate left ventricular diastolic dysfunction.⁴³ The authors reported the difference in systolic LA strain and early diastolic strain rate (reservoir and conduit LA function, respectively) between the diabetic patients with no and mild diastolic dysfunction, the difference in systolic LA strain and late diastolic strain rate (reservoir and pump LA function, respectively) among the participants with no and moderate diastolic dysfunction, whereas the difference between the subjects with mild and moderate diastolic dysfunction existed only in late diastolic strain rate (LA pump function).⁴³

Liu et al, in the subjects with diabetes and hypertension, found lower strain and strain rates during systole and early diastole, whereas no difference was found during late diastole.⁴⁴ This corresponds with impaired-reduced LA reservoir and conduit function, and preserved pump function. The authors reported that patients with hypertension and diabetes had decreased strain/strain rate only during early diastole, which corresponds with LA conduit

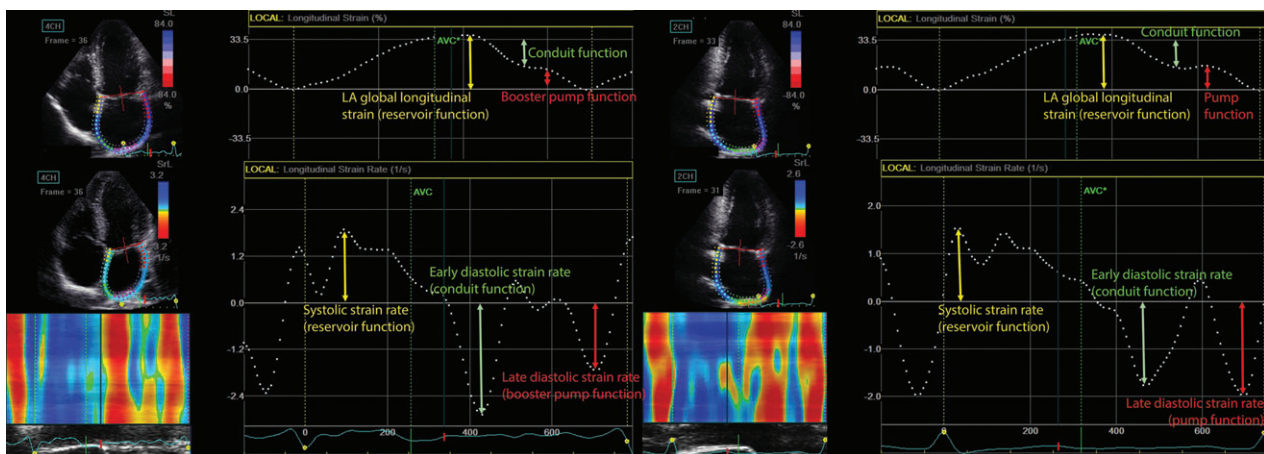


Figure 2. Determination of left atrial (LA) mechanics using 2-dimensional speckle tracking imaging (strain and strain rates) in 2-chamber (2Ch) and 4-chamber (4Ch) apical views. Abbreviation: AVC, aortic valve closure.

function. Similar results were obtained by Muranaka et al, who studied the difference between patients with coexisting diabetes and hypertension, and diabetic subjects.³³

Mechanical function of the LA is best assessed by 2DE strain. However, the most recent studies even use other modalities like 3DE or CMR in determination of 3-dimensional LA strain,^{45,46} but not yet in diabetic patients.

The mean difference for intraobserver agreement for 2DE LA global longitudinal strain was -1.1% (95% confidence interval [CI]: -3.1% to 0.9%).⁴⁷ The mean difference for interobserver agreement for 2DE LA global longitudinal strain was 2.8% (95% CI: 0.3% to 5.3%).⁴⁷ Mondillo et al reported that variability coefficients are $<6\%$ for 2DE LA longitudinal strain measurements in both interobserver and intraobserver analyses.³⁶

Mechanisms of Left Atrial Remodeling in Diabetes

Atrial remodeling could be considered in 3 different ways: structural, functional, and electrical. The precise mechanisms that lead to LA remodeling in diabetes are not quite clear; however, there are several mechanisms that could explain the relation between altered atrial phasic function and impaired glucose regulation (Figure 3). First, left ventricular diastolic dysfunction has been proven as an independent predictor of atrial phasic function,⁴⁸ and diabetic patients usually have diastolic dysfunction.⁴² Second, subendocardial fibrosis, which occurs in the diabetic atrium, causes decreased wall elasticity, an important factor for regulation of atrial reservoir function.⁴⁹ Third, atrial enlargement seen in diabetes might be the reason of impaired LA atrial function. Fourth, increased blood pressure induced by insulin resistance in diabetic patients could also impact LA mechanics.^{36,44} Fifth, electrical remodeling of the LA, reflected in conduction and refractory disorders,⁵⁰ could make additional problems in atrial phasic function in diabetic patients. Furthermore, autonomic nervous system disbalance with enhanced sympathetic activation in diabetic hearts could be suitable atrial arrhythmogenic substrate, which could result with LA dysfunction and atrial fibrillation.⁵¹ Oxidative stress and inflammation, frequently associated with diabetes, might also cause LA deformation changes. Studies already demonstrated that markers of oxidative stress and inflammation correlated with left

ventricular deformation in diabetes,⁵² thus it is reasonable to hypothesize that the same relationship exists between these markers and parameters of LA mechanics.

