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Left Atrial Appendage-Flow Velocity Predicts Cardioversion Success in Atrial Fibrillation

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Akdeniz, B., Badak, Ö., Barış, N., Aslan, Ö., Kirimli, Ö., Göldeli, Ö. and Güneri, S. *Left Atrial Appendage-Flow Velocity Predicts Cardioversion Success in Atrial Fibrillation*. Tohoku J. Exp. Med., 2006, **208** (3), 243-250 —— Restoration of sinus rhythm by electrical cardioversion is a therapeutic option in appropriately selected patients with atrial fibrillation. It is important to determine predictors of electrical cardioversion outcome in patients with atrial fibrillation. Predictive value of clinical and conventional echocardiographic parameters for predicting cardioversion outcome is limited. The role of left atrial appendage (LAA) function, which may reflect left atrial contractile function, for prediction of cardioversion outcome remains unclear. We conducted a single center prospective study to evaluate the role of LAA function for prediction of cardioversion success in patients with atrial fibrillation. One hundred sixty three patients with atrial fibrillation underwent transthoracic and transesophageal echocardiography (TEE) before electrical cardioversion. LAA functions, including LAA peak flow velocity, LAA area and LAA ejection fraction, were examined. Cardioversion was successful in 133 patients and unsuccessful in 30 patients. Mean LAA peak emptying flow velocity was significantly higher in the patients with successful cardioversion than in those with unsuccessful cardioversion (0.34 ± 0.14 vs 0.27 ± 0.1 m/sec; $p = 0.013$). At multivariate logistic regression analysis, only LAA flow velocity (> 0.28 m/sec, odds ratio = 2.8 ; $p = 0.03$) proved to be an independent predictor of cardioversion success. LAA area ($p = 0.18$) and LAA ejection fraction ($p = 0.52$) were not different between successful and unsuccessful cardioversion groups. Therefore, measurement of LAA flow velocity provides valuable information for prediction of cardioversion outcome in patients with atrial fibrillation before TEE guided cardioversion. ———— cardioversion; left atrial appendage (LAA) function; atrial fibrillation

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Atrial fibrillation (AF) is the most common sustained disturbance of cardiac rhythm (Feinberg et al. 1995; Ryder and Benjamin 1999) and its incidence increases with aging (Watanabe et al. 2005). Restoration of sinus rhythm is a therapeutic option in appropriately selected patients with atrial fibrillation. External direct electrical cardioversion remains the most common and effective method for restoring normal sinus rhythm in patients with atrial fibrillation. There are few

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clinical and echocardiographic parameters of cardioversion success such as the duration of atrial fibrillation and the diameter of the left atrium (Henry et al. 1976; Brodsyk et al. 1989). The predictive value of these parameters is limited (Dittrich et al. 1989). It is important to establish more precise predictors of cardioversion outcome in order to reduce patient risk and health care cost.

It is important to eliminate the possibility of cardiac thrombi before cardioversion in order to reduce the risk of thromboembolism. Transesophageal echocardiography visualizes better the left atrial appendage (LAA), which is the most common source of thrombi and thus allowing earlier cardioversion in patients with atrial fibrillation (Tracy et al. 2000; Klein et al. 2001; Isbell and Dent 2004).

The assessment of thromboembolic risk by measurement of LAA velocities during transesophageal echocardiography in atrial fibrillation has become accepted (The Stroke Prevention in atrial fibrillation Investigators 1998; Kamp et al. 1999). LAA flow velocity may also represent LAA contractile function. Recent studies have suggested that the conversion from atrial fibrillation to sinus rhythm may be predicted by evaluating LAA velocities before cardioversion (Mitusch et al. 1995; Tabata et al. 1997; Palinkas et al. 2001). However, there have been conflicting data in the literature (Perez et al. 1997; Verhost et al. 1997). Furthermore, other parameters related to LAA function (i.e., left atrium area and left atrial ejection fraction) have not been assessed for cardioversion success. We aimed to evaluate the effect of LAA functions on cardioversion success in patients with atrial fibrillation who underwent transesophageal echocardiography (TEE) guided cardioversion in a prospective single centre study.

