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The association of left atrial volume index and coronary artery disease in type 2 diabetic patients without a history of hypertension and valvular heart disease

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Abstract

BACKGROUND: Left atrial volume index (LAVI) evaluated using echocardiography serves a powerful predictor of cardiovascular outcomes. Since type 2 diabetes mellitus (T2DM) is a main risk factor for coronary artery disease (CAD), the present investigation was conducted to examine the association between LAVI and incidence of CAD in diabetic patients.

METHODS: In this case-control study, 90 type 2 diabetic patients aged 18–70 years who underwent coronary angiography at Imam Hossein Hospital, Tehran, between 2023 and 2024 were consecutively enrolled. Patients with hypertension, valvular heart disease, heart failure, or respiratory diseases were excluded. Cases (n = 45) had coronary artery disease (≥ 50% stenosis on angiography), while controls (n = 45) had no significant stenosis. Left atrial volume index (LAVI) was measured by echocardiography and classified as abnormal if ≥ 34 mL/m². All variables including LAVI were compared between two groups. Multivariate logistic regression was performed to investigate the role of variables in predicting CAD incidence in diabetic patients.

RESULTS: A total of 90 patients with type 2 diabetes were included (45 with CAD and 45 without CAD); the mean age was 51.48±5.68 years, and 60% were male. Analyses revealed that LAVI values were significantly higher in patients with CAD compared to those without (P = 0.018), while there were no significant differences between two groups regarding gender, age, smoking, insulin dependence, diabetes duration, HbA1c, FBS, EF. also, no significant differences were observed in other echocardiographic measures including mild LVH, mild diastolic dysfunction, heart rate. Multivariate logistic regression identified LAVI as an independent predictor of CAD (OR = 1.24; 95% CI: 1.06–1.45), P = 0.006. ROC curve analysis showed that a LAVI cut-off of 28 mL/m² predicted CAD with 71% sensitivity and 51% specificity (P = 0.016).

CONCLUSION: LAVI could be a potentially useful, accessible and practical index for screening CAD in diabetic patients. It may be proposed as part of the workup for the diagnosis and management of CAD in type 2 diabetic patients.

Keywords: Left Atrial Volume Index; Coronary Artery Disease; Type 2 Diabetes; Echocardiography

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Introduction

Diabetes mellitus is the most prevalent endocrine disorder worldwide and has experienced a significant rise in recent years[1,2]. According to the World Health Organization (WHO), diabetes is projected to become one of the top seven causes of death globally by 2030[3]. Type 2 diabetes mellitus (T2DM), accounting for 90-95% of cases, results from inadequate insulin secretion or insulin resistance, leading to impaired cellular glucose uptake[4].

Poorly controlled T2DM increases the risk of multiple complications, including cardiovascular disease (CVD), vision loss, renal failure, neuropathy, and hypertension[5,6]. In Iran, coronary artery disease (CAD) remains the leading cause of death, driven by rising rates of smoking, hypertension, diabetes, and obesity. Notably, CAD is the primary cause of mortality in diabetic patients. Globally, cardiovascular diseases account for approximately 30% of deaths, with this figure rising to 40% in high-income countries[7]. Of these, CAD is the most lethal CVD, accounting for more than 50% of cardiovascular deaths worldwide[8–10]. With increasing life expectancy and aging populations worldwide, the prevalence of heart disease, diabetes, and hypertension is rapidly increasing[11,12].

Left atrial (LA) analysis using the LA volume index (LAVI) is a suitable method for estimating the cumulative impact of elevated left ventricular (LV) filling pressures throughout a prolonged duration. LA enlargement occurs in the setting of systolic and diastolic dysfunction[13]. LA volume divided by body surface area is described as LAVI and recommended as a standard measure of LA size by[14] the American Society of Echocardiography[15]. Studies have shown that CAD comorbidities, including arterial stiffness and myocardial infarction, as well as mortality after CAD, are significantly associated with LAVI[14]. However, the predictive power of LAVI in clinical settings that frequently encounter outpatient adults with CAD, especially in diabetic patients with otherwise healthy heart disease, is not yet fully established and depends on several factors[16,17]. Additional risk factors for CAD, including hypertension, aging, and diabetes, can contribute to decreased myocardial flexibility and elevated filling pressures, resulting in left atrial enlargement[17].