Impact of LA Remodeling Morbidity and Mortality in Type 2 Diabetes

There are very limited data about the impact of LA volumes and mechanics on the prognosis in diabetic patients. Poulsen et al reported that LA volume index is an independent and incremental predictor of cardiovascular morbidity and mortality in diabetic patients without history of cardiovascular disease.¹³ In this study, increased LA volume index was a predictor of death and major adverse cardiac events, even after adjustment for age and hypertension. Additionally, the authors demonstrated that LA volume index predicted cardiovascular morbidity and mortality independently of myocardial ischemia.¹³

The Strong Heart Study, which included patients without overt cardiovascular disease but with high prevalence of hypertension and diabetes, demonstrated that high LA systolic force, a measure of LA mechanical function, was a predictor of cardiovascular events, including heart failure, independent of the traditional risk factors.⁵³

Cameli et al, in a population of patients with prevalent hypertension (63%) and diabetes (25%), found that global longitudinal LA strain is a strong and independent predictor of cardiovascular events, even better than conventional parameters of LA analysis.³⁹

Investigations demonstrated that pulsed Doppler measurements of LA appendage flow velocity are excellent predictors of thrombus formation in patients with atrial fibrillation, as well as predictors of successful cardioversion, maintenance of sinus rhythm after both electrical cardioversion and pulmonary vein isolation, and risk of thromboembolism.^{54,55} A recent study showed that left ventricular diastolic dysfunction is associated with reduced LA appendage function in patients with atrial fibrillation, which represents a potential risk factor for formation of thrombus and stroke.⁵⁶ This is especially important for diabetic patients who frequently have left ventricular diastolic dysfunction.^{1-4,8-11}

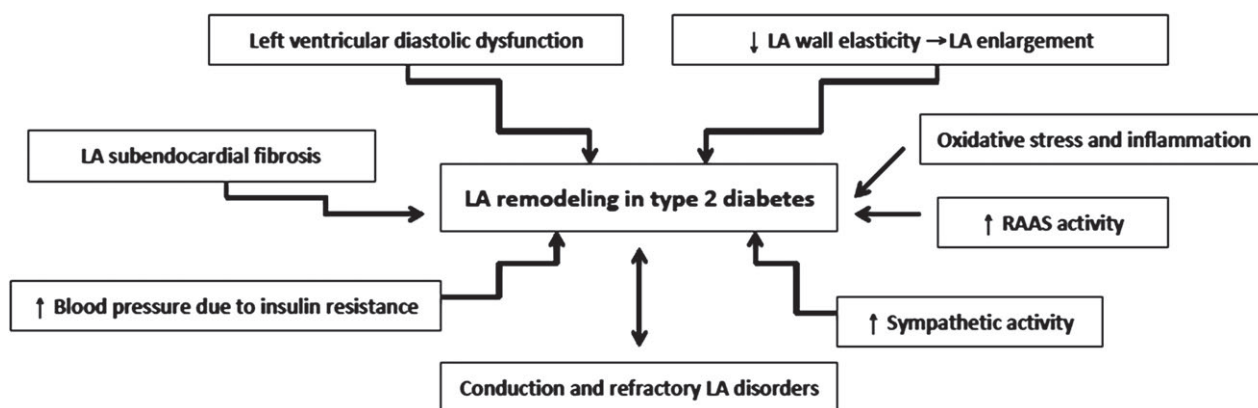


Figure 3. Mechanisms that induce left atrial (LA) remodeling in type 2 diabetes. Abbreviation: RAAS, renin-angiotensin-aldosterone system.

Potential Clinical Implications

There are many clinical implications of LA dysfunction in diabetic patients. LA dysfunction is highly associated with left ventricular diastolic dysfunction, which is closely associated with abnormal myocardial perfusion on myocardial perfusion scintigraphy, as well as with vascular function in diabetic subjects.⁴ Studies also show that LA dysfunction is an important predictor of cardiovascular events (myocardial infarction, stroke, new onset of atrial fibrillation) and mortality in diabetic population. LA dysfunction is associated with development of atrial fibrillation and significantly contributes to the worsening of systolic and diastolic left ventricular function, which leads to heart failure, an important cause of death in the modern world. It was reported that HbA1c correlates with LA function, which provides us an effective, indirect follow-up method of LA function improvement in diabetic patients.

These significant clinical implications of LA dysfunction demonstrate the importance of comprehensive assessment of LA function in everyday clinical life and emphasize that determination of only LA maximal volume, or even worse, only LA diameter, is not enough to estimate the cardiovascular risk of our patients with diabetes. In light of recent studies that show that normal LA size in diabetic and hypertensive patients does not necessarily mean normal LA function,³⁶ it is even more important to introduce a more sophisticated and sensitive LA echocardiographic analysis—2-dimensional speckle tracking—into daily practice to reliably assess baseline LA function and, more importantly, the changes induced by pharmacologic and lifestyle interventions.

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