Materials and Methods

One hundred sixty three patients with AF, lasting longer than 2 days, who were planned to TEE guided electrical cardioversion and were admitted to Dokuz Eylul University Hospital between January 2002 and July 2004, were enrolled in the study. Patients who could not tolerate TEE, and who did not approve the procedure or who were planned to pharmacologic cardioversion as well as the patients with atrial thrombus, atrial flutter, hyperthyroidism, acute coronary syndrome, pulmonary embolism, and recent heart surgery, were all excluded. Patients with mild to moderate valvular heart disease were included in the study. Patients whose arrhythmia had converted to sinus rhythm spontaneously before cardioversion were excluded from the study. Informed written consent was obtained from each patient and the study protocol was approved by the institutional ethic committee (Dokuz Eylül University School of Medicine) for clinical trial.

Echocardiography

Conventional transthoracic and TTE was performed using Hewlett Packard, Agilent Technologies Sonos 4500 system, or Acuson XP 128 devices in all patients before cardioversion. We performed TEE in all patients in order to rule out left atrial appendage thrombi, which could not be seen easily in TTE. Transesophageal echocardiography was performed with multiplane probes with a 7.0-MHz transducer. The TTE measurements were obtained from parasternal long axis view by 2-D targeted M mode tracings according to the recommendations of the American Society of Echocardiography (Sahn et al. 1978). Left atrial diameter, left ventricular end systolic and end diastolic diameter, left ventricular ejection fraction (according to Teickoff formula and modified Simpson's method in patients with segmental wall motion abnormalities) were measured. All TEE procedures were performed by an experienced cardiologist for the presence of intracardiac thrombus. Patients with intracardiac thrombus were excluded from the study. In order to view the maximal size and to obtain the highest resolution of the LAA, the most appropriate section was used for the analysis. Special attention was paid to assess the presence or absence of left atrial thrombi and degree of spontaneous echo-contrast (SEC) during TEE examination. A thrombus was considered to be present when a well-circumscribed echodense intracavitary mass that was acoustically distinct from the underlying endocardium was detected. The degree of spontaneous echocontrast was graded according the following criteria: mild was defined as minimal echogenicity located in the LAA or sparsely distributed in the main cavity of the left atrium, which was possible to detect only transiently during the cardiac cycle, but imperceptible at operating gain settings for two-dimensional echochardiographic analysis. "Moderate" was defined as a dens, swirling pattern

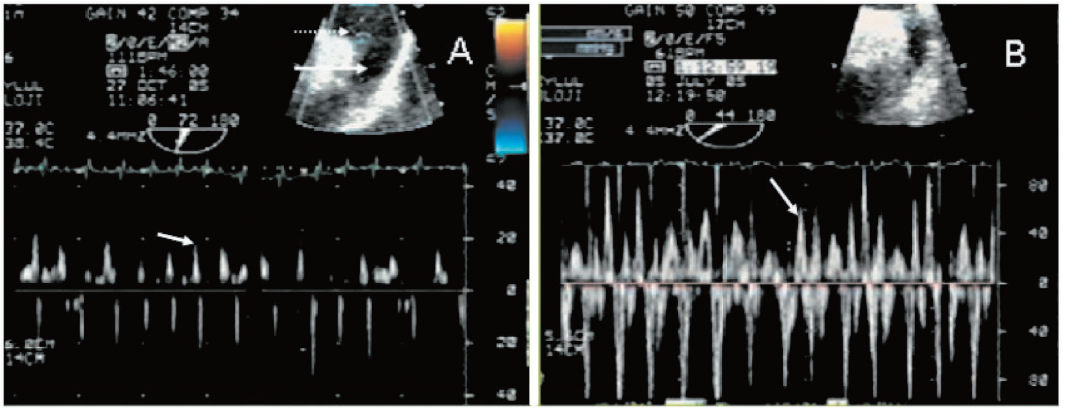


Fig. 1. Pulse Doppler tracings of LAA in the two patients with atrial fibrillation. Left panel (panel A) shows low peak flow velocity signals in a patient with unsuccessful cardioversion (mean flow velocity was 0.2 m/sec). Panel B shows higher peak flow velocity signals in a patient who had been successfully cardioverted. In the upper portion of the left panel, white arrow indicates left atrial appendage and dotted white arrow indicates sample volume of pulsed Doppler tracings. White arrows in the bottom of both panels show LAA flow velocity.

in the LAA, generally associated with somewhat lesser intensity in the main cavity, which may fluctuate in intensity but detectable constantly through the cardiac cycle "Severe" was defined as an intense, echo density and a very slow swirling pattern in the LAA, usually with similar density in the main cavity (Daniel et al. 1988).

