2nd Department of Medicine and Cardiology Center,
Faculty of Medicine, University of Szeged

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

Attila Pálinkás, MD

PhD thesis

Szeged

2002

CONTENTS

LIST OF PUBLICATIONS RELATED TO THE THESIS

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. Eur Heart J 2001; 22: 2201-2208 ***(IF:5.153)***

II. Antonielli E, Pizzuti A, **Pálinkás A**, Tanga M, Gruber N, Michelassi C, Varga A, Bonzano A, Gandolfo N, Halmai L, Bassignana A, Imran MB, Delnevo F, Csanády M, Picano E. Clinical value of left atrial appendage flow for prediction of long-term sinus rhythm maintenance in patients with nonvalvular atrial fibrillation.
J Am Coll Cardiol 2002; 39: 1143-49 ***(IF:6.374)***

III. **Pálinkás A,** Varga A, Nyúzó B, Gruber N, Forster T, Nemes A, Horváth T, Fogas J, Boda K, Sepp R, Hőgye M, Vass A, Csanády M. A bal pitvari fülcse áramlás szerepe a kardioverzió rövid és hosszú távú sikerességének előrejelzésében nem valvuláris eredetű pitvarfibrilláció fennállásakor. Orv Hetil 2002; 143: 2035-2041

IV. **Pálinkás A,** Jambrik Z, Varga A, Forster T, Csanády M. A bal pitvari fülcse echocardiographiás vizsgálatának klinikai jelentősége.
Orv Hetil, 2003; 104: 23-31

V. **Pálinkás A,** Varga A, Forster T, Nyúzó B, Eiler J, Nemes A, Gruber N, Nagy V, Halmai L, Kovács Zs, Csanády M. A bal pitvari fülcse kontraktilis funkció kapcsolata klinikai és echocardiographiás paraméterekkel pitvarfibrilláló betegeknél.
Cardiologia Hungarica 2003 (accepted for publication)

LIST OF ABSTRACTS RELATED TO THE THESIS

1. **Pálinkás A,** Nyúzó B, Marosi Gy, Papp I, Nemes A, Sepp R, Forster T, Csanády M. Relationship between left atrial appendage flow and the outcome of cardioversion Eur Heart J (Suppl.)1999; 20: 1596 (p 290)
2. **Pálinkás A,** Nyúzó B, Pratali L, Gruber N, Pasanisi E, Amyot R, Varga A, Boda K, Nemes A, Forster T, Csanády M, Picano E. Relationship between left atrial appendage flow and the outcome of cardioversion. Circulation (Suppl.) 2000; 102: 3202 (page 662)
3. **Pálinkás A,** Nyúzó B, Gruber N., Varga A., Sicari R., Alegret J.M., Borthaiser A., Vass A., Picano E., Csanády M. Prognostic value of left atrial appendage flow for assessment of long-term maintenance of sinus rhythm in patients with nonvalvular atrial fibrillation. Eur Heart J (Suppl.) 2001; 22: 2927 (page 544)
4. **Pálinkás A,** Antonielli E , Pizzuti A, Tanga M, Delnevo F, Bonzano S, Coppolino A, Nyúzó B, Varga A, Csanády M, Baralis G, Alegret JM, Picano E. Clinical value of left atrial appendage flow velocity for predicting of cardioversion success in patients with nonvalvular atrial fibrillation Circulation (Suppl) 2001; 104: 3464 (page 733)
5. Varga A, **Pálinkás A,** Antonielli E , Pizzuti A, Bonzano A, Forster T, Csanády M, Picano E. Clinical value of left atrial appendage flow velocity for prediction of success of electric cardioversion in patients with non-valvular atrial fibrillation of unknown duration J Mol Cell Cardiol. (Suppl) 2002; 34: A67
6. Antonielli E, Pizzuti A, **Pálinkás A**, Avogadri E, Bonzano A, Varga A, Dogliani S, Giuseppe Riva G, Stasi M, Antonio Tomasello A, Gaita F, Doronzo B. Left atrial appendage flow velocity predicts success of cardioversion and sinus rhythm maintenance in patients with atrial fibrillation of unknown duration Circulation (Suppl) 2002; 106: 3484

