

**Clinical value of left atrial appendage velocity  
assessment by transesophageal echocardiography  
in patients with atrial fibrillation**

**Summary of PhD thesis**

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## **INTRODUCTION**

Atrial fibrillation is one of the most common rhythm abnormalities of the heart. This arrhythmia has been shown to be associated with increased risk for cardiovascular morbidity or mortality. As we enter the 21<sup>st</sup> century, this arrhythmia has assumed increasing importance as the global demographic tide results in a burgeoning population of elderly individuals. The impact of atrial fibrillation on mortality and morbidity is substantial, as are the socioeconomic consequences in relationship to hospital admissions, chronic disease management and disabilities. These adverse trends, nonetheless, are superimposed on a background of several new therapeutic options. Consequently, a more complete understanding of pathology, pathophysiology and clinical background of atrial fibrillation is crucial to the future allocation of an expanding range of therapies aimed at reducing the impact of this disease on an aging population.

One of the most important sequelae of atrial fibrillation is its association with thromboembolic disease and stroke. The absence of synchronized, regular contraction of the atrium and appendage produces markedly reduced blood flow and stasis of blood and predisposes thrombus formation, predominantly within left atrial appendage (LAA). In the past, the LAA has been considered to be a relatively insignificant portion of cardiac anatomy. It is now recognised that it is a structure with important pathological associations and therefore in recent years considerable scientific interest has been focused on assessment of morphology and function of the appendage - the main target of this thesis - in healthy and pathologic conditions.

The LAA remained a 'blind spot' until the advent of transesophageal echocardiography. The use of this echocardiographic method has made clear imaging of the LAA possible, so that its size, shape, flow patterns and contents can be assessed in health and disease. Complete structural and functional assessment of the LAA should consist of two-dimensional imaging of LAA size, morphology and contraction. Two-dimensional imaging is used to determine the presence of LAA spontaneous echocardiographic contrast (SEC), semiquantitative grading of SEC, and defining the presence, size and mobility of LAA thrombi.

Assessment of LAA function by pulsed Doppler echocardiography is used in the clinical practice to evaluate contractile function of the LAA. In contrast to what is described in sinus rhythm, i.e. well organized, regular, high velocity Doppler flow signals, in atrial fibrillation, an irregular flow is seen with pulsed Doppler interrogation of the LAA. Repetitive biphasic, sawtooth-appearing flow signals of variable amplitude are the most commonly described pulsed Doppler echocardiographic patterns in patients with atrial fibrillation. In general, an average of peak anterograde flow velocities over at least five cardiac cycles are widely used for characterisation of mechanical function of the LAA in atrial fibrillation.

## **PRIMARY GOALS OF THE THESIS**

## **Part I. : Evaluation of clinical and echocardiographic correlates of left atrial appendage flow velocity in patients with atrial fibrillation**

Relationship between various clinical and echocardiographic parameters and LAA flow velocities in atrial fibrillation has been assessed in previous investigations. However controversial results have been reported in the literature regarding the association between certain variables and left atrial emptying velocities. The conclusions were frequently weakened by the small sample size or heterogeneous patient population of the available studies. Moreover, correlation between LAA flow velocity and some parameters have never been studied previously in atrial fibrillation. Considering the recently described important clinical and pathological associations of the appendage, it would be substantial to define more precisely the factors influencing the transesophageal echocardiographically assessed LAA mechanical function.

*Therefore the aim of our study was to evaluate the detailed determinants of the left atrial appendage flow velocities in a large cohort of patient with atrial fibrillation.*

## **Part II-III: Evaluation of clinical value of left atrial appendage flow velocity for prediction of short and long-term success of cardioversion in patients with nonvalvular atrial fibrillation**