LAA velocity profiles were obtained by pulsed wave Doppler imaging in both the transverse and longitudinal views. Sample volumes were placed 1 cm within the orifice of the LAA, and LAA flow velocities were assessed during atrial fibrillation (Fig. 1). LAA peak emptying velocities were averaged with each R-R interval over a minimum of five consecutive cardiac cycles (Mitusch et al. 1995; Tabata et al. 1997). LAA area and LAA ejection fraction were also measured. Maximal and minimal areas of LAA were traced by planimetric method in vertical plane. LAA ejection fraction was calculated using formula = maximum area − minimum area/maximum area × 100 (Isbell and Dent 2004).

Cardioversion

All patients underwent TEE-guided electrical cardioversion in the coronary care unit. Direct current cardioversion was attempted externally with Haewlett Packard Lifepack device within 24 hrs after TEE while patients were sedated with intravenous midazolam and propofol. Initial synchronized shock was delivered 100 joule from anterolateral paddle position. If necessary, the procedure was repeated with 200, 300 and 360 joule. Anteroposterior electrode position was tried in a few patients if current cardioversion was unsuccessful with the anterolateral electrode position. Antiarrhythmic treatment (amiodarone or propafenone) was begun after successful electrical cardioversion for maintenance sinus rhythm. Successful cardioversion was defined as a stable sinus rhythm lasting for at least 1 day after successful cardioversion (Van Gelder et al. 1991). Low molecular weight heparin (enoxaparine; 0.6 ml twice a day) was given subcutaneously before cardioversion and up to 1-2 days after cardioversion. During this period, warfarin treatment was also begun. The goal of anticoagulation with warfarin was an international normalized ratio of 2.0 to 3.0. Patients in whom thrombi were not detected by TEE, cardioversion was performed within 24 hrs. Warfarin therapy was maintained for 4 weeks after successful cardioversion and continuously maintained in those in whom failed cardioversion.

Statistical analysis

All continuous variables are expressed as a mean ± S.D. Statistical analysis was assessed by Student's *t*-test for continuous variables. Comparison of proportions was performed using chi-square analysis. Spearman correlation analysis was used in assessment of correlation between left atrial SEC and mean LAA velocity. Receiving operating characteristics analysis was used to determine the optimal cut-off value for prediction of cardioversion with respect to mean LAA peak anterograde flow velocity (Fig. 2). Univariate and multivariate logis-

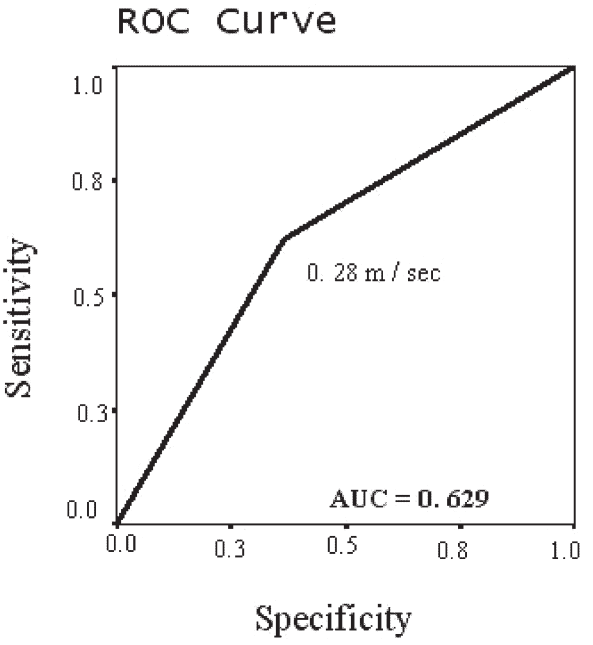


Fig. 2. Receiver operating characteristics curve of the mean LAA emptying flow velocity prediction of succesful cardioversion.

tic regression analysis for assessment of cardioversion success was performed using an SPSS 11 software package. A p value < 0.05 was considered significant.

Results

TEE guided electrical cardioversion were performed in total of 163 patients within 24 hrs after TEE. Mean duration of atrial fibrillation was 140.2 days. Almost half of patients had shorter AF duration (less than 30 days) (Table 1). Percentage of severe, moderate and mild degree spontaneous echo-contrast were 8.4%, 23.1%, and 37.1%, respectively. Cardioversion was successful in 133 patients (81%). Sinus rhythm was not restored in 30 patients after cardioversion; six of them had early recurrence. The success rate was higher (90.2%) in patients with shorter atrial fibrillation duration. Mean delivered cumulative shock energy during cardioversion was 405.67 ± 278.34 joule (range 100 to 1,060 J) with an average number of 1.97 shock. There were no side effects during cardioversion.