LIST OF ABBREVIATIONS

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

SEC = spontaneous echo contrast

AF= atrial fibrillation

ROC = receiver-operating characteristic

OR = odds ratio

CI = confidence interval

LA = left atrium, left atrial

LAA= left atrial appendage

LV= left ventricle

LVEF= left ventricular ejection fraction

EDD = end diastolic diameter

IVS = interventricular septum

LVPW= left ventricular posterior wall

1. INTRODUCTION

Atrial fibrillation is one of the most common rhythm abnormalities of the heart. Development of atrial fibrillation is concentrated in individuals who have overt congestive heart failure, sinus node dysfunction, hypertensive, valvular, coronary artery and congenital heart disease (1, 2, 3, 4). Other important risk factors are diabetes and electrocardiographically demonstrated left ventricular hypertrophy (5). A substantial proportion of patients however have no identifiable structural heart disease. Noncardiac causes of atrial fibrillation that have been reported including thyreotoxicosis, alcohol abuse, electrolyte imbalance, severe infections and pulmonary pathology.

Atrial fibrillation has been shown to be associated with increased risk for cardiovascular morbidity or mortality (6, 7). As we entered the 21st 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 (8).

1.1 Clinical consequences of atrial fibrillation

The clinical manifestations of atrial fibrillation are highly variable, ranging from complete absence of symptoms to hemodynamic collapse. Symptoms are as a result of atrial fibrillation are determined by multiple factors, the most important of which is the underlying cardiac status. Rapid, asynchronous atrial contraction results in a loss of atrial booster pump function, which may result in a decline in cardiac output. The irregular and often fast heart rate interferes with the filling of the ventricles and is also component of the hemodynamic impairment. Some of the diastolic intervals are too short to fill the ventricle adequately, and others may overstretch the myocardium and make the next stroke volume large. The total circulating blood flow is thus usually decreased already at rest, and the increase of cardiac output during exercise is very often compromised compared to what is seen in sinus rhythm

(9). A marked symptomatic decrease in cardiac output can occur in patients with preexisting abnormality of the left ventricular diastolic filling as it has been demonstrated in hypertensives, mitral valve stenosis, hypertrophic, dilated or restrictive cardiomyopathy. Other non specific symptoms associated with the aforementioned mechanisms include palpitations, angina, dyspnea, confusion and weakness. The variability of the filling of the arterial tree interferes to some extent with the fine tuning of the arterial pressure and may thus influence the circulation of the brain, causing typical lightheadedness.

One of the most important sequelae of atrial fibrillation is its association with thrombembolic disease and stroke (10). A four- to six-fold increase (15-fold with a history of rheumatic heart disease) makes atrial fibrillation one of the most potent risk factor for embolic stroke (11, 12). 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 (13, 14). In the past, the left atrial appendage 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.

1.2 Morphology and function of the left atrial appendage: anatomy, physiology and pathology data

1.2.1. Anatomy and physiology of the left atrial appendage

The left atrial appendage is the remnant of the original embryonic left atrium. It is a tubular, wavy, hooked muscular extension of the left atrium arising near the left pulmonary veins and has a narrow junction with the venous component of the atrium. This structure arises anterolaterally and lies in the left atrioventricular sulcus atop the proximal portion of the left circumflex artery (Fig. 1). Left atrial appendage is trabeculated with muscle bars largely running parallel to each other giving a comb-like appearance (hence termed pectinate muscles) (Fig. 2). Detailed anatomy and morphology of normal human left atrial appendage were assessed in previous autopsy studies. The length and diameter of the left appendage varied considerably in these studies (length: 1.5-4 cm, diameter 0.5-2 cm). The left atrial

appendage was bilobed in 54% and multilobed (≥ 2 lobes) in 80% of normal human hearts (15,16). In 70% of the cases, the principal axis was markedly bent or spiral.

