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ORIGINAL PAPER

Relationship of ischemic times and left atrial volume and function in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention

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Abstract Little is known about the impact of duration of ischemia on left atrial (LA) volumes and function during acute phase of myocardial infarction. We investigated the relationship of ischemic times, echocardiographic indices of diastolic function and LA volumes in patients with ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI). A total of 433 consecutive STEMI patients underwent echocardiographic examination within 48 h of primary PCI, including the measurement of LA volumes and the ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity (E/e′). Time intervals from onset of chest pain to hospital admission and reperfusion were collected and magnitude of Troponin I release was used to assess infarct size. Patients with LA volume index (LAVI) $\geq$28 ml/m^2 had longer total ischemic time (410 $\pm$ 347 vs. 303 $\pm$ 314 min, $p = 0.007$) and higher E/e′ ratio (15 $\pm$ 5 vs. 10 $\pm$ 3, $p < 0.001$) than those with LAVI <28 ml/m^2, while the indices of LA function were similar between the study groups ($p > 0.05$, for all). Significant correlation was found between E/e′ and LA volumes at all stages of LA filling and contraction (r = 0.363–0.434; $p < 0.001$, for all) while total ischemic time along with E/e′ and restrictive filling pattern remained independent predictor of LA enlargement. Increased LA volume is associated with longer ischemic times and may be a sensitive marker of increased left ventricular filling pressures in STEMI patients treated with primary PCI.

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Keywords Left atrial volume · Ischemic time · Diastolic dysfunction · Myocardial infarction

Abbreviations

ADM	Hospital admission
BMI	Body mass index
BSA	Body surface area
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CI	Confidence interval
CVA	Cerebrovascular accident
Cx	Circumflex
EF	Ejection fraction
LA	Left atrium
LAD	Left anterior descending
LAEF	Left atrial ejection fraction
LAVI	Left atrial volume index
LV	Left ventricle
LVEDP	Left ventricular end diastolic pressure
MI	Myocardial infarction
OR	Odds ratio
PAD	Peripheral arterial disease
PCI	Percutaneous coronary intervention
RCA	Right coronary artery
RFP	Restrictive filling pattern
STEMI	ST-segment elevation myocardial infarction
SV	Stroke volume
TIMI	Thrombolysis in myocardial infarction

Introduction

Left atrium (LA) contributes significantly to total cardiac output with its reservoir, conduit and pumping function.

Contribution of LA function to stroke volume is particularly important when left ventricular (LV) diastolic function is impaired and LA dilation has been suggested as a marker of the severity and duration of diastolic dysfunction [1, 2]. Diastolic dysfunction in the setting of acute myocardial infarction (AMI) arises from profound regional asynchrony between ischemic and normal myocardium resulting in disturbed ventricular relaxation and elevated myocardial stiffness [3]. Several studies have demonstrated that LA undergoes significant remodelling following AMI due to increased left ventricular end-diastolic pressure (LVEDP) [4–6] and it has also been shown that LA volume is an important predictor of morbidity and mortality after AMI [7, 8]. On the other hand, the relationship of duration of ischemia and LA volumes during acute phase of myocardial infarction has not been previously investigated.

We therefore investigated the impact of ischemic times on echocardiographic indices of diastolic function and LA volumes in patients with acute ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI).

Methods

We retrospectively studied 639 consecutive patients presenting with first-ever STEMI treated with primary PCI in an academic, high-volume centre. Patients were excluded from the analysis if they suffered previous MI or underwent coronary revascularization, received thrombolytics, presented in cardiogenic shock, had significant valvular disease, were in atrial fibrillation or had previously implanted pacemaker. Furthermore, patients in whom primary PCI did not succeed in restoring coronary flow in the culprit artery, also were not eligible for the study. Data regarding time intervals were collected from the patient, the emergency medical service (EMS) team members (report from the patients' relatives, exact timing of telephone calls to EMS and arrival to hospital) and the cath lab protocol sheets. Any disagreement in reported time intervals was settled by using times reported by EMS and cath lab report sheet. Troponin I assays (peak Troponin I) were collected serially at admission and after 12, 24, 48 h to assess enzymatic infarct size.