There were no differences in age, sex, body mass index and underlying disease between patients with successful and unsuccessful cardioversion (Table 1). The percentage of patients with shorter AF duration was higher in successfully converted group (54.5%) than in the other group without success (23.5%; $p = 0.02$).

Echocardiographic variables

Transthoracic echocardiographic parameters were not found to be related to cardioversion success. Left atrial diameter, left ventricular end systolic and end diastolic diameters and left ventricular ejection fraction were similar between

Table 1. *Clinical variables in patients with successful and unsuccessful cardioversion*

	All patients (n = 163)	Success (n = 133)	Failure (n = 30)	p value
Mean age (years)	66.3 ± 10.4	66.5 ± 10.4	65.3 ± 10.5	0.59
Sex (Men) n (%)	70 (42.9%)	57 (42.9%)	13 (43.3%)	0.96
(Women) n (%)	93 (57.1%)	76 (57.1%)	17 (56.7%)	
Body mass index (gr/m^2)	28.4 ± 3.5	28.4 ± 3.6	28.3 ± 3.1	0.86
Hypertension (%)	51.6	50.4	56.7	0.53
Diabetes mellitus (%)	15	14.6	16.7	0.77
Congestive heart failure (%)	9.4	8.5	13.3	0.48
Valvular heart disease (%)	19.5	19.2	20.7	0.85
Coronary heart disease (%)	20	20	20	1
Atrial fibrillation duration (days)	140.2 ± 211.9	126.1 ± 206.8	203.9 ± 229.2	0.17
Proportion of patients with atrial fibrillation duration < 30 day (%)	48.9%	54.5%	23.5%	0.021

TABLE 2. *Comparison of echocardiographic variables in patients with successful and unsuccessful cardioversion*

Echocardiographic variables	All patients	Success	Failure	*p* value
LA diameter (mm)	43.9 ± 4.5	43.9 ± 4.0	43.8 ± 6.0	
LA diameter > 50 mm (%)	6.2	5.1	10.7	0.37
LVEDD (mm)	48.5 ± 5.5	48.4 ± 5.4	48.3 ± 6.3	0.93
LVESD (mm)	33.5 ± 5.9	33.6 ± 0.6	33.2 ± 0.64	0.77
Left ventricular Ejection Fraction (%)	56.2 ± 10.1	56.8 ± 9.5	53.9 ± 12.0	0.15
Left atrial SEC (%)	68.5	67	75	0.051
Left atrial severe SEC (%)	8.4	5.2	21.4	0.013
Mean LAA peak flow velocity (m/sec)	0.32 ± 0.14	0.34 ± 0.14	0.27 ± 0.1	0.017
Mean LAA peak flow velocity > 0.28 m/sec (%)	57.7	62.4	36.7	0.019
LAA area (mm^2)	57.3 ± 4.66	53.9 ± 3.7	70.6 ± 7.3	0.18
LAA ejection fraction (%)	45.2 ± 14.3	45.7 ± 14.5	40 ± 13.2	0.52

successful and unsuccessful cardioversion groups (Table 2). However left atrial diameter influenced cardioversion success when it was larger than 50 mm. The rate of cardioversion success was lower in patients with larger left atrium (> 50 mm) (66.7% - 81.6%, $p = 0.37$) but the difference did not reach statistical significance.

Unlike transthoracic echo parameters, TEE parameters were found to affect the cardioversion success. Mean LAA peak anterograde flow velocity (0.34 ± 0.14 m/sec) was higher in patients with successful cardioversion than unsuccessful cardioversion (0.27 ± 0.1 m/sec; $p = 0.017$) (Fig. 3). The percentage of patients with left atrial severe SEC was significantly lower in patients with successful cardioversion than unsuccessful cardioversion ($p = 0.013$). Cardioversion success was not different among patients with mild to moderate SEC (83% - 81.3%) and without SEC (84%, $p > 0.05$). In patients with shorter duration of AF (< 30 day), all of 28 cases with mean LAA peak flow velocity > 0.28 m/sec and all of 14 cases without severe left atrial SEC had successful cardioversion.