Previous studies reported that left atrial appendage is more distendable than the left atrium proper (17, 18). Because of its increased distensibility, the left atrial appendage may augment hemodynamic function by modulating left atrial pressure volume relationship in states of increased left atrial pressure and volume overload (18). The atria and appendage are supplied by a variety of nerves and receptors. Evidences support that activation of stretch sensitive receptors and nerves of the left atrial appendage mediate reflexes that result in an increase of heart rate and urine excretion (19). Cardiocytes of the left atrial appendage contains the greatest density of atrial natriuretic factor granules found in the left atrium and this may result in an increased capacity for secretion of this peptide during an elevation of the atrial pressure (20). These complex properties render the appendage ideal to act as a reservoir in conditions of volume overload, and to effect the adaptive responses for the reduction of circulating blood flow.

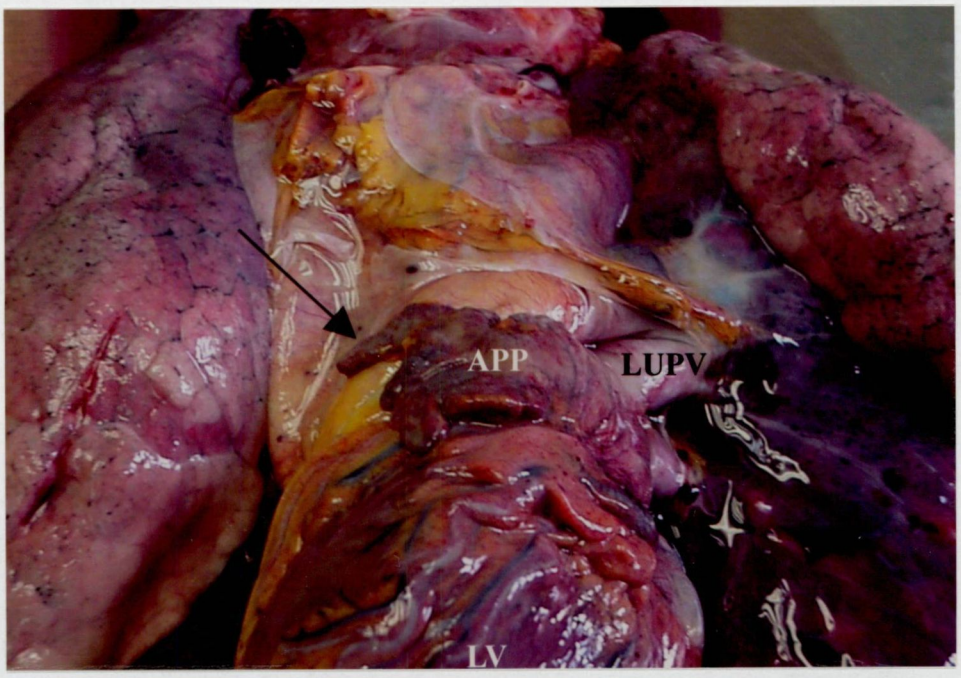

Figure 1. Gross picture of the antero-lateral aspect of the heart. The left atrial appendage (APP) is shown to its anatomical relationship to the left ventricle (LV) and left upper pulmonary vein (LUPV). The black arrow shows an additional lobe of the left appendage.