Potential benefits of restoring and maintaining sinus rhythm include elimination of symptoms caused by atrial fibrillation, improved rate control and hemodynamics, and reduced susceptibility to thromboembolic complications. Clinical and echocardiographic predictors for assessing cardioversion success and long-term sinus rhythm maintenance after successful cardioversion of nonvalvular atrial fibrillation are not accurately defined in the literature. Moreover, the predictive value of the proposed few parameters is far from the optimal. In order to minimize patient risk and to reduce health care costs it would be essential to establish more precise predictors of short and long-term cardioversion outcome. It would be also substantial to stratify the patients to tailor their treatment. Conflicting data are available in the medical literature regarding the role of the LAA flow velocities - measured by transesophageal echocardiography in atrial fibrillation - for prediction of cardioversion success and long-term preservation of sinus rhythm after successful conversion. Furthermore, the conclusions of these available studies are weakened by the small sample size, heterogeneous patient population and the retrospective study design. In view of the above mentioned conflicting data the aims of our studies were:

*1., to clarify the real prognostic value of left atrial appendage velocities for prediction of cardioversion success in patient with nonvalvular atrial fibrillation.*

*2., to determine the real long-term prognostic role of left atrial appendage velocities - measured in atrial fibrillation - for prediction of 1-year maintenance of sinus rhythm in patients with successful cardioversion.*

## **Part I.**

### **EVALUATION OF CLINICAL AND ECHOCARDIOGRAPHIC CORRELATES OF LEFT ATRIAL APPENDAGE FLOW VELOCITY**

#### **Study group**

Two hundred and seventy seven patients with atrial fibrillation were enrolled in the study. Indication of transesophageal echocardiography (TEE) was exclusion of intracardiac thrombi before cardioversion in 189 patients (68%) or searching for cardiac source of systemic embolism in 88 patients (32%). All patients had a continuous atrial fibrillation lasting longer than 48 hours.

#### **Echocardiographic studies**

All transthoracic and transesophageal echocardiographic studies were performed in atrial fibrillation with commercially available ultrasonographic systems. Standard transthoracic echocardiographic measurements were taken by parasternal long-axis view from according to the recommendations of the American Society of Echocardiography. Following the transthoracic echocardiography and after a 6 hour fasting period all patients underwent transesophageal echocardiographic examination. Videotape and/or digitally stored images were subsequently analyzed off-line for the grading of LAA spontaneous echo contrast (SEC) and mitral valve regurgitation by two independent observers, unaware of the patients' history. Left atrial appendage velocity profiles were obtained by pulsed-wave Doppler interrogation 1 cm within the orifice of the left atrial appendage. The LAA peak emptying velocities were averaged with each RR interval over a minimum of 5 consecutive cardiac cycles.

#### **Results**

##### **Relationship between clinical parameters and left atrial appendage flow velocity**

On the basis of presence or absence of diabetes, hypertension, previous myocardial infarction and gender there were no differences in left atrial flow velocities. Left atrial appendage peak contraction

velocity was lower in patients who had a history of mitral valve stenosis or dilated cardiomyopathy compared to those who did not have these features. Appendage velocities were markedly reduced in both group of patients ( $17.4 \pm 10.7$  and  $20.3$  cm/sec, respectively). Duration of atrial fibrillation was correlated inversely with the LAA emptying velocity ( $r = -0.43$ ,  $p < 0.001$ ). Age was not significantly related to the appendage flow velocities ( $r = 0.003$ ,  $p = 0.96$ ).

### **Relationship between echo parameters and left atrial appendage flow velocity**

Left atrial appendage contraction velocities were significantly lower in patient demonstrating thrombus in the appendage during TEE than those without this feature ( $14.6 \pm 10.2$  vs  $32.2 \pm 18.7$  cm/sec,  $p < 0.001$ ). The mean peak atrial appendage emptying velocity was  $< 40$  cm/sec in all subjects with appendage thrombus and 75% of these patients had a mean velocity value  $< 20$  cm/sec. The prevalence of LAA thrombus was higher in patients demonstrating low mean anterograde appendage velocity profile ( $< 20$  cm/sec) when compared to those with higher velocity values than  $20$  cm/sec ( $16/94 = 6.4\%$  vs  $5/183 = 2.7\%$ ;  $p < 0.001$ ). Left atrial appendage velocities were significantly lower in patients with intra-appendage SEC formation than those without this echocardiographic feature ( $22.6 \pm 13.1$  vs  $45.8 \pm 18.3$  cm/sec;  $p < 0.001$ ). Increasing grades of LAA SEC and mitral valve regurgitation were associated with decreasing peak LAA velocities. Left atrial appendage velocities were inversely correlated with the left atrial dimension ( $r = -0.326$ ,  $p < 0.001$ ) and left ventricular end-diastolic diameter ( $r = -0.148$ ,  $p < 0.05$ ). Positive correlation was found between left ventricular ejection fraction and the LAA emptying velocities ( $r = 0.328$ ,  $p < 0.001$ ). Left ventricular mass was not related to the appendage flow velocities ( $r = -0.09$ ,  $p = 0.124$ ).