There was a weak but significant negative correlation between LAA peak flow velocity and left atrial SEC ($r = –0.30$, $p < 0.001$). Other parameters related to LAA function (i.e., LAA area [$p = 0.18$] and LAA ejection fraction [$p = 0.52$] did not influence the cardioversion success

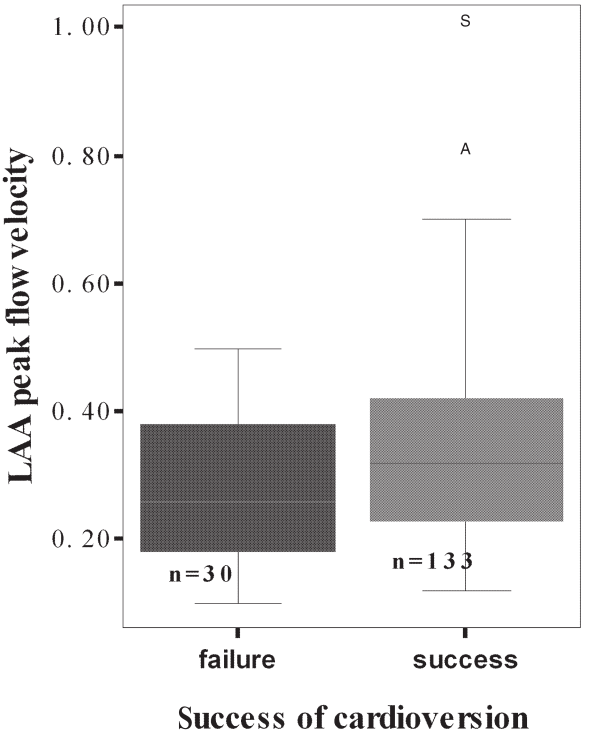


Fig. 3. The comparison of patients with successful and unsuccessful cardioversion regarding to of LAA peak flow velocities.
The box and plot graphics show that mean LAA peak flow velocity (0.34 ± 0.14 m/sec) was higher in patients with successful cardioversion than those with unsuccessful cardioversion (0.27 ± 0.1 m/sec $p = 0.017$)

TABLE 3. *Univariate and multivariate predictors of successful cardioversion outcomes*

Univariate predictors	OR	95% CI	*p*
LAA peak flow velocitiy > 0.28 m/sec	2.61	1.15 - 5.92	0.019
Absence of left atrial severe SEC	4.95	1.46 - 16.79	0.013
Duration of atrial fibrillation < 30 day	3.90	1.16 - 13.04	0.021
Multivariate analysis			
LAA peak flow velocitiy > 0.28 m/sec	3.73	1.07 - 12.97	0.039
Absence of left atrial severe SEC	3.55	0.74 - 17.01	0.11
Duration of atrial fibrillation < 30 day	3.08	0.88 - 10.79	0.079

OR, odds ratio; CI, confidence interval.

[Table 1]).

According to the receiver operating characteristic (ROC) analysis, a mean LAA peak anterograde flow velocity > 0.28 m/sec could be the best distinguishing parameter between patients with and without successful cardioversion (Fig. 1). Sensitivity, specificity, and positive predictive value and negative predictive value of LAA peak flow velocities > 0.28 m/sec for prediction of cardioversion success were found to: 62.4%, 63.3% 88.3% and 27.5% respectively. These values are more evident in patients with shorter duration of AF (< 30 days). The sensitivity, specificity, and positive predictive values were found: 66.7%, 100% and 100%, respectively.

Three predictors were found for cardioversion success by univariate regression analysis; LAA peak flow velocity > 0.28 m/sec, absence of left atrial severe SEC and duration of atrial fibrillation < 30 days. Multivariate analysis revealed that only LAA flow velocity > 0.28 m/sec proved to be independent predictors of successful cardioversion (Table 3).

DISCUSSION

Our results suggest that measurement of LAA peak flow velocity in patients with atrial fibrillation during TEE provides valuable information for prediction of subsequent electrical cardioversion. In multivariate analysis, presence of LAA peak anterograde flow velocity > 0.28 m/sec was found to be the best discriminator of subsequent cardioversion success (Odds ratio = 3.73; $p = 0.039$). The predictive value of higher LAA flow velocity is especially prominent in patients with shorter atrial fibrillation duration. The shorter duration of atrial fibrillation ($p = 0.079$) and absence of left atrial severe SEC ($p = 0.11$) also displayed a trend for significance.