Therefore, considering the significance of this topic, this study was conducted for the first time in Iran to investigate the association between left atrial volume index (LAVI) and coronary artery disease (CAD) in type 2 diabetic patients without a history of hypertension or valvular heart disease.

Materials and Methods

In this case-control study, 90 diabetic patients who admitted to Imam Hossein Hospital, Tehran, Iran between 2023-2024 and underwent angiography were selected consecutively and non-randomly. Patients from all categories were included in the study, including 50% ACS, 23% MI, and 27% unstable angina. Patients with T2DM without a history of hypertension and valvular heart disease, aged 18 to 70 years who underwent coronary angiography based on clinical and laboratory findings, were included in the study. Exclusion criteria included hypertension (systolic blood pressure above 130 and diastolic blood pressure above 80 mmHg) according to ACC/AHA guidelines[18], previous history of heart failure or valvular diseases, history of surgery due to heart disease, Diastolic Dysfunction grade 2 or higher, respiratory disease, asthma or COPD (chronic obstructive pulmonary disease), use of blood pressure medications or inhalers, pregnancy, thyroid problems. Smoking patients were people who were at least light smokers[19]. Participants were divided into two groups including those with CAD (narrowing of at least one coronary artery with a severity of more than 50%)[20], and those without CAD. Angiographic procedures were performed by an interventional cardiologist.

Angiography data were extracted from the Coronary Angiography and Angioplasty Registry System (CAAR). The CAAR protocol was used according to the following reference[21].

Then, demographic data and cardiac

findings (LAVI) were collected by a specialist cardiologist. LAVI greater than or equal to 34 mL/m² was classified as abnormal LAVI[22]. Then, LAVI levels were compared in the two groups. Echocardiography was executed by conventional and STE approaches (Siemens®, Health Care Acuson SC2000). According to the American Society of Echocardiography protocol, the procedure was performed in the left lateral position[15]. Also, the LV volumes were evaluated based on the BSA. Echocardiography was performed by a general cardiologist under the supervision of an echocardiography fellowship.

Assuming a prevalence of elevated LAVI, approximately 15% in controls, an anticipated odds ratio of 3.9 based on prior literature[23], α = 0.05 and 80% power, we determined that 45 cases and 45 controls would be sufficient to detect a statistically significant association.

Statistical analysis

Quantitative variables were expressed as means and standard deviations (SDs), while qualitative variables were reported as frequencies and percentages. Differences between groups were evaluated by an independent sample t-test for continuous variables and a Chi-squared test for categorical variables. Univariate and multivariate regression analyses were performed to identify predictors of CAD. Also, the predictive value of LAVI was examined by ROC curve and AUC calculation. In all tests, $P < 0.05$ was considered statistically significant. Data analysis was performed using SPSS version 22 software. Also, the study graphs were drawn using PRISM version 8 software.

Ethical Considerations

The research protocol received approval from the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1402.597).

Results

As shown in Tables 1 and 2, the demographic, clinical and echocardiographic variables of the patients were evaluated overall and, in each group, separately. Accordingly, it was observed that the patients in the two groups did not differ significantly in terms of potential confounding factors, indicating adequate matching of the two groups. Case and control groups didn't show significant differences in the term of the demographic and clinical characteristics including gender, age, smoking, insulin dependence, diabetes duration, HbA1c, FBS, EF. Also, as shown in Table 2 no significant differences was observed in echocardiographic measures including mild LVH, mild diastolic dysfunction, SPAP, heart rate except that LAVI. As shown in Figure 1, the left atrial volume index (LAVI) in patients with CAD was significantly

