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Determinants of the Volumetric Markers of Left Atrial Contraction Function in Coronary Artery Disease: A Cross-sectional Study

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ABSTRACT

BACKGROUND: A body of research advocates the prognostic role and usefulness of the volumetric markers of left atrial (LA) phasic functions in the diagnosis of LA dysfunction. We aimed to determine the independent determinants of the volumetric markers of LA contraction function in candidates for coronary artery bypass graft (CABG) surgery. **METHODS:** This cross-sectional study enrolled 516 candidates for CABG. The biplane maximal, minimal, and pre-P volumes of the LA were measured with two-dimensional echocardiography, and LA active emptying fraction was calculated. The standardized correlation coefficient for the correlation between each factor and LA active emptying fraction was calculated by using univariate and backward multivariable regression analyses. **RESULTS:** The multivariable regression analysis demonstrated that the heart rate ($\beta = 0.15$; p = 0.001), S ($\beta = 0.09$; p = 0.036), E/e' ratio ($\beta = -0.11$; p = 0.014), left ventricle (LV) ejection fraction ($\beta = 0.15$; p = 0.001), and LA enlargement ($\beta = -0.19$; p < 0.001) were the independent determinants of LA active emptying fraction.

CONCLUSIONS: The independent determinants of LA contraction function were the heart rate, S, LV ejection fraction, LA enlargement, and E/e' ratio in candidates for CABG surgery.

Keywords: Left atrium; Echocardiography; Coronary artery disease

INTRODUCTION

The left atrial (LA) is a cardiac chamber with multiple functions: reservoir, conduit, and contraction. The coordination and dynamic interactions between the LA and the left ventricle (LV) result in the modulated filling of the latter.¹⁾ Each phasic function of the LA contributes to LV filling and, thus, 25% to 40% of LV stroke volume.²⁾ During LA reservoir phase, the mitral annulus is stretched by LV contraction toward the apex, the LA relaxes, and the pulmonary vein blood flows into the LA. During LA conduit phase, the relaxation of LV myocardium causes the mitral annulus to return to its baseline position, and the stored blood is delivered to the LV. During LA contraction phase, the remaining blood is actively pushed into the LV.¹³⁾

The phasic functions of the LA can be clearly depicted by echocardiography, which is deemed the main method for the evaluation of LA functions.⁴⁾ The measurement of the

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Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Etemad T, Hosseinsabet A; Data curation: Hosseinsabet A, Omidi N, Mohseni-Badalabadi R; Formal analysis:

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Hosseinsabet A; Funding acquisition: Hosseinsabet A; Investigation: Etemad T, Hosseinsabet A, Omidi N, Mohseni-Badalabadi R; Methodology: Etemad T, Hosseinsabet A, Omidi N, Mohseni-Badalabadi R; Project administration: Etemad T, Hosseinsabet A, Mohseni-Badalabadi R; Resources: Etemad T, Hosseinsabet A, Omidi N; Software: Hosseinsabet A; Supervision: Hosseinsabet A; Validation: Hosseinsabet A; Visualization: Hosseinsabet A; Writing original draft: Hosseinsabet A; Writing - review & editing: Etemad T, Hosseinsabet A, Omidi N, Mohseni-Badalabadi R. maximal, minimal, and pre-contraction volumes of the LA provides markers that facilitate the evaluation of the phasic functions of this chamber.⁵⁾ Research corpus underscores the usefulness of the volumetric markers of LA phasic functions in the diagnosis of LA dysfunction in such conditions as coronary artery disease (CAD),⁶⁾ LV diastolic dysfunction,⁷⁾ heart failure,⁸⁾ diabetes,⁹⁾ hypertension,¹⁰⁾ and obesity.¹¹⁾ Previous investigations have also demonstrated the prognostic role of these markers vis-à-vis atrial fibrillation (AF), heart failure, death after myocardial infarction,¹²⁾¹³⁾ in-hospital mortality, and AF following coronary artery bypass graft (CABG) surgery.¹⁴⁾¹⁵⁾