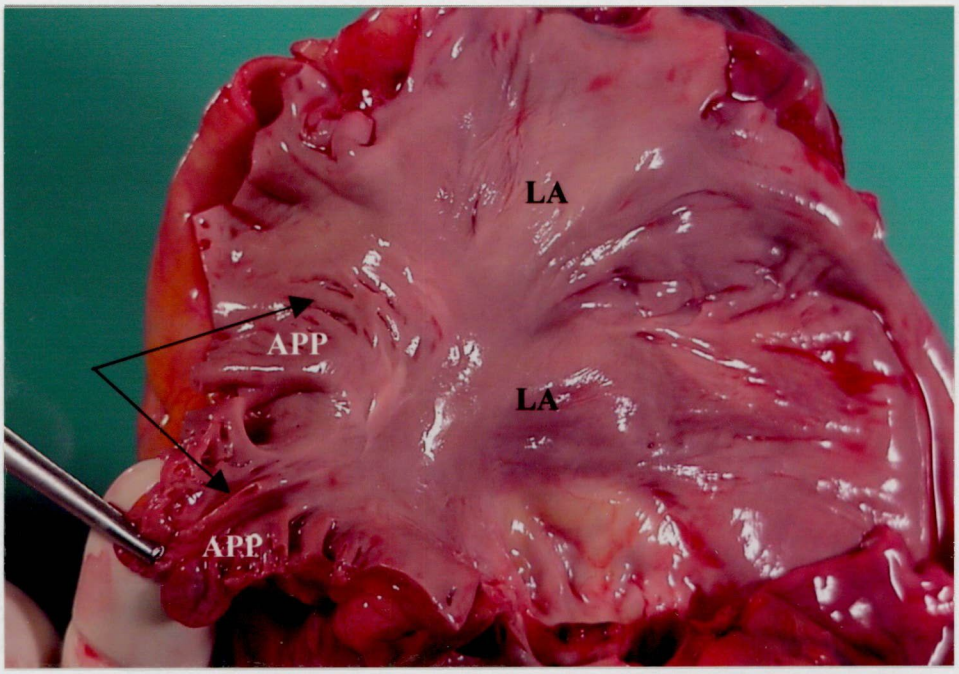

Figure 2. Section of pathology specimen of the trabeculated left atrial appendage (APP) displaying thick pectinate muscles (black arrows) in contrast to the smooth walled left atrial (LA) body.

1.2.2. Structural alterations of the left atrial appendage in atrial fibrillation: macroscopic data

Necropsy data suggest that left atrial appendage frequently undergoes significant remodelling during chronic atrial fibrillation (21). Left atrial appendage volumes and luminal surface areas are significantly larger in patients with atrial fibrillation compared to those in sinus rhythm (16, 21). A significant reduction in the relative volume of the pectinate muscles and marked endomyocardial thickening were also observed in patients with chronic atrial fibrillation. The latter appeared to embed the pectinate muscles, thus, producing a smooth luminal surface compared to the highly trabeculated left atrial appendage surface in those without atrial fibrillation.

1.3. Morphology and function of the left atrial appendage: echocardiographic data

The left atrial appendage remained a 'blind spot' until the advent of transesophageal echocardiography. The use of this echocardiographic method has made clear imaging of the

left atrial appendage possible, so that its size, shape, flow patterns and contents can be assessed in health and disease. Although the left atrial appendage may, at times, be imaged by transthoracic echocardiography, at present the transesophageal approach is mandatory for consistent and precise delineation of the left atrial appendage, particularly in the adult population (22, 23, 24). Complete structural and functional assessment of the left atrial appendage should consist of two-dimensional imaging of left atrial appendage size, morphology and contraction. These data are integrated with those from the complete echocardiographic examination, including assessment of left atrial size, left ventricular systolic and diastolic function and associated valvular disease.

1.3.1. Transesophageal two-dimensional imaging of left atrial appendage

Left atrial appendage area and ejection fraction have been assessed and reported in numerous studies (25, 26, 27). However, measurements of left atrial appendage cross-sectional areas are inherently prone to substantial interobserver variability, during both data acquisition and off-line analysis, primarily because of the complex three-dimensional anatomy of the left atrial appendage, which limits accurate definitions of standard tomographic imaging planes of this structure (23, 24, 28). Attempts to quantitate left atrial appendage size and function by planimetric methods are time-consuming and therefore these echocardiographic parameters are not widely used in the clinical practice. Two-dimensional imaging is used to determine the presence of left atrial appendage spontaneous echocardiographic contrast (SEC), semiquantitative grading of SEC, and defining the presence, size and mobility of left atrial appendage thrombi. Left atrial appendage has to be scanned in multiplane echocardiographic planes, and the number of lobes determined. A detailed examination of all lobes is recommended for exclusion of thrombi. Owing to the complex three-dimensional structural features of the left atrial appendage, the diagnosis of left atrial appendage thrombi by TEE is prone to misdiagnosis, both overdiagnosis (false interpretation of prominent pectinate muscles) and underdiagnosis (occult thrombi in multilobed appendages) (29, 30). Nothwithstanding these pitfalls, in comparison with intra-operative observations, the sensitivity and specificity of transesophageal echocardiography were 100 % and 99%, respectively, with a negative predictive value of 100 % and a positive predictive value of 86 % for the diagnosis of left atrial appendage thrombi (31).