Comprehensive transthoracic echocardiogram was performed within 48 h after primary PCI, using Vivid 7 scanner (General Electric, Horton, Norway) and a 2.5- to 5-MHz phased-array transducer. The echocardiographic examination was performed according to American Society of Echocardiography recommendations [9] and included 2-dimensional, color flow, continuous and pulse-wave (PW) Doppler, and tissue Doppler imaging. Detailed measurements were performed offline using dedicated software EchoPac version 11.0 (General Electric, Horton, Norway). Three measurements were made for each parameter and averaged. LV ejection fraction as measurement of systolic function was obtained using the Simpson biplane method of discs. Mitral inflow Doppler and tissue Doppler data were obtained according to guidelines [10]. The ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity (E/e′) was calculated by using the average of the septal and the lateral e′ wave velocity. Diastolic function was graded 0–4 according to guidelines [10]. Left atrial volume was obtained using the Simpson biplane method of discs from apical 4- and 2-chamber views at three time points during heart cycle: (1) maximum volume (LAmax) at the end of systole, right before mitral valve opening; (2) minimal volume (LAmin) at the end of diastole, right before mitral valve closure; (3) volume before atrial contraction (LApreA) acquired at the point of P wave on surface ECG. All volumes are indexed to body surface area (BSA). LA enlargement was defined as LAmax $\geq$28 ml/m^2 (normal $\pm$ 1SD) [11, 12]. Mechanical function of LA was calculated based on following formulas: *total ejection fraction,* LAEF = (LAmax − LAmin/LAmax) × 100; *active ejection fraction*, as an index of active contraction LAEFa = [(LApreA − LAmin)/LApreA × 100]; *passive ejection fraction,* as an index of conduit function LAEFp = [(LAmax − LApreA/LAmax) × 100]; *LA expansion index*, expressing LA reservoire function [(LAmax − LAmin/LAmin) × 100] [13]. Echocardiograms were analysed by an investigator blinded to clinical and angiographic data.

The reproducibility of the measured echocardiographic parameters, (ESV, EDV, EF, E wave velocity, average e′ wave, maximum, minimum and before A wave LA volume index) was tested by two experienced observers and twice by each observer in 20 randomly selected patients. Interobserver coefficients of variation for measuring ESV, EDV, E wave velocity, average e′ wave, maximum, minimum and before A wave LA volume index were 3, 5, 8, 9, 9, 5 and 3 %, respectively. Intraobserver coefficients of variation for repeated same measurements were 3, 5, 6, 5, 7, 4 and 3 %, respectively.

All patients underwent coronary angiography and primary PCI on Siemens Axiom Artis XFA (Siemens, Erlangen, Germany) angiography scanner. Patients were pretreated with loading dose of aspirin (300 mg) and clopidogrel (600 mg), while heparin (80–100 IU/kg), was given before insertion of coronary guidewire. Glycoprotein IIb/IIIa inhibitors were given periprocedurally according to indication by the operator. After PCI aspirin, 100 mg per day, was given indefinitely with clopidogrel, 75 mg per day. Recommended duration of clopidogrel treatment was 12 months. Vascular access, PCI technique, use of guiding catheters, coronary gudiewires, manual thrombus aspiration, predilation and stent implantation were used according to operators' decision.

A culprit artery was defined as an artery with an identifiable thrombus and/or significant lesion on angiogram corresponding to ECG changes. Coronary artery stenosis was defined as narrowing of the lumen of more than 70 %. Coronary artery blood flow was graded 0–3 according to according to Thrombolysis In Myocardial Infarction (TIMI) scale [14].

Statistical analysis

Continuous variables are presented as mean values ± standard deviation (SD). Categorical variables are presented as percentages. Depending on the distribution of the data, *t* test or Mann–Whitney test were used to compare continuous variables, whereas Chi square and Fisher's test were used for categorical variables. Correlation between continuous variables was tested using Pearson's correlation method. Univariate regression analysis was performed to identify variables associated with LAVI $\geq$28 ml/m^2: the value of $p < 0.2$ was considered significant and those variables entered Cox multivariate analysis model to determine independent predictors of LA enlargement. p value of <0.05 was considered significant. Statistical analysis was performed using commercially available software (PASW Statistics, version 18, SPSS, Inc., Chicago, IL, USA).