Table 1. Baseline demographic and clinical characteristics of patients with CAD and without CAD

Variables	Total N=90	With CAD N=45	Without CAD N=45	P-value
Male	54 (60)	29 (64.4)	25 (55.6)	0.519[a]
Female	36 (40)	16 (35.6)	20 (44.4)	
Age (year)	51.48 ± 5.68	51.46 ± 6.19	51.51±5.18	0.971[b]
Smoking (yes)	26 (28.9)	11 (24.4)	15 (33.3)	0.366[a]
Insulin dependence (yes)	10 (11.1)	6 (13.3)	4 (8.9)	0.379[c]
Oral anti diabetic (yes)	53 (58.9)	29 (64.4)	24 (53.3)	0.392[a]
Diabetes duration (year)	6.76±6.81	7±5.98	6.53±7.61	0.747[b]
HbA1c (%)	8.33±2.09	8.27±1.64	8.39±2.57	0.829[b]
FBS (mg/dl)	149.34±57	142.63±37.93	154.94±69.07	0.386[b]
EF (%)	54.56±4.45	53.88±3.82	55.24±4.95	0.150[b]

Data are presented as mean ± SD or number (%). $P < 0.05$ was considered statistically significant. HbA1c: hemoglobin A1c; FBS: Fasting blood sugar; EF: Ejection fraction. [a] Calculated by the Chi-square test. [b] Calculated by the independent samples t-test. [c] Calculated by Fisher's exact test

Table 2. Comparison of the values of the echocardiographic measures between the patients with and without CAD

Variables	Total N=90	With CAD N=45	Without CAD N=45	P-value
LAVi (mL/m²)	29.36±5.5 (18-38)	30.73±4.82 (19-38)	28±5.85 (18-36)	0.018[a]
mild LVH (yes)	3 (3.3)	2 (4.4)	1 (2.2)	> 0.99[b]
mild diastolic dysfunction (yes)	64 (71.1)	35 (77.8)	29 (64.4)	0.245[c]
SPAP (mmHg)	25.32±6.48 (17-56)	25.87±7.76 (18-56)	24.78±4.96 (19-50)	0.454[a]
HR (per min)	93.3±14.97 (85-117)	90.55±14.36 (85-102)	96.04±15.22 (85-117)	0.082[a]

Data are presented as mean±SD or number (%). p <0.05 was considered statistically significant. LAVi: Left atrial volume index; LVH: Left ventricular hypertrophy; LVE: Left ventricular enlargement; SPAP: Systolic pulmonary artery pressure; HR: Heart rate. [a] Calculated by the independent samples t-test. [b] Calculated by Fisher's exact test. [c] Calculated by the Chi-square test.

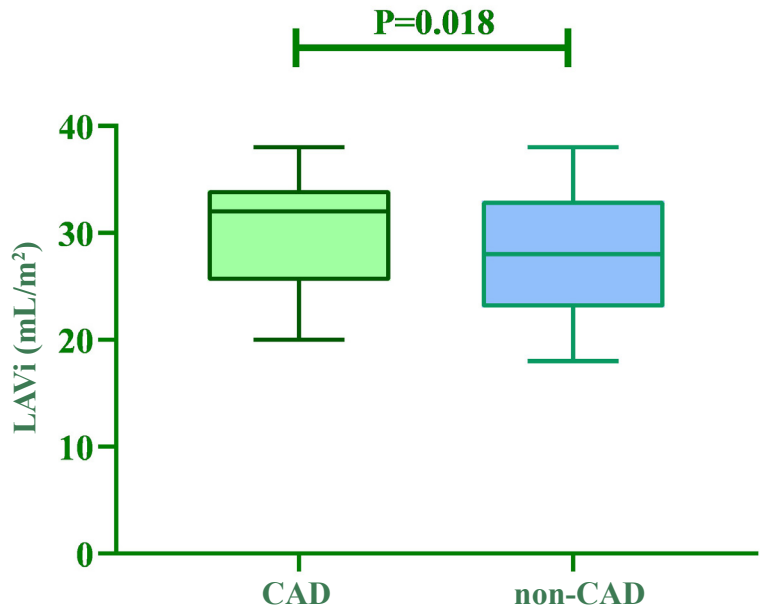


Figure 1. Comparison of LAVI between diabetic patients in CAD and non-CAD groups

higher than in patients without CAD (P = 0.018).