1.3.2. Transesophageal pulsed Doppler evaluation of left atrial appendage

In contrast to the planimetric measurements of left atrial appendage areas and ejection fraction, assessment of left atrial appendage function by pulsed Doppler echocardiography, is easily performed, reproducible and highly relevant clinically, therefore are widely used in the clinical practice to evaluate contractile function of the appendage (22, 24). An optimal transesophageal echocardiographic view should be selected for Doppler interrogation of left atrial appendage in which parallel alignment of Doppler cursor with appendage flow can be achieved. Left atrial appendage is sampled at the site of maximal flow velocities (determined by color flow imaging), while avoiding wall motion Doppler artifacts, which are commonly observed in the more distal (narrow) portions of the appendage. In practice, technically adequate tracings of maximal left atrial appendage flow velocities are commonly recorded within the proximal third of the appendage. Distinct flow patterns have been described during different atrial rhythms (26).

1.3.2.1.1. Flow pattern of the left atrial appendage in sinus rhythm

Doppler measured left atrial appendage flow in patients with sinus rhythm was initially described as biphasic, but additional emptying and filling waves resulting in quadriphasic appendage flow pattern have been described in 40-70% of patients (28, 32). *Left atrial appendage contraction* results in a late positive (i.e., toward the TEE transducer) Doppler outflow signal, shortly following the onset of the ECG P wave (Fig. 3). This signal coincides with two-dimensional and color flow imaging of left atrial appendage contraction and outflow and is related temporally to late diastolic mitral flow (mitral A wave) (24). Measurements of contraction velocities, which are easily reproducible, correlate with two-dimensional measurements of left atrial appendage ejection fraction (33). The *left atrial filling wave* is an early systolic, negative (i.e., away from the TEE transducer) Doppler inflow signal, immediately following the contraction of the atrium and appendage (28, 32) (Fig. 3). Contraction and filling waves are usually the two dominant flows on the pulsed Doppler tracing of the left appendage in sinus rhythm. Corresponding mean value for peak left atrial appendage contraction velocity in a group of healthy volunteers in sinus rhythm was 64 ± 19 cm/sec (32). Although not studied systematically in various patient populations, there is generally a gross correlation between left atrial appendage contraction and filling velocities. A

variable number of alternating outflow and inflow signals of diminishing amplitude are commonly recorded following the late diastolic filling wave of the appendage. These *systolic reflection waves* are usually observed in subjects with high left atrial appendage velocities (34) (Fig. 3). Low velocity, *early diastolic left atrial appendage outflow and inflow* signals are detectable in some individuals following early diastolic mitral flow (mitral E wave). Clinical significance of systolic reflection and early diastolic waves of the left appendage have not been yet determined. Numerous studies have uniformly demonstrated the phenomenon of postcardioversion left atrial appendage stunning, i.e. a paradoxical reduction in left atrial appendage velocities, compared with the precardioversion velocity values in atrial fibrillation, despite the reversion to regular sinus rhythm (35, 36, 37).