Factors that can determine the volumetric markers of LA functions have been previously assessed in studies with small samples. Nonetheless, these investigations each focused on only a single factor and failed to assess data regarding the clinical or echocardiographic determinants of LA phasic functions. Moreover, most of the aforementioned studies excluded patients with CAD, amongst whom the prevalence of factors that affect the phasic functions of the LA is high. Additionally, the inflammatory milieu in patients with CAD may differentiate them from other patients¹⁶ inasmuch as inflammation can affect LA phasic functions.¹⁷

Several investigations have reported alterations in LA phasic functions among patients suffering from CAD by comparison with control groups.⁶⁾¹⁸⁻²⁰⁾ The LA in patients with CAD is in interaction with LV that has impaired diastolic function and systolic deformation. Additionally, LA phasic functions are not usually cited in echocardiography reports. Regrettably, there is a paucity of information on the assessment of the phasic functions of the LA in the presence of CAD. One of the few studies conducted on this topic found no difference between patients with diabetes and those without it concerning LA phasic functions,²¹⁾ which is in contrast to the results obtained in a group of patients without CAD in another investigation.²²⁾ In sum, what such findings indicate is that patients suffering from CAD differ from those without it with respect to the factors that influence LA phasic functions.

The reservoir and conduit functions of the LA are significantly correlated with the systolic and diastolic functions of the LV, respectively. The contraction function of the LA presents intrinsic LA contractility properties. However, this property is to some extent dependent on LV compliance and diastolic pressure.³⁾ Accordingly, we selected the contraction function of the LA, which represents the systolic function of this chamber, for the evaluation of LA phasic functions. We previously defined the independent determinants of left intra-atrial electromechanical delay as a marker of pump synchronicity in patients who were candidates for CABG.²³⁾ In the present study, we sought to determine the independent determinants of LA contraction in the same sample by reanalyzing the same data.

METHODS

Study population

We previously presented the characteristics of the study population and the method of echocardiography in detail.²³⁾ Briefly, our cross-sectional study recruited 516 patients in sinus rhythm who were candidates for isolated CABG. The study population was without a history of AF, cancer, previous cardiac surgery, cardiomyopathies, pericardial disease, significant valvular disease, thyroid disease, liver disease, end-stage renal disease, and inflammatory disease. The research proposal was approved by the Institutional Review Board of Tehran Heart Center (No. 1397/08/14-920), and written informed consent was obtained from the study subjects.²³⁾

Echocardiography

The maximal, minimal, and pre-P volumes of the LA in the apical 4 and 2-chamber views were measured according to the modified Simpson method, and the average value of these 2 views was presented. The pre-P LA volume was measured in the pre-P wave frame of electrocardiography on the echocardiography machine monitor. The active emptying fraction of the LA was defined as $100 \times (1 - [LA \text{ minimal volume} \div LA \text{ pre-A volume}])$ and was considered the marker of LA contraction function.

In addition, the early and late diastolic peak velocities of the mitral flow (E and A, respectively); the systolic and diastolic peak flow velocities of the pulmonary vein (S and D, correspondingly); and the peak systolic, early diastolic, and peak diastolic (s', e', and a', respectively) velocities of the septal and lateral mitral annuli were obtained, and the mean values of the velocities of the septal and lateral mitral annuli were presented.

Statistical analysis

Categorical data were presented as frequencies and percentages. Continuous data with normal distributions were presented as the mean ± the standard deviation and those with non-normal distributions as the median and the interquartile range. The correlation between each continuous variable and LA active emptying fraction was determined by using the Pearson or the Spearman rank correlation coefficient. The LA active emptying fraction values in the presence and absence of the categorical data were compared by using the Mann-Whitney U test. Statistical significance was defined as a p-value of less than 0.05.