As shown in Tables 3 and 4, in order to confirm the accuracy of the results, univariate and multivariate regression were performed. Based on the results, we observed that LAVI as a single variable with (OR = 1.1, 95%CI = 1.01-1.19) P = 0.020 and along with other variables with (OR = 1.24, 95%CI = 1.06-1.45) P = 0.006 is considered as an independent predictive factor of CAD in patients with diabetes. Based on p-values obtained in univariate and multivariate regression analyses none of other variables had no predictive value in predicting the incidence of CAD in diabetic patients.

In examining the predictive value of LAVI in assessing the occurrence of CAD in diabetic

Table 3. Univariate logistic regression analysis for the role of variables in predicting the incidence of CAD in diabetic patients

Variables	OR (95%CI)	P-value
LAVI (mL/m²)	1.1 (1.01-1.19)	0.020
Sex (male)	1.45 (0.62-3.38)	0.260
Smoking (yes)	1.7 (0.68-4.25)	0.361
Insulin dependence (yes)	0.63 (0.16-2.41)	0.372
Oral anti diabetic (yes)	0.63 (0.27-1.46)	0.195
Age (year)	0.99 (0.92-1.07)	0.970
EF (%)	0.93 (0.84-1.02)	0.152
Diabetes duration (year)	1.01 (0.95-1.07)	0.744
HbA1c (%)	0.97 (0.76-1.23)	0.826
FBS (mg/dl)	0.99 (0.98-1)	0.384

Data are presented as OR (95% confidence interval) and obtained from univariate logistic regression analysis. P < 0.05 was considered statistically significant.

Table 4. Multivariate logistic regression analysis for the role of variables in predicting the incidence of CAD in diabetic patients

Variables	OR (95%CI)	P-value
LAVI (mL/m²)	1.24 (1.06-1.45)	0.006
Sex (male)	1.17 (0.17-19.47)	0.130
Smoking (yes)	3.4 (0.67-17.21)	0.139
Insulin dependence (yes)	0.07 (0.003-1.62)	0.098
Oral anti diabetic (yes)	0.27 (0.04-1.54)	0.143
Age (year)	0.97 (0.86-1.11)	0.132
EF (%)	0.9 (0.73-1.11)	0.337
Diabetes duration (year)	0.92 (0.78-1.09)	0.370
HbA1c (%)	1.17 (0.75-1.84)	0.478
FBS (mg/dl)	0.98 (0.96-1)	0.077

Data are presented as OR (95% confidence interval) and obtained from multivariate logistic regression analysis. $p < 0.05$ was considered statistically significant.

Table 5. Measures of diagnostic accuracy of LAVI for discrimination of CAD in diabetic patients

Measures of diagnostic accuracy	Value	95% CI
Sensitivity	71.11	-
Specificity	51.11	-
Positive Predictive Value	16.55%	12.24-22%
Negative Predictive Value	92.84%	88.32-95.7%
Positive Likelihood Ratio	1.45	1.02-2.07
Negative Likelihood Ratio	0.57	0.33-0.97
AUC	0.64	0.53-0.74
Accuracy	53.51%	42.69-64.1%
Youden index	0.22	-

patients, it was observed that LAVI has a relatively fairly good value in predicting the occurrence of CAD in diabetic patients, considering a cutoff of 28 (Table 5 and Figure 2). ROC Curve analysis showed that LAVI had an AUC of 0.64 with a Sensitivity of 71.11% and a Specificity of 51.11% (PPV = 16.55%, NPV = 92.84%, Accuracy of 53.51%, and Youden index of 0.22).