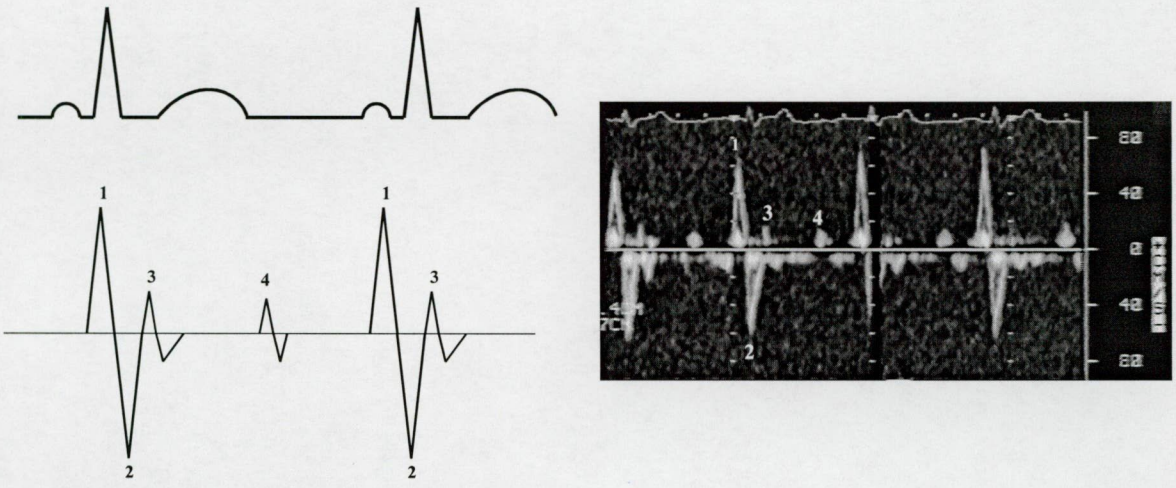

Figure 3. Schematic drawing (left sided panel) and pulsed Doppler tracing (right sided panel) of the left atrial appendage flow in sinus rhythm. 1, telediastolic, contraction (outflow) wave 2, early systolic filling (inflow) wave 3, systolic reflexion wave 4, early diastolic outflow wave.

1.3.2.1.2. Flow pattern of the left atrial appendage in atrial fibrillation

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 left atrial appendage. Repetitive biphasic, sawtooth-appearing flow signals of variable amplitude that consist of ejection and filling components are the most commonly described patterns (25,26,28) (Fig. 4). In addition to flow resulting from active

appendage contraction, a discrete early diastolic outflow signal, similar to that in sinus rhythm, is observed occasionally, although commonly it is difficult to identify this signal clearly and to differentiate it from fibrillatory flow signals (26). Characteristically, flow signals in atrial fibrillation have lower velocities during ventricular systole (left atrial appendage contraction in the presence of a closed mitral valve) than during diastole (38). An average of peak anterograde flow velocities over at least five cardiac cycles are widely used for characterisation of mechanical function of the left atrial appendage in atrial fibrillation (34, 39, 40, 41).

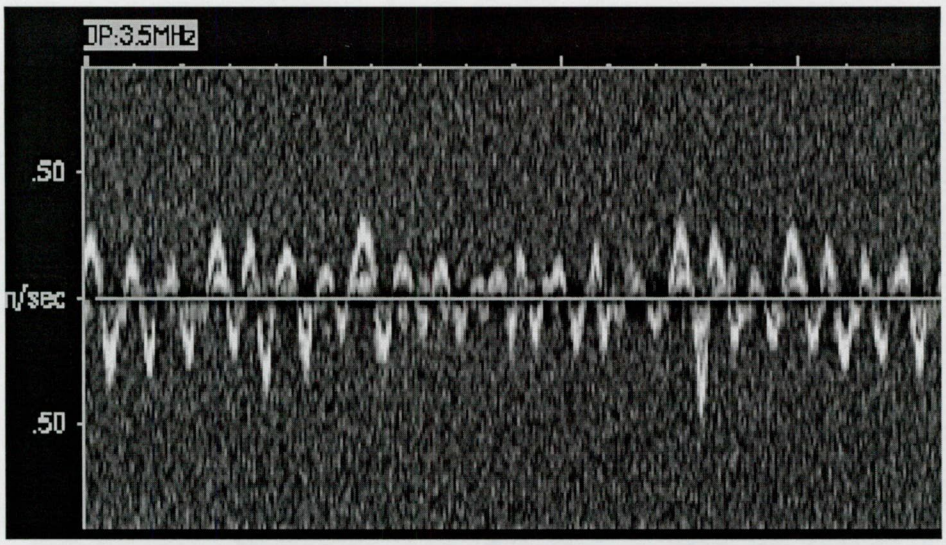

Figure 4. Pulsed Doppler tracing of left atrial appendage flow in atrial fibrillation. Note the rapid, alternating positive and negative sawtooth-appearing flow signals of variable amplitude and regularity.