### **Independent correlates of left atrial appendage flow velocity in atrial fibrillation**

In multivariate regression analysis the presence of LAA SEC during TEE showed the strongest association with LAA velocities [regression coefficient ( $\beta$ ) =  $-0.491$ ,  $p < 0.001$ ]. History of idiopathic dilated cardiomyopathy ( $\beta = -0.201$ ,  $p < 0.001$ ), LAA thrombus ( $\beta = -0.151$ ,  $p < 0.01$ ) and duration of atrial fibrillation ( $\beta = -0.118$ ,  $p < 0.05$ ) were also independently related to LAA flow velocities in multivariate regression analysis

### **Discussion**

This study defines the significant correlates of the LAA anterograde velocity in atrial fibrillation. Moreover, our study constitutes the first multivariate analysis that incorporates several clinical and echocardiographic parameters for assessing independent correlates of LAA flow velocities in a large

cohort of patients with atrial fibrillation. In this analysis LAA SEC, idiopathic dilated cardiomyopathy, presence of LAA thrombus and duration of atrial fibrillation composed the best predictive model for LAA emptying flow velocity.

### **Association between left atrial appendage flow velocity, spontaneous echo contrast and thrombus formation**

The phenomenon of SEC has been attributed to increased ultrasonic backscatter from aggregation of cellular components of blood in conditions of blood stasis. Previous experimental studies have reported qualitative increase in blood echogenicity with the onset of blood stasis. Association of SEC with low flow states - such as mitral valve stenosis - known to predispose to intracardiac thrombus formation. Impairment of the contractile function of the appendage - as mirrored in its reduced pulsed Doppler flow velocity - also may result in blood stasis and predispose to thrombus development in the appendage of patients with atrial fibrillation. In a previous study of Fatkin et al. demonstrated a close relationship between the emptying flow velocity of the appendage, its SEC and thrombus formation. In the present study, the severity of SEC and thrombus formation within the left appendage showed an association with the left atrial anterograde flow velocity that was independent from other clinical and echocardiographic variables. The presence of LAA thrombus was almost uniformly accompanied by notable dysfunction of the appendage, manifested in its low-to-absent Doppler flow velocity profile. Taken together, these data suggest that low LAA flow pattern - similarly to the SEC - is a valuable marker of intraauricular thrombus formation. However, validation of the grade of SEC is transducer and operator-dependent. In contrast, the measurement of appendage flow velocity is more objective and highly reproducible. Our observation is concordant with those of previous studies demonstrating an association between reduced flow velocities of the appendage and future systemic embolic events.

### **Relationship between other variables and left atrial appendage flow velocity**

Our study demonstrates for the first time that increasing grades of mitral regurgitation is - albeit weakly - associated with decreasing LAA velocities in atrial fibrillation. Chronic volume and pressure overload of the atrium and appendage due to hemodynamically significant mitral valve regurgitation may impair the mechanical function of the appendage. Despite a possible deleterious effect of mitral valve insufficiency on LAA contractile function, mitral regurgitation has an overall protective effect against thrombembolism by prevention of blood stasis.

Controversial data are available in the medical literature considering the association between LAA flow velocity and left atrial and ventricular size and left ventricular systolic function. The relatively large sample allowed us to demonstrate that the LAA emptying flow velocity is - albeit weakly - related to these echocardiographic parameters. It is known that all of these variables are

related to the left atrial pressure. Moreover, the loading conditions of the left atrium may affect the contraction of the appendage. Based on these data - although left atrial pressures was not measured in our study - we may hypothesise that the relationship between these echocardiographic variables and the LAA contraction flow velocities may be partially determined by the left atrial pressure in atrial fibrillation.