Next, physiologically related variables with a p-value of less than 0.15 in the univariate analysis were entered in a backward multivariable regression analysis to define the independent determinants of LA active emptying fraction after the assumptions of the multivariable regression analysis were checked. The use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs), heart rate, S, LV ejection fraction, LA enlargement, LV mass index, and E/e' ratio fulfilled the criteria for entrance into the multivariable regression analysis. The unstandardized correlation coefficient (B) with a 95% confidence interval and a standardized correlation coefficient were presented. In this analysis, a p-value of less than 0.05 was considered statistically significant. Inter and intraobserver variabilities were assessed by applying intraclass correlation coefficients, and 95% limits of agreement were demonstrated. The statistical analyses were conducted with the IBM Statistical Package for the Social Sciences (SPSS) for Windows, version 24.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The results of the univariate analysis of LA active emptying fraction and the categorical variables are presented in **Table 1** and the results of the univariate analysis of LA active emptying fraction and the continuous variables in **Table 2**. The active emptying fraction of the LA was $37 \pm 9\%$, and the maximal volume index of the LA was $28 \pm 7 \text{ mL/m}^2$.

In the univariate analysis, LA active emptying fraction was correlated with the consumption of ACEIs/ARBs, heart rate, LV ejection fraction, LV end-diastolic volume index, LV end-systolic volume index, LA enlargement, LV mass index, S, S/D ratio, E, A, E/A ratio, s', e', a', E/e' ratio, minimal LA volume index, and pre-P LA volume index (p < 0.05) (**Tables 1** and **2**).

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Table 1. Univariate ana	lysis of la active e	mptying fraction and	a categorical variables

Variables	Frequency	LA active emptying fraction	Mann-Whitney U	p-value
Demographic and clinical data				
Sex (female)	122 (24)	38 (31-44)	23,349.0	0.634
Sex (male)		37 (31-43)		
Obesity +	142 (28)	37 (31-42)	25,616.0	0.535
Obesity –		37 (31-43)		
Hypertension +	305 (59)	37 (31–43)	30,325.0	0.266
Hypertension –	()	37 (30-43)		
Diabetes +	245 (47)	37 (31-42)	31,571.5	0.336
Diabetes –		38 (31–43)		
Cigarette smoking +	126 (24)	37 (31-42)	24,390.0	0.902
Cigarette smoking –		37 (31–43)		
History of STEMI +	47 (9)	37 (27–41)	9,892.5	0.247
History of STEMI –		37 (31–43)		
History of NSTEMI +	19 (4)	37 (27–43)	4,618.5	0.872
History of NSTEMI –		37 (31–43)	.,	
History of cerebrovascular accident +	33 (16)	36 (31–44)	7,801.0	0.839
History of cerebrovascular accident –	()	37 (31–43)	.,	
Beta-blockers +	356 (69)	36 (31-42)	26,439.5	0.193
Beta-blockers –	000 (00)	38 (31–44)	20,10010	01100
Calcium-channel blockers +	89 (17)	37 (30–45)	18,887.0	0.929
Calcium-channel blockers –	00 (17)	37 (31–43)	10,00710	01020
Statins +	457 (88)	37 (31–43)	12,104.0	0.201
Statins –	107 (00)	34 (30-43)	12,10 1.0	0.201
ACEIs/ARBs	317 (61)	38 (31–43)	29,012.0	0.125
ACEIs/ARBs		36 (31-42)	20,012.0	0.120
Nitrates +	391 (76)	37 (31–43)	23,163.0	0.380
Nitrates –	001 (70)	36 (29-43)	20,100.0	0.000
Diuretics +	87 (17)	37 (31–43)	18,044.0	0.626
Diuretics –	07 (17)	37 (31–43)	10,01110	01020
Antiplatelet agents +	488 (94)	37 (31–43)	6,592.0	0.754
Antiplatelet agents –	100 (01)	37 (30-45)	0,00210	01/01
Left main stenosis +	40 (8)	40 (32-46)	8,212.0	0.149
Left main stenosis –	(0)	37 (31–43)	0,21210	01110
LAD stenosis	516 (100)	-	-	_
LCX stenosis +	467 (90)	37 (31–43)	9,693.0	0.078
LCX stenosis –	107 (00)	37 (29–40)	0,000.0	0.070
RCA stenosis +	435 (84)	37 (31–43)	16,998.5	0.615
RCA stenosis –	433 (04)	36 (30-42)	10,330.5	0.015
Single-vessel disease +	26 (5)	35 (30-39)	5,349.0	0.168
Single-vessel disease –	20 (3)	37 (31–43)	0,040.0	0.100
Two-vessel disease +	79 (15)	37 (29–43)	16,768.0	0.686
Two-vessel disease –	73 (13)	37 (23-43)	10,700.0	0.000
Three-vessel disease +	411 (80)	37 (31-43)	20,063.5	0.267
	411 (80)		20,003.5	0.207
Three-vessel disease –		36 (29–42)		
chocardiography data LA volume index > 34 mL/m²	02 (16)	20 (05 40)	11 024 0	< 0.001
,	83 (16)	32 (25-40)	11,834.0	< 0.001
LA volume index < 34 mL/m ²	00 (15)	38 (32-43)	0.000.0	0.700
Aneurysmal interatrial septum +	28 (15)	36 (32-43)	6,636.0	0.798
Aneurysmal interatrial septum –	10 (10)	37 (31–43)	10.007.0	0.15.1
	49 (10)	. ,	10,027.0	0.154
Mitral annular calcification + Mitral annular calcification –	49 (10)	35 (30–42) 37 (31–43)	10,027.0	0.1