Previous studies have demonstrated that left atrial size and the duration of atrial fibrillation are predictors of cardioversion success (Mitusch et al. 1995; Agmon et al. 1999). However the duration of the atrial fibrillation is either unknown or cannot be determined accurately, which weakens the clinical value of this parameter. Even among patients with documented symptomatic atrial fibrillation, asymptomatic recurrences are common (Page et al. 1994). In our study, patients with longer duration of atrial fibrillation were included in the study and the standard deviation of duration of atrial fibrillation was very high. All these factors may weaken the statistical power of this study. Moreover shorter duration of atrial fibrillation (< 30 days) was found to be univariate predictors of cardioversion success.

LAA flow velocity represents LAA contractile function. It is highly variable in patients with atrial fibrillation ranging from preserved contraction to absence of movement of appendage (Page et al. 1994). Recent reports have suggested that cardioversion success of atrial fibrillation may be predicted by the assessment of LAA flow velocity before cardioversion, but some methodological problems have weaken the outcomes of these studies, and moreover, some other studies have not confirmed their findings (Mitusch et al. 1995; Verhost et al. 1997).

Palinkas et al. (2001) studied the role of LAA flow velocity by TEE for prediction of cardioversion outcome before cardioversion in patients with nonvalvular atrial fibrillation. Their prospective multicenter study consisted of larger sample size and strict selection criteria (duration of atrial fibrillation was less than 1 year). They found that LAA peak emptying velocity has an independent and additive prognostic value over other clinical and echocardiographic predictors such as larger left atrial diameter and shorter atrial fibrillation duration. However, the study population appeared to be heterogeneous due to inherent nature of multicenter trial with regarding the mode of cardioversion (electrical or chemical), type of chemical cardioversion protocol. Use of some antiarrhythmic drugs at the point of cardioversion might have some influence on conversion rate.

We conducted a single center study consisted of 163 patients; all patients underwent electrical cardioversion within 24 hrs and most of them within the 6 hrs after TEE. All echocardiographic analysis was performed to single experienced observer. Patients who were pharmacologically cardioverted or whose arrhythmia had converted to sinus rhythm spontaneously before cardioversion were not included to the study. We included a larger heterogeneous population of atrial fibrillation representing the real cardiology practice. Some of the patients have longer atrial fibrillation duration (> 1 year) and some of them have valvular heart disease (19.5%) except moderate to severe mitral stenosis. Therefore, the conclusion of this study may be applied to more patients encountered in hospital practice.

Other LAA function tests (LAA areas and LAA ejection fraction) did not show any prognostic contribution for cardioversion success. LAA area and LAA ejection fraction were not found to be different between successful and unsuccessful cardioversion groups. These measurements are inherently prone to substantial interobserver and intraobserver variability during data registration due to complex three - dimensional anatomy. We performed to echocardiographic analysis by a single experienced observer. More prospective studies are necessary to verify these data.

It is controversial to convert into sinus rhythm in patients with severe SEC in LAA due to the risk of thromboembolic complications. We conducted electrical cardioversion in 12 patients with severe SEC in LAA. Thromboembolic complications were not observed in any patients. But the success of cardioversion was very low (50%). A negative correlation was found between left atrial severe SEC and left atrial peak flow velocity. This finding suggests that it may not be logical to attempt electrical cardiovesion in patients with AF and who have severe SEC in LAA.

Interestingly we did not find an effect of left atrial diameter to cardioversion success. This may be due to our patient characteristics with the relative smaller left atrial diameter (mean left atrium diameter: 4.38 cm). Only minority of the patients had larger (> 50 mm) left atrium. The rate of cardioversion success was lower, if left atrial diameter was larger than 50 mm (66.7% - 81.6%, $p = 0.37$), but the difference did not reach statistical significance probably due to the low number of case with larger left atrium. Measurement of let atrial area could have been more appropriate than left atrial diameter because of complex anatomy of left atrium.

In conclusion, it is possible to obtain predictive information about cardioversion success by examining LAA flow velocity pattern during transesophageal echocardiography before cardioversion. Measurements of LAA areas and LAA ejection fraction do not have any prognostic contribution for cardioversion success. We do not recommend cardioversion in patients with low LAA peak velocity and presence of severe LAA SEC in tranesophageal echocardiography.

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