Our results support previous studies showing low mean appendage contraction velocities in patients with mitral valve stenosis, idiopathic dilated cardiomyopathy and reduced left ventricular systolic function. This reduced LAA contractile function may explain why these aforementioned clinical conditions are predictors of LAA thrombus formation and systemic thromboembolism in atrial fibrillation .

Similarly, as reported in a previous study the duration of atrial fibrillation in our study showed an inverse correlation with LAA emptying flow velocity. However, time course of decline and determinants of progression of left atrial flow velocities in atrial fibrillation have not been yet reported in the literature.

### **Clinical implications**

Because of the complex structural features of the LAA, the diagnosis of its thrombus formation by TEE is prone to both overdiagnosis (false interpretation of prominent pectinate muscles) and underdiagnosis (hidden thrombus in an additional lobe). In our study no patient with high appendage emptying velocity profile ( $> 40$  cm/sec) had intra-appendage thrombus on TEE. On the contrary, majority of patients with clot formation in the appendage demonstrated severely impaired auricular contractility assessed by pulsed Doppler echocardiography. Hence, from practical echocardiographic standpoint, assessment of the velocity profile of the appendage may assist in the accurate diagnosis of the intra-appendage masses and "pseudomasses". Significant impairment of LAA function supports a diagnosis of appendage thrombus, whereas normal function suggests an alternative diagnosis.

## **Part II.**

### **PREDICTION OF CARADIOVERSION SUCCESS BY LEFT ATRIAL APPENDAGE FLOW VELOCITIES IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION**

#### **Study group and methods**

Four hundred and eight patients with nonvalvular atrial fibrillation lasting longer than 48 hours and less than 1 year were recruited consecutively from four international cardiology department including the Cardiology Center of Medical Faculty of University of Szeged, Hungary. Indication for transesophageal echocardiography in all cases was to rule out intracardiac thrombi before the cardioversion attempt. All echocardiographic data were recorded in atrial fibrillation. Patients with LAA thrombus found by transesophageal echocardiography were excluded from the study. Echocardiographic studies and mode of data collection was same as described in part I. All patients underwent either pharmacological (n=84) or electric cardioversion (n=324) attempt, decided on clinical basis by the physician in charge. Successful cardioversion was defined as a stable sinus rhythm lasting for at least 1 day after successful conversion.

### **Outcome of cardioversion**

The cardioversion was successful in 328 (80%) and unsuccessful in 80 (20%) patients. Electric cardioversion effectively restored the sinus rhythm in 266 of 324 patients (82%) while during pharmacological cardioversion attempt 62 of 84 patients (74%) converted to sinus rhythm.

### **Clinical parameters and cardioversion success**

There were no differences in age, sex and underlying diseases between patients with and without successful conversion. Successfully converted patients had shorter atrial fibrillation duration compared to those who failed cardioversion attempt. An atrial fibrillation duration cutoff value of 2 weeks provided the best separation between patients with and without successful restoration of sinus rhythm.

### **Echocardiographic parameters and cardioversion success**

On the basis of transthoracic echocardiographic parameters, successfully cardioverted patients had lower left ventricular end-diastolic diameter and left atrial parasternal diameter. Left ventricular ejection fraction tended to be higher in patient with cardioversion success, whereas left ventricular wall thickness were not related to the outcome of cardioversion. Cutoff values of a left atrial diameter < 47 mm, a left ventricular end-diastolic diameter < 58 mm and a left ventricular ejection fraction > 56% provided the best separation between patients with and without cardioversion success. Transesophageal echo parameters also could separate the 2 groups on the basis of the mean LAA peak anterograde flow (higher in patients with cardioversion success) and the presence of left atrial SEC (less frequent in patients with cardioversion success), whereas no difference could be observed when the degree of mitral valve regurgitation was considered. The mean LAA peak anterograde flow



velocity cutoff of 31 cm/sec provided the best separation between patients with and without cardioversion success.