Discussion

Based on the results of this study, in a study of 90 diabetic patients in two groups with and without CAD, it was observed that there was a significant difference in LAVI parameter. So that LAVI had higher values in patients with CAD. Also, in multivariate regression analysis, LAVI remained

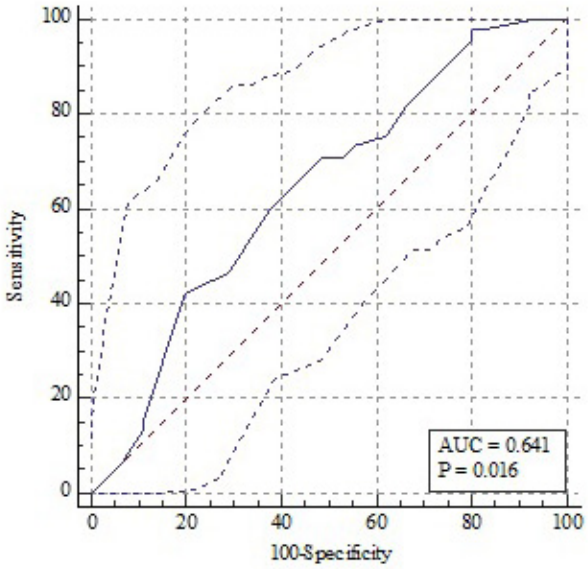


Figure 2. ROC curve analysis for evaluating LAVI predictive value for discriminating CAD in diabetic patients

strong as an independent predictor of CAD in patients with diabetes with (OR = 1.24, 95%CI = 0.48-4.98) P = 0.018. Besides, the predictive value of LAVI in assessing the occurrence of CAD in diabetic patients was relatively good considering the cut-off of 28, with a sensitivity of 71% and a specificity of 51%.

Over recent years, research has demonstrated that LAVI serves as a robust indicator of cardiovascular outcomes and provides a more precise approach for evaluating LA enlargement than LA area or diameter measurements. Previously, the majority of studies concentrated on patient groups following myocardial infarction (MI), resulting in limited data regarding the prognostic value of LAVI[24].

Globally, ischemic heart disease continues to be the primary cause of mortality[25]. One of the initial hemodynamic changes in patients with myocardial ischemia is impaired diastolic function, which can lead to persistent left atrial pressure due to elevated left ventricular filling pressure[26–28]. Elevated LAVI may result from chronic conditions that decrease myocardial flexibility and increase filling pressure. This increased left ventricular filling pressure heightens myocyte stretch and atrial wall stress, potentially causing myocardial rupture, myocyte

lysis, apoptosis, and subsequent fibrosis, ultimately leading to atrial enlargement[29,30]. LA size can be accurately determined by measuring left atrial volume[31,32]. Furthermore, evaluating left atrial volume indexed to body surface area (LAVI) has been linked to overall cardiovascular risk and may offer additional predictive insights into common coronary risk factors across various patient populations[33,34]. Notably, LAVI shows a strong correlation with dobutamine stress echocardiography (DSE) test outcomes, serving as an indicator of myocardial ischemia[35].

A study be El-Sherbeny et al. evaluated the predictive role of LAVI in patients with suspected CAD. Participants were categorized into two groups based on resting LAVI values: Group A consisted of 14 patients with normal LAVI (≤ 28 mL/m^2). Group B included 16 patients with high LAVI values (> 28 mL/m^2). Patients with abnormal LAVI were significantly older, while there was no significant association with gender. Regarding CAD risk factors, diabetes and hypertension were the most prevalent in patients with high LAVI, followed by smoking, dyslipidemia, and obesity[36]. Interestingly, our study also showed a cutoff of more than 28 for LAVI to predict CAD in diabetic patients.

Assiri et al., who investigated 90 patients undergoing DSE with suspected ischemic heart disease (IHD) in Saudi Arabia over a 2-year period, showed a significant association between ischemic ECG abnormalities and LAVI and proposed that LAVI is an effective, accessible, and practical method for screening low-risk IHD patients[36].