1.3.3. Structural alterations of the left atrial appendage in atrial fibrillation: transesophageal echocardiographic data

In previous transesophageal echocardiographic studies left atrial appendage areas were larger in atrial fibrillation than in sinus rhythm. Structural changes in the left atrial appendage were most profound in patients with rheumatic mitral valve disease, SEC and thrombus formation (27, 42, 43, 44, 45). In atrial fibrillation left atrial appendage SEC and thrombus were reported in 44 ± 15% and 13 ± 11% of patients (42, 46). The highest incidence of SEC in nonvalvular atrial fibrillation was noted in patients with thrombus formation.

1.3.4. Functional alterations of the left atrial appendage in atrial fibrillation: a short summary of transesophageal echocardiographic data

Generally, flow velocities in the left atrial appendage during atrial fibrillation are lower than those during sinus rhythm (46, 47, 48). However, flow velocities in patients with atrial fibrillation are highly variable, with high velocity flows on one end of the spectrum (velocities similar to, or even exceeding, those observed in sinus rhythm), and minimal to absent flow on the other end (24, 48). This represents the wide continuum of left atrial appendage contractile dysfunction in patients with atrial fibrillation, from relatively preserved contraction to complete paralysis of the appendage. A recent follow-up study suggests that left atrial appendage flow velocities may decrease with time in patients with atrial fibrillation and this change is associated with a new occurrence of left atrial SEC formation (49).

2. THE PRIMARY GOALS OF THE THESIS

2.1. Evaluation of clinical and echocardiographic correlates of left atrial appendage flow in patients with atrial fibrillation

Relationship between various clinical and echocardiographic parameters and left atrial appendage flow velocities in atrial fibrillation has been assessed in previous investigations (39, 43, 46, 48, 50, 51). However controversial results have been reported in the literature regarding the association between certain variables and left atrial emptying velocities (24, 26, 28, 43, 46, 52, 53). The conclusions were frequently weakened by the small sample size or heterogeneous patient population of the available studies (26, 28, 40, 43, 46, 54). Moreover, correlation between left atrial appendage flow and some parameters have never been studied previously in atrial fibrillation (24). 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 left atrial appendage 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.

2.2. - 2.3. 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 (55, 56, 57). Moreover, the predictive value of the proposed few parameters is far from the optimal (53, 58). 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, i.e. the mode of cardioversion, the preventive anti-arrhythmic drug treatment and the recently developed specific anti-arrhythmic device management modes. In recent years transesophageal echocardiography has become an accepted tool to guide management of patients with atrial fibrillation by screening for left atrial appendage thrombi and allowing earlier cardioversion (22, 59). Furthermore, the assessment of thrombembolic risk by measurement of left atrial appendage velocities during transesophageal echocardiography in atrial fibrillation has become widely accepted (24, 50, 60). Conflicting data are available in the medical literature regarding the role of the left atrial appendage flow velocities in atrial fibrillation for prediction of cardioversion success and long-term preservation of sinus rhythm after successful conversion (44, 51, 53, 61, 62). 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 patients with nonvalvular atrial fibrillation lasting < 1 year.

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.

In order to fulfil these goals, we organized two large scale, multicenter, international, prospective studies.

3. STUDY GROUPS AND METHODS

3.1. Evaluation of clinical and echocardiographic correlates of left atrial appendage flow velocities in patients with atrial fibrillation

Study group

Two hundred and seventy seven patients with atrial fibrillation were enrolled from the Albert Szent-Györgyi Medical University, Szeged, Hungary between September 1996 and July 2002. Indication of transesophageal echocardiography was exclusion of intracardiac thrombi before cardioversion in 189 patients (68%) or searching for cardiac source of systemic embolism in 88 patients (32%). Clinical data including the duration of atrial fibrillation were read from the patients' record and obtained by the interview with the patient, his attending physician, and home practitioner. Patients with pulmonary embolism, resting hemodynamic instability, hyperthyreodism, permanent pacemaker treatment and acute coronary syndromes were excluded from the study. All patients had a continuous atrial fibrillation lasting longer than 48 hours. Duration of atrial fibrillation was determined by careful examination of the patient's medical record, by questioning the patient and by reviewing all previous electrocardiograms available. The patient's demographic and clinical characteristics are shown in table 1.