### **Prediction of cardioversion success by integrated clinical, transthoracic and transesophageal echocardiographic variables**

Univariate logistic regression analysis revealed that the mean LAA peak anterograde flow velocity > 31 cm/sec was the most powerful predictor of successful cardioversion followed by atrial fibrillation duration < 2 weeks, left atrial diameter < 47 mm, left ventricular ejection fraction > 56%, absence of left atrial SEC during transesophageal echocardiography and the left ventricular end-diastolic diameter < 58 mm. By multivariate logistic regression analysis, 3 parameters proved to be independent predictors of cardioversion success: atrial fibrillation duration < 2 weeks (OR = 4.9, CI 95%=1.9-12.7; chi-square: 10.6, p=0.0011) followed by the mean LAA peak anterograde velocity > 31 cm/sec (OR = 2.8, CI 95%=1.5-5.4; chi-square: 10.4, p=0.0013) and left atrial parasternal diameter < 47 mm (OR =2.0, CI 95%=1.2-3.4; chi-square: 6.8, p=0.009).

### **Discussion**

Our study demonstrated that measurement of the LAA emptying velocity profile by TEE before cardioversion in patients with nonvalvular atrial fibrillation provides valuable additional information for prediction of cardioversion success. Previous studies have already demonstrated that the LAA velocity is related to the left atrial size and the duration of atrial fibrillation, all of which are predictors of cardioversion success. Furthermore, recent reports have suggested that the success of cardioversion (drug induced or electrical) in patients with nonvalvular atrial fibrillation may be predicted by assessing LAA function before cardioversion, although this was not a uniform observation. Mitusch et al. reported transesophageal echocardiography data from 93 patients with nonvalvular atrial fibrillation. They found a significant difference in LAA peak emptying velocity between patients with and without successful cardioversion. Although our results are consistent with those of Mitusch et al., one should consider that the majority of their patients had atrial fibrillation duration longer than 1 year and, moreover, in half of those who converted to sinus rhythm the LAA velocity was measured only after restoration of the sinus rhythm, creating a methodologically heterogeneous study group. Our data are also in keeping with the results obtained by Tabata et al. assessing the LAA flow velocities by transesophageal echocardiography before cardioversion in patients with nonvalvular atrial fibrillation. However, they studied only a small group of patients (n=26) which weakened their conclusion. On the contrary, in a study of 82 patients with atrial fibrillation < 6 months duration, Perez et al. found no relationship between LAA flow velocities and outcome of the cardioversion. However in this study the small number of patients with failure of cardioversion (n=7) led to a high level of beta-error: i.e., high

probability of rejecting as false an existing difference between groups. In another study of 62 patients with nonvalvular atrial fibrillation, Verhorst et al. were unable to show difference in LAA velocity values between successful and unsuccessful cardioversion groups, but the LAA flow velocities tended to be higher in patients who converted to sinus rhythm. Similarly, as reported in previous studies, we also found that the duration of atrial fibrillation is a predictor of successful conversion. However, in a substantial number of patients with atrial fibrillation of nonvalvular etiology, the duration of the atrial fibrillation is either unknown or can not be determined accurately which weakens the clinical value of this parameter. In broad terms, our results are therefore consistent with previous reports. However, our study is also unique for several reasons: 1. the prospective, multicenter design; 2, the large number of patients enrolled (408, whereas previous studies enrolled 25 to 82 patients); 3, the strict selection criteria. The relatively large sample size allowed us to demonstrate that the mean LAA peak emptying velocity has independent and additive prognostic value over other clinical and echocardiographic predictors.

### **Part III.**

## **PREDICTION OF LONG-TERM SINUS RHYTHM MAINTENANCE BY LEFT ATRIAL APPENDAGE FLOW VELOCITIES IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION**