Other studies have also published results consistent with our results. Poulsen et al. demonstrated that, in patients with type 2 diabetes mellitus (T2DM) without evident cardiovascular disease, an enlarged left atrium was linked to higher morbidity and mortality, independent of other significant risk factors[22]. Therefore, left atrial dilation in T2DM represents a morphological alteration tied to elevated cardiovascular risk. Decreased left ventricular compliance in T2DM patients may stem from microvascular dysfunction, changes in myocardial metabolism, and structural myocardial changes with increased fibrosis[37,38].

In the present study, patients with diabetes had no history of hypertension or valvular disease. Therefore, the etiology of LAVI being affected by hypertension in our study was excluded. It has also been shown that in the absence of notable mitral valve pathology, an elevated LAVI typically serves as an indicator of increased left ventricular end-diastolic pressure (LVEDP) and progressive left ventricular diastolic dysfunction[39].

In the phase of ventricular diastole, the LA is directly subjected to LV diastolic pressure via the open mitral valve. The increased diastolic pressure propagates to the LA, increasing its ventricular pressure. Given the thinner LA wall compared with the LV, the atrial tissue stretches under elevated pressure, resulting in an enlarged atrial cavity. Such changes affect the ability of the LA cavity to accommodate the persistent increase in pressures in response to left ventricular pressures[40]. Consequently, the elevated LA pressure is transmitted to the pulmonary venous system, leading to pulmonary venous hypertension and, ultimately, pulmonary arterial hypertension[41]. These alterations in LV-LA pressures and pulmonary circulation likely account for the significantly poorer clinical outcomes observed in patients with elevated LAVI compared to those with lower LAVI. These pathophysiological LV-LA abnormalities are amplified in patients presenting with ACS as the abrupt, even partial, loss of ventricular myocardial function, including subclinical dysfunction, elevates diastolic and left atrial pressures, thereby heightening the risk of ventricular arrhythmias independently of the extent of coronary artery disease[42,43].

Our results are supported by the findings of Ahmeti et al., who showed that patients who had elevated LAVI were more probable to exhibit poorer diastolic function and a higher prevalence of multivessel CAD which effects the overall LV function[44]. Moreover, studies have shown that LA enlargement is associated with risk factors such as diabetes, hypertension, and previous

ACS, which are recognized for compromising LV diastolic function and increasing LV filling pressure[45,46].

Finally, it seems that LAVI, despite its influence on various conditions in diabetic patients, can be considered as a worthy parameter in predicting coronary artery disease.

The present study had its own limitations. Although efforts were made to explore key demographic factors related to patients, certain variables, such as patient medications, were not accounted for. It is advised that future studies include these factors. Additionally, the omission of other echocardiographic indices and parameters represents a limitation of this study. Another limitation of this study was that based on our data, LAVI has a relatively fairly good value in predicting the occurrence of CAD in diabetic patients, considering a cutoff of 28 and this should be considered in interpretation of its power as a predictive tool in discrimination CAD and non-CAD in diabetic patients.

Conclusions

We have shown that LAVI could be proposed as a valuable, accessible, and practical index for screening diabetic patients for CAD. In many centers, complex stress echocardiographic or angiographic studies may not be readily available or feasible for all patients, and therefore LAVI, which we recommend, may be considered as part of the workup for the diagnosis and management of CAD in diabetic patients. A comprehensive assessment of diabetic patients at risk for coronary artery disease in a large, multicenter cohort is recommended prospectively.

Conflict of interests

The authors declare no conflict of interest.

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Author's Contributions

Study Conception or Design: RS; MS
Data Acquisition: RS; MHA
Data Analysis or Interpretation: FO; MPM; MR
Manuscript Drafting: MS
Critical Manuscript Revision: RS; MHA; FO; MPM; MR

All authors have approved the final manuscript and are responsible for all aspects of the work.

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