Results

From 639 patients evaluated for inclusion in the study, after accounting for the exclusion criteria, 433 patients were analysed. Patient flow through the study is shown in Fig. 1. Patients were grouped based on maximal LA volume indexed for BSA in the group with enlarged LA (LAVI $\geq$28 ml/m^2) and the group with normal LA volume index (LAVI $<$28 ml/m^2). Clinical characteristics of the study groups are given in Table 1.

Patients from both groups had similar door to balloon time, while those with larger LAVI had longer time intervals from the onset of pain to hospital admission and longer total ischemic time (Table 2).

Angiographic and procedural characteristics were similar in the study groups. There was no significant difference in infarct-related coronary artery, initial TIMI flow, thrombus aspiration and glycoprotein IIb/IIIa inhibitors use and success of the intervention. The study groups had similar maximum values of troponin I representing surrogate of infarct size (Table 3).

The groups had similar LV wall thickness, but demonstrated significant differences in LVEF. In contrast to significant difference in E/e′ ratio between the study groups, indices of LA function (LAEF, LAEF active, LAEF passive, LA expansion index) were similar between the study groups (Table 4).

Significant correlations were found between E/e′ and LA volume and between minimal LA volume and LA volume before atrial contraction (Table 5; Fig. 2).

Patients with severe disturbance of diastolic function (restrictive filling pattern) had higher maximum values of Troponin I representing surrogate of infarct size (55.1 ± 33.7 vs. 32.4 ± 28.7 ng/ml; $p < 0.001$) (Fig. 3).

In a logistic regression model, including known predictors of LA dilation (smoking, left ventricular ejection fraction, hypertension, thrombus aspiration, maximum troponin I value, average E/e′, grade III diastolic dysfunction and total ischemic time), only total ischemic time, average E/e′ and grade III diastolic dysfunction (restrictive filling pattern) remained independent predictors of LAVI $\geq$28 ml/m^2 (Table 6).

Discussion

Our study demonstrated that STEMI patients with larger LA volumes had longer total ischemic time and higher E/e′ ratio than those with normal LA volumes, while the indices of LA function and infarct size were not related to LA enlargement. On the other hand, restrictive filling pattern (RFP) was not related to ischemic times but was associated with larger myocardial infarctions.

Time from the onset of chest pain to reperfusion is considered as an important prognostic parameter in patients with AMI [15]. Time delays from symptom onset to reperfusion in our study are long, but they are comparable with data from large European registries of acute coronary syndrome [16, 17], as are in-hospital delays from admission to reperfusion [18]. Several studies have shown that Doppler-derived LA filling indices, such as LA volume, E/e′ ratio and restrictive filling pattern, are independent predictors of adverse outcomes in patients with AMI [8, 19–24].

Our findings of LA enlargement with maintained LA function and increased E/e′ ratio suggests that LA volume may be an indicator of an acute rise in LV end-diastolic pressure (LVEDP) in the setting of AMI, besides being well known indicator of chronic elevation of LVEDP. It has been previously reported that LA during AMI responds to volume increase provoked by LVEDP rise by increasing work of contraction, thus maintaining forward LA emptying [25–27]. This mechanism is functional up to certain LA volumes when increased volume load cannot be further compensated by increased work and LA further dilates, indicating that Frank-Starling mechanism is also operative in the LA [28]. Our findings are also in line with study by Bozkurt