Values are presented as number (%) or number (range). + indicates presence condition and – indicated absence of a condition.

ACEIs/ARBs: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, LA: left atrial, LAD: left anterior descending artery, LCX: left circumflex artery, NSTEMI: non-ST-elevation myocardial infarction, RCA: right coronary artery, STEMI: ST-elevation myocardial infarction.

In the multivariable regression analysis of the determinants of LA active emptying fraction, the heart rate (β = 0.15; p = 0.001), S (β = 0.09; p = 0.036), E/e' ratio (β = -0.11; p = 0.014),

Variables	Values	Correlation coefficient	p-value
Demographic and laboratory data	·		
Age (year)	62 ± 9	-0.04	0.357
Fasting blood sugar (mg/dL)	102 (89–137)	0.03	0.475
Hemoglobin (g/dL)	13.6 ± 1.8	-0.04	0.421
Creatinine (mg/dL)	1.0 ± 0.3	0.04	0.335
Cholesterol (mg/dL)	138 ± 40	-0.02	0.636
LDL (mg/dL)	75 (59–101)	-0.06	0.211
HDL (mg/dL)	36 ± 9	-0.01	0.854
Triglyceride (mg/dL)	137 (104–187)	0.05	0.302
Echocardiographic data			
Heart rate (bpm)	68 ± 11	0.15	0.001
Systolic blood pressure (mmHg)	118 ± 13	-0.03	0.536
Diastolic blood pressure (mmHg)	74 ± 9	0.02	0.742
LVEDV index (mL/m ²)	50 ± 13	-0.17	< 0.001
LVESV index (mL/m ²)	24 (19–30)	-0.18	< 0.001
LVEF (%)	48 ± 9	0.18	< 0.001
Septal thickness (mm)	9 ± 1	0.01	0.778
Posterior wall thickness (mm)	9 ± 1	0.02	0.606
LV mass index (g/m²)	87.6 ± 22.1	-0.16	< 0.001
Aortic root (mm)	32 ± 4	-0.05	0.266
E (cm/s)	64 ± 17	-0.11	0.012
A (cm/s)	77 ± 19	0.09	0.049
E/A ratio	0.8 (0.7-1.0)	-0.09	0.036
Deceleration time (ms)	208 ± 58	0.03	0.535
S (cm/s)	52 ± 11	0.11	0.015
D (cm/s)	36 ± 9	-0.05	0.273
S/D ratio	1.5 ± 0.3	0.09	0.034
Mean s' (cm/s)	7.0 ± 1.5	0.18	< 0.001
Mean e' (cm/s)	7.3 ± 1.2	0.12	0.005
Mean a' (cm/s)	9.4 ± 1.8	0.27	< 0.001
Mean e'/a' ratio	0.8 ± 0.3	-0.08	0.085
E/e' ratio	9 (7–11)	-0.16	< 0.001
Pre-P LA volume index (mL/m²)	19 ± 6	-0.30	< 0.001
Minimal LA volume index (mL/m²)	12 (9–15)	-0.61	< 0.001