### **Study group and methods**

We prospectively studied 193 patients with successful cardioversion (electrical, n=147 or pharmacological, n=46) of nonvalvular atrial fibrillation lasting longer than 48 hours and less than 1 year at four international cardiology centers, including the 2<sup>nd</sup> Department of Medicine, Faculty of Medicine, University of Szeged, Hungary. Indication for transesophageal echocardiography in all cases was to rule out intracardiac thrombi before the cardioversion attempt and all echocardiographic data were recorded in atrial fibrillation. The mode of collection of clinical data and exclusion criteria

was identical as described in the previous section. Of the 193 patients studied, 80 (41%) had a history of previous episode of atrial fibrillation. All enrolled patients underwent a 1-year follow-up program for assessment of sinus rhythm maintenance. Patients were followed-up regularly every 3 months up to 1 year. Serial electrocardiograms were recorded at each visit to document the maintenance of sinus rhythm or recurrence of atrial fibrillation. In addition, referring physicians and patients were told to confirm suspected recurrences of atrial fibrillation by a 12-lead electrocardiogram. Starting of preventive antiarrhythmic drug treatment during the follow-up was decided by the referring physician of the patient on the basis of integrated clinical assessment, which included access to echocardiographic data. According to this, 72 of the 193 (37%) successfully converted patient were treated by preventive antiarrhythmic drugs during follow-up period. Drug therapy for arrhythmia prevention was flecainide (n=9), amiodarone (n=19), sotalol (n=2) and propafenone (n=42).

## **RESULTS**

### **Prediction of long-term sinus rhythm maintenance by left atrial appendage flow velocities**

#### **Follow-up**

During the follow-up period 4 patients died (2 for non-cardiac and 2 for cardiac cause) and 3 patients were lost for other reasons. Finally the one-year follow-up was completed in 186 patients (94 %) with successful cardioversion of nonvalvular atrial fibrillation. At the end of one year period, 91 (49%) patients remained in sinus rhythm, and the atrial fibrillation recurred in 95 (51%) patients.

#### **Clinical parameters and maintenance of sinus rhythm**

There were no differences in age, sex and underlying diseases between patients with and without sinus rhythm maintenance. Patients who continued to have sinus rhythm for 1 year had shorter atrial fibrillation duration before cardioversion compared to those with atrial fibrillation relapse. On the basis of ROC analysis, an atrial fibrillation duration of 1 week provided the best separation between patients with and without sinus rhythm maintenance (shorter in patients with sinus rhythm preservation). Antiarrhythmic drug use was more frequent in patients who continued to have sinus rhythm at 1-year follow-up compared to those with atrial fibrillation relapse.

### **Echocardiographic variables and preservation of sinus rhythm**

On the basis of TTE parameters, patients without atrial fibrillation relapse had lower left atrial parasternal diameter. Left ventricular ejection fraction tended to be higher in those patient who continued to have the sinus rhythm for 1 year, whereas left ventricular wall thickness and end-diastolic diameter were not related to the long-term maintenance of sinus rhythm. On the basis of the ROC analysis, cut-off values of a left atrial diameter < 44 mm and a left ventricular ejection fraction > 46% provided the best separation between patients with and without 1 year sinus rhythm maintenance. According these cut-off points, 85 (46%) patients had left atrial diameter < 44 mm and 142 (76%) patients had ejection fraction > 46 %. Transesophageal parameters could separate the 2 groups on the basis of the mean LAA peak anterograde flow (higher in patients with sinus rhythm maintenance) and presence of left atrial SEC (less frequent in patient with sinus rhythm maintenance) whereas no difference could be observed when the degree of mitral valve regurgitation was considered. According to the ROC analysis derived mean LAA anterograde flow velocity cut-off of 40 cm/sec, 70 patients (38 %) had higher mean LAA peak anterograde velocity than 40 cm/sec.

### **Prediction of long-term maintenance of sinus rhythm by integrated clinical and echocardiographic variables**

Univariate logistic regression analysis revealed that mean LAA peak anterograde flow velocity >40 cm/sec was the strongest predictor of 1-year sinus rhythm maintenance followed by atrial fibrillation duration <1 week before cardioversion, left atrial diameter <44 mm, left ventricular ejection fraction >46%, absence of left atrial SEC on TEE, and use of preventive antiarrhythmic drug during follow-up. By multivariate logistic regression analysis only 2 parameters proved to be independent predictors of 1-year preservation of sinus rhythm: the mean LAA peak anterograde velocity > 40 cm/sec (OR=5.2, CI 95% =2.7-10.1; chi-square: 23.9, p<0.0001) and the use of preventive antiarrhythmic drug during follow-up (OR=2.0, CI 95%=1.0-3.8; chi-square: 4.2, p<0.05).