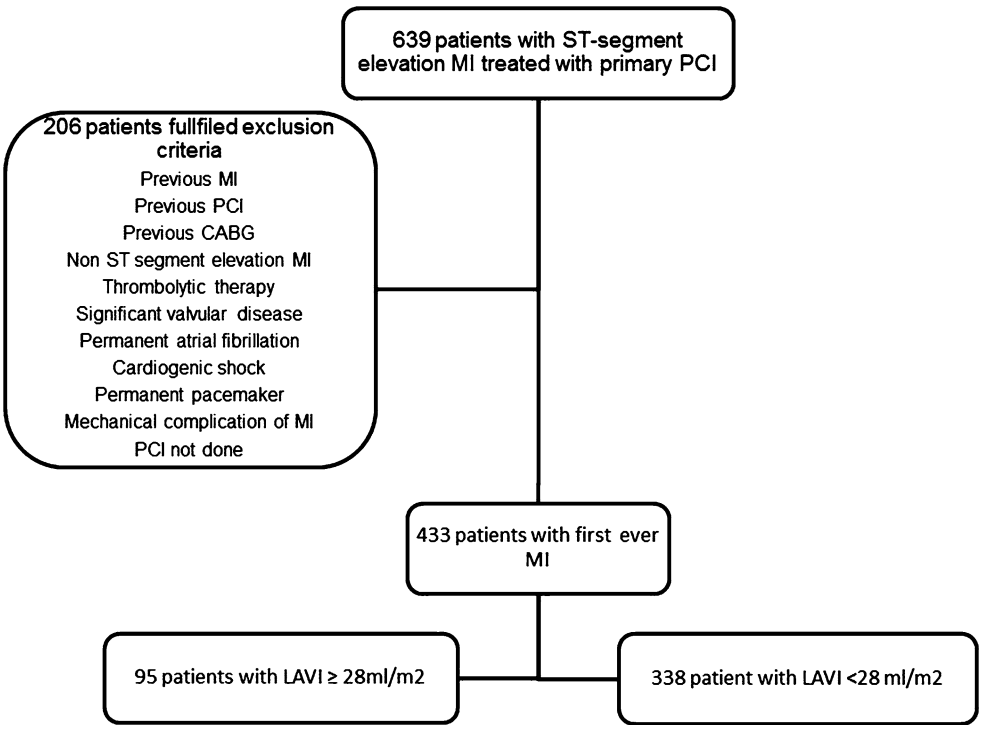

Fig. 1 Study flow chart representing number of patients evaluated, excluded and analysed in the study. All exclusion criteria are given separately

Table 1 Clinical characteristics of the patients

Clinical characteristics	LAVI ≥28 ml/m^2 n = 95 (21.9 %)	LAVI <28 ml/m^2 n = 338 (78.1 %)	*p* value
Age (years)	59.7 ± 11.7	57.7 ± 10.8	0.162
Male gender (%)	69.4	74.3	0.361
Heredity (%)	41.0	47.3	0.296
Smoking (%)	49.5	65.7	0.006
Hypertension (%)	68.4	65.1	0.625
Dyslipidemia (%)	34.7	39.9	0.405
Diabetes mellitus (%)	17.9	17.4	0.880
PAD (%)	2.1	1.5	0.651
Previous CVA (%)	2.1	5.9	0.211
Chronic renal failure (%)	1.0	0.9	1.000
BMI (kg/m^2)	28.1 ± 17.3	30.5 ± 34.4	0.523
Killip class (%)			0.276
Class I	81.0	85.8	
Class II	14.8	10.4	
Class III	4.2	3.8	

BMI body mass index, *CVA* cerebrovascular accident, *LA* left atrium, *LAVI* left atrial volume index, *PAD* peripheral arterial disease

et al. [4] where echocardiography was performed on admission and after a week, 1 and 3 months, showing that LA volume increased significantly starting from hospital admission. The compensatory mechanism of stroke volume increase responded to volume change, but the difference became significant after a period of 1 month [4]. Left atrial remodeling, defined as increase in LA volume of 8 ml/m^2 has been shown to occur in about one fifth of patients after AMI leading to LA functional deterioration over a 12-month period [5].

Previous studies demonstrated that LA volume >34 ml/m^2 (normal value ± 2SD) [11, 12] was an independent predictor of adverse events after MI [7, 8]. However, the large LA may not able to further dilate faced with increased LVEDP in MI [25–28] which is why we postulated that mild increase in LAVI (normal ± 1SD or 28 ml/m^2) can

Table 2 Ischemic times to reperfusion

Ischemic times	LAVI ≥28 ml/m^2	LAVI <28 ml/m^2	*p* value
Door-to-balloon time, min	59 ± 28	54 ± 37	0.305
Time from pain onset to ADM, min	348 ± 335	248 ± 304	0.009
Total ischemic time, min	410 ± 347	303 ± 313	0.007