Table 2. Univariate analysis of left atrial active emptying fraction and continuous variables

HDL: high-density lipoprotein, LA: left atrial, LDL: low-density lipoprotein, LV: left ventricle, LVEDV: left ventricular end-diastolic volume, LVEF: left ventricular ejection fraction, LVESV: left ventricular end-systolic volume.

Table 3. Multivariable regression analysis results to define the independent determinants of left atrial active	
emptying fraction	

Variables	β	B (95% CI)	p-value
S (cm/s)	0.09	0.07 (0.01, 0.14)	0.036
Heart rate (bpm)	0.15	0.11 (0.05, 0.18)	0.001
E/e' ratio	-0.11	-0.27 (-0.49, -0.06)	0.014
LA volume index > 34 mL/m ²	-0.19	-4.41 (-6.41, -2.41)	< 0.001
LVEF (%)	0.15	0.15 (0.06, 0.23)	0.001

CI: confidence interval, LA: left atrial, LVEF: left ventricular ejection fraction.

LV ejection fraction (β = 0.15; p = 0.001), and LA enlargement (β = -0.19; p < 0.001) were the independent determinants of the active emptying fraction of the LA (**Table 3**).

The intraclass correlation coefficients and the 95% limits of agreement for the intraobserver variabilities regarding LA maximal, minimal, and pre-P volumes were 0.964 (0.937–0.979), 0.847 (0.732–0.912), and 0.840 (0.722–0.908), respectively. The intraclass correlation coefficients and the 95% limits of agreement for the interobserver variabilities concerning LA maximal, minimal, and pre-P volumes were 0.925 (0.787–0.966), 0.779 (0.585–0.878), and 0.847 (0.734–0.912), correspondingly.

DISCUSSION

We evaluated the determinants of LA contraction function in terms of its volumetric parameter, LA active emptying fraction, in patients with CAD. Briefly, we found that the heart rate, S, E/e' ratio, LV ejection fraction, and LA enlargement were independently correlated with the active emptying fraction of the LA.

LA enlargement is a marker of the structural remodeling of this chamber and is indicative of the severity and chronicity of LV diastolic dysfunction. In other words, chronically increased LA afterload can lead to the structural remodeling of this chamber, manifested as enlargement.³⁾ Decreased LA contraction in patients suffering from CAD with LA enlargement has been previously demonstrated.¹⁸⁾ Some evidence suggests that LA functional remodeling precedes the structural remodeling of this chamber.²⁴⁾²⁵⁾

The contraction function of the LA is dependent on the compliance and systolic function of the LV.³⁾²⁶⁾ Previous research has shown diminished LA active emptying fraction in patients with ischemic cardiomyopathy by comparison with normal subjects.^{27/28)} This finding is concordant with our finding regarding diminished LV ejection fraction as an independent determinant of LA contraction function.