## **DISCUSSION**

Our study demonstrated that measurement of the LAA emptying velocity profile by TEE before cardioversion in patients with nonvalvular atrial fibrillation provides important information for prediction of long-term sinus rhythm maintenance.

### **Comparison with previous studies**

Previous studies have already demonstrated that the LAA velocity is related to the left atrial size and the duration of atrial fibrillation, all of which are predictors of long-term sinus rhythm maintenance. However, conflicting and scarce data exist on the usefulness of LAA flow to predict long-term preservation of sinus rhythm. The discrepancy of the data can be easily reconciled by taking into account the limited sample size and variable inclusion criteria of the previous reports. Our study has distinct features: 1, the prospective, multicenter design, whereas all previous studies came from single center experience; 2, the large number of patients enrolled (186, whereas previous studies enrolled 38 to 75 patients); 3, the strict selection criteria, which allowed to exclude patients with organic valvular heart disease. The relatively large sample size allowed us to demonstrate that mean LAA peak emptying velocity has independent and additive prognostic value over other echocardiographic and clinical predictors, such as left atrial diameter, left atrial SEC, ejection fraction and duration of atrial fibrillation whose prognostic value is totally eclipsed by LAA flow.

### **The possible link between left atrial appendage velocity and prediction of short and long-term success of cardioversion**

In chronic nonvalvular atrial fibrillation a time related structural and histological remodeling develops both in the LAA and in the left atrium (chamber dilatation, loss of myofibrils, fragmentation of sarcoplasmic reticulum and marked collagen formation). These unfavorable degenerative changes may cause inhomogeneity of atrial repolarization, non-uniform anisotropy or slowing of conduction and are important components in the pathogenesis of atrial fibrillation. Loss of contractile elements of LAA may result in its reduced mechanical function which could be expressed in low LAA flow velocities profile. However, according to our knowledge, there is no published data in the literature studying the direct link between LAA flow and histopathological changes in the appendage in patients with nonvalvular atrial fibrillation.

## **CONCLUSIONS**

Our studies showed that the assessment of contractile function of the LAA by pulsed Doppler echocardiography during TEE provides important clinical information in atrial fibrillation.

We defined several correlates of the LAA anterograde flow velocity in a large cohort of patients with atrial fibrillation. Spontaneous echo contrast and thrombus formation within the LAA, history of dilated cardiomyopathy and duration of atrial fibrillation showed an association with the left atrial anterograde flow velocity that was independent from other clinical and echocardiographic variables.

The presence of LAA thrombus was almost uniformly accompanied by extreme dysfunction of the appendage, manifested in its low-to-absent pulsed Doppler velocity profile. According to our results and those of previous investigations, low LAA velocity pattern can be considered as a valuable marker of LAA clot formation.

We reported for the first time that increasing grades of mitral regurgitation is - albeit weakly - associated with decreasing LAA flow velocities in atrial fibrillation.

Left atrial appendage flow velocity pattern determined by TEE before cardioversion has an independent value in predicting cardioversion success in patients with nonvalvular atrial fibrillation less than one year duration. This value is incremental over important predictors derived from clinical history and transthoracic echo, such as duration of atrial fibrillation and left atrial dimension.

High LAA flow measured by TEE before cardioversion identifies well those patients who will remain in sinus rhythm for 1 year. In patients with nonvalvular atrial fibrillation, the same TEE derived parameter often used to assess the embolic risk and acute success of cardioversion (i.e. LAA flow), can be of use in predicting 1-year outcome of successful cardioversion.

**LIST OF FULL PAPERS RELATED TO THE THESIS**

- I.** **Pálinkás A**, Antonielli E, Picano E, Pizzuti A, Varga A, Nyúzó B, Alegret JM, Bonzano A, Tanga M, Coppolino A, Forster T, Baralis G, Delnevo F, Csanády M. Clinical value of left atrial appendage flow velocity for predicting of cardioversion success in patients with nonvalvular atrial fibrillation.  
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