ADM hospital admission, *LAVI* left atrial volume index

Table 3 Angiographic and procedural characteristics of the study groups

Angiographic characteristics	LAVI ≥28 ml/m^2 (%)	LAVI <28 ml/m^2 (%)	*p* value
Extension of CAD			0.054
Single vessel	31.6	39.6	
Two vessel	30.5	35.2	
Three vessel	37.9	25.1	
Infarct related artery			0.447
LAD	47.4	41.7	
Cx	17.9	14.6	
RCA	34.7	43.7	
Thrombus aspiration	51.5	49.4	0.729
Glycoprotein IIb/IIIa inhibitors	15.8	20.1	0.299
TIMI before primary PCI			0.546
TIMI 0	69.5	66.0	
TIMI 1	10.3	10.4	
TIMI 2	13.7	12.2	
TIMI 3	6.5	11.4	
Angiographic success	96.8	98.8	0.181
No reflow phenomenon	5.2	2.1	0.147
Maximum troponin I value (ng/ml)	37.4 ± 31.2	32.5 ± 28.8	0.159

CAD coronary artery disease, *Cx* left circumflex coronary artery, *LAD* left anterior descending coronary artery, *LAVI* left atrial volume index, *RCA* right coronary artery, *PCI* percutaneous coronary intervention, *TIMI* thrombolysis in myocardial infarction

Table 4 Echocardiographic characteristics of the study groups

	LAVI ≥28 ml/m^2	LAVI <28 ml/m^2 (%)	*p* value
Septal thickness (mm)	11.5 ± 1.2	11.6 ± 2.1	0.759
Posterior wall thickness (mm)	9.6 ± 1.1	9.7 ± 4.3	0.807
Biplane LVEF (%)	44 ± 8	47 ± 10	0.021
Mitral inflow E wave (m/s)	0.82 ± 0.19	0.70 ± 0.17	<0.001
Mitral inflow A wave (m/s)	0.74 ± 0.22	0.76 ± 0.18	0.457
Mitral inflow E/A	1.2 ± 0.5	1.0 ± 0.3	<0.001
Deceleration time (ms)	159 ± 36	186 ± 42	<0.001
Average septal/lateral e′ (m/s)	0.06 ± 0.02	0.07 ± 0.02	0.171
E-wave/average e′	15 ± 5	10 ± 3	<0.001
LA EF (%)	47 ± 14	47 ± 12	0.660
LA active EF (%)	25 ± 15	27 ± 13	0.307
LA passive (%)	47 ± 13	46 ± 11	0.436
LA expansion index (%)	173 ± 61	169 ± 54	0.619

EF ejection fraction, *LA* left atrium, *LAVI* left atrial volume index, *LAEF* left atrial ejection fraction, *LVEF* left ventricular ejection fraction

more accurately reflect initial rise in LVEDP and duration of ischemia.

Our data also suggest that initial rise of LVEDP may cause LA dilatation before restrictive filling pattern develops, indicating that LA volume may be a more sensitive indicator of duration of ischemia than restrictive filling pattern. The potential of LA volume to reflect the increase in LVEDP during AMI has been investigated in the study including more than 600 patients, who underwent simultaneous cardiac catheterization with LVEDP

Table 5 Correlation coefficient (r) between LA volumes and E/e′ average

LA volume index	E/e′ avg. (r)	*p* value
Maximum	0.434	<0.001
Minimum	0.448	<0.001
Before atrial contraction	0.363	<0.001

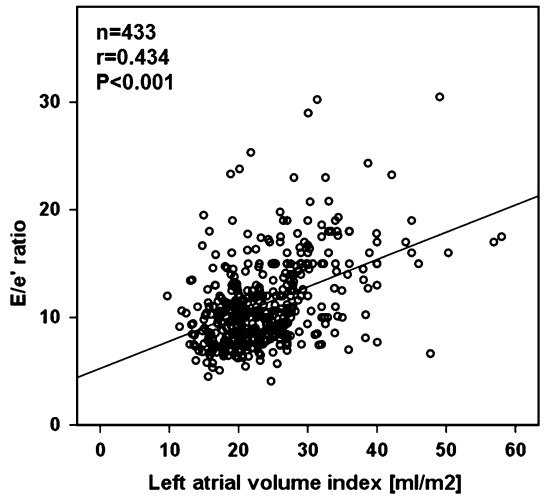

Fig. 2 Correlation between E/e′ and maximum LA volume. The diagram shows significant correlation between maximal LA volume expressed as ml/m^2 and average E/e′ value