The E/e' ratio is an index of LV filling pressure. Patients suffering from heart failure with preserved ejection fraction tend to have reduced LA contraction. It appears that increased afterload is detrimental to myocardial contraction function.²⁹⁾³⁰⁾

The S wave of the pulmonary vein is a maker of LA reservoir function,⁴⁾ which is correlated with LA contraction function.³¹⁾ This may be explained by the Frank-Starling law as preload to some extent accentuates contraction.³²⁾

According to our results, increased heart rate is in tandem with increased LA active emptying fraction. An increase in heart rate concurs with a decrease in LA filling and contraction time and, thus, maintains the filling of the heart. What ensues as a compensatory mechanism might be an increase in LA contraction.³³⁾

The evaluation of LA phasic functions has several clinical implications that should be interpreted with caution. In its different phases, the LA functions in a manner that is not entirely independent from the function of the LV.³⁾⁴⁾²⁶⁾ Indeed, some researchers have considered the systolic longitudinal strain of the LA, which is a marker of the reservoir function of the LA, to be a parameter that is no more informative than the global longitudinal strain of the LV.⁴⁾ On the other hand, the contraction function of the LA is one of the components of LA intrinsic myocardial contraction.³⁾ The reservoir function of the LA as evaluated by volumetric or deformation study is in correlation with the occurrence of postoperative AF, increased in-hospital mortality, elevated LV diastolic pressure, and prolonged lengths of stay in the intensive care unit in patients who undergo CABG. 14/15/34/35/ The conduit function of the LA correlates with postoperative AF and longer stays in the intensive care unit in the aforementioned population.³⁵⁾ The ability of LA contraction function to predict postoperative AF has yet to be elucidated.³⁶⁾ Nevertheless, one of the few investigations in this regard demonstrated that postoperative LA contraction function could predict the occurrence of postoperative AF.³⁷ This may imply that not only is LA contraction function homogeneously impaired in patients with CAD, which precludes the capability

to predict postoperative AF and other clinical events, but also revascularization creates a condition whereby variety in LA contraction function appears. This hypothesis is supported by the evidence that LA contraction function is impaired in patients with CAD¹⁸ and that this impairment is aggravated by the severity of CAD.³⁸ This hypothesis should be evaluated in a well-designed study.

In the current study, we evaluated LA contraction function in terms of its two-dimensional (2D) volumetric parameter. Such an echocardiographic evaluation relies on geometrical assumptions, which may not be accurate. Furthermore, not only is this assessment modality load dependent but also it is less sensitive than other imaging modalities and only confers an indirect estimation of the phasic functions of the LA. Despite these shortcomings, the 2D measurement of this volumetric parameter expedites the evaluation of LA contraction function, lacks serious contraindications, is low cost and rapid, and does not require complex hardware/software, high expertise, radiation, or contrast injection. The issue with other imaging modalities is that some present vendor-dependent values, some suffer from a dearth of normative values, and some need confirmation of their clinical value in future investigations.^{1)3/4} It is deserving of note that the values obtained by the 2D echocardiographic measurement of the volumetric parameters of LA phasic functions correlate with those obtained by other imaging modalities.³⁹

Our findings should assist in the identification of patients more likely to develop LA dysfunction. Patients who are candidates for CABG need stringent adherence to a therapeutic regimen that prevents the aggravation of LV systolic function and increased filling pressure, optimally controls factors that affect LV diastolic function, and prevents/treats factors associated with LA structural remodeling.

In the main, the cross-sectional design of our study precludes the establishment of causal relationships. Another salient limitation is that our investigation is a single-center study. Our results would be more robust had we been able to perform patient follow-up to evaluate the following: the phasic functions of the LA by other imaging modalities, other conditions that affect LA phasic functions such as obstructive sleep apnea and airway disease, and the presence of AF by long-term Holter monitoring and not merely by snapshot electrocardiography. What should also be taken into account concerning our study is that the results may be generalized only to candidates for CABG.

The findings of our study demonstrated that the heart rate, S, LV ejection fraction, LA enlargement, and E/e' ratio were the independent determinants of LA contraction function as evaluated by LA active emptying fraction in 2D echocardiography.

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