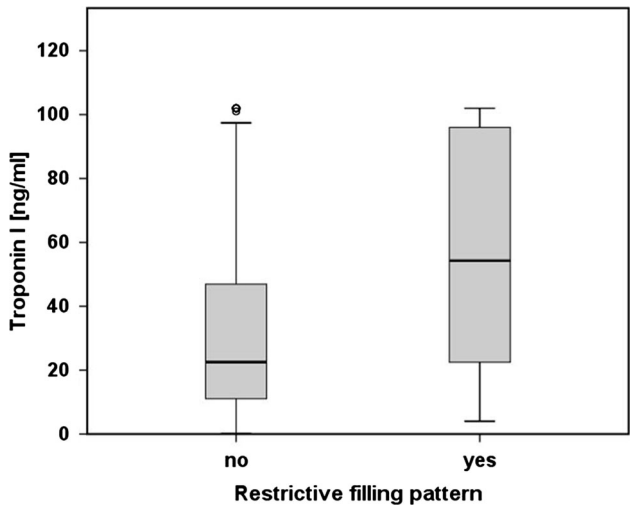

Fig. 3 Maximum Troponin I release in patients with restrictive filling pattern (RFP) versus non RFP. The *box-plot diagram* displays significant difference in troponin release comparing patients with grade III diastolic dysfunction and those without it

measurement and transthoracic echocardiography [29]. This study demonstrated that maximal and minimal LA volumes and LAEF were associated linearly with LV filling pressures. It was further shown that LA distensibility and LA ejection fraction had logarithmic association with filling pressures and were more accurate in predicting LVEDP >15 mmHg than E/e′ ratio [29].

Nonetheless, it has been recently shown that RFP may also be related to duration of myocardial ischemia [23], which was not confirmed in our study. This discrepancy may be explained by a relatively loose definition of RFP used by Prasad et al. [23] as opposed to strict, guideline-proposed definition used in our study [9, 10]. However, our data confirmed that RFP was associated with larger infarct size in terms of magnitude of troponin I release. Further studies are warranted to determine temporal changes of diastolic function during AMI and to clarify exact relationship between LA volumes and its functional indices and ischemic times in STEMI patients.

Study limitations

Patients were retrospectively evaluated and did not have previous echocardiographic exams which could help to identify those with diastolic dysfunction prior to coronary event. Further, direct measurements of LVEDP by catheterization of the left ventricle were not performed. The effect of standard pharmacological therapy known to influence patients' outcomes (beta-blockers, ACE inhibitors) was not accounted for, although the guideline-proposed treatment for STEMI, if not contraindicated or poorly tolerated, was given to all patients. Finally, it may be argued that maximum troponin value used in our study may have lower accuracy compared to serial measurements and total troponin release (area under curve) in determining exact infarct size in patients who underwent mechanical reperfusion; however, single-point values, except the ones at admission, have shown good correlation with infarct size estimated by cardiac magnetic resonance imaging or single photon emission tomography [30, 31].

Conclusions

In this retrospective analysis of consecutive STEMI patients treated with primary PCI, greater left atrial volume indexes were associated with longer ischemic times, while functional performance of LA was not impaired. The

Table 6 Univariate and multivariate predictors of LAVI $\geq$28 ml/m^2

	Univariate		Multivariate	
	OR [95 % CI]	*p* value	OR [95 % CI]	*p* value
Smoking	0.512 [0.323–0.811]	0.004	0.585 [0.305–1.123]	0.107
LV ejection fraction	0.970 [0.945–0.996]	0.022	0.976 [0.940–1.014]	0.209
E/e′ average	1.351 [1.256–1.454]	<0.001	1.347 [1.234–1.471]	<0.001
Grade III diastolic function	0.009 [0.001–0.071]	<0.001	0.010 [0.001–0.086]	<0.001
Maximum troponin I	1.009 [1.002–1.017]	0.016	1.003 [0.993–1.014]	0.529
Thrombus aspiration	0.917 [0.581–1.446]	0.709	–	–
Total ischemic time	1.001 [1.000–1.002]	0.024	1.001 [1.000–1.002]	0.027
Diabetes mellitus	1.031 [0.568–1.869]	0.921	–	–
Hypertension	1.162 [0.714–1.891]	0.545	–	–

CI confidence interval, *LAVI* left atrial volume index, *LV* left ventriclular, *OR* odds ratio

restrictive filling pattern was associated with larger infarctions, but it was not associated with longer ischemic times.

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Conflict of interest Other authors have no conflict of interest to declare regarding this manuscript.

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