Table 1. Clinical and echocardiographical data of patients with atrial fibrillation (n = 277)

Clinical variables	**mean ± SD or number of patients (%)**
age (years)	65 ± 10
male gender (%)	167 (60%)
diabetes mellitus (%)	22 (8%)
hypertension (%)	104 (59%)
dilatated cardiomyopathy (%)	8 (7%)
coronary artery disease (%)	33 (12%)
rheumatic mitral valve disease (%)	13 (5%)
previous myocardial infarct (%)	18 (6%)
duration of atrial fibrillation (days)	50 ± 78
Transthoracic echocardiographic parameters	
left atrial diameter (mm)	45 ± 6
left ventricular ejection fraction (%)	54 ± 13
left ventricular mass (gramm)	221 ± 63
left ventricular end-diastolic diameter (mm)	54 ± 7
Transesophageal echocardiographic parameters	
left atrial appendage thrombus (%)	21 (8%)
left atrial appendage spontaneous contrast (%)	
absent	99 (35%)
mild	80 (29%)
medium	82 (30 %)
severe	16 (6 %)
degree of mitral valve regurgitation (%)	
absent or mild	215 (52%)
medium	40 (14 %)
severe	13 (5 %)
peak left atrial appendage anterograde flow (cm/sec)	31 ± 19

3.2. Prediction of cardioversion success by left atrial appendage flow velocities

3.2.1. Study group

Four hundred and eight patients with nonvalvular atrial fibrillation lasting longer than 48 hours and less than 1 year were recruited consecutively from the Albert Szent-Györgyi Medical University, Szeged, Hungary, the SS. Annunziata Hospital, Savigliano, Italy, the Mauriziano Umberto I° Hospital, Torino, Italy and the Institute of Clinical Physiology, Pisa, Italy between December 1997 and October 2000. Exclusion criteria were: duration of atrial fibrillation of >1 year, unknown duration of atrial fibrillation, organic valvular heart disease, presence of prosthetic valve, pericardial diseases, acute myocarditis, acute myocardial infarction, chronic obstructive lung disease, pulmonary embolism, congenital heart disease, recent heart surgery, latent or manifest hyperthyroidism, permanent pacemaker treatment and sick sinus syndrome. Mitral valve regurgitation due to mitral annular dilation was not an exclusion criterion. 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 left atrial appendage thrombus found by transesophageal echocardiography were excluded from the study. The mode of collection of clinical data was identical as described in the previous section. The patient's demographic and clinical characteristics are shown in table 2.

Table 2. Clinical and echocardiograhic variables in patients with and without successful cardioversion (n = 408)

Clinical variables	all patients n = 408	success n = 328	Failure n = 80	p value
Mean age (years)	66 ± 10	66 ± 10	65 ± 9	ns
Male sex (%)	257 (63%)	205 (63%)	52 (65%)	ns
Diabetes (%)	33 (8%)	25 (8%)	8 (10%)	ns
Hypertension (%)	235 (58%)	196 (60%)	39 (49%)	ns
Ischemic heart disease (%)	46 (11%)	38 (12%)	8 (17%)	ns
prior myocardial infarction (%)	29 (7%)	26 (8%)	3 (4%)	ns
atrial fibrillation duration (days)	46 ± 75	40 ± 66	81 ± 107	p<0.01
atrial fibrillation duration > 2 weeks	302 (74%)	229 (70%)	73 (91%)	p<0.001
Transthoracic echocardiographic variables				
LA diameter (mm)	45.0 ± 6.0	44.6 ± 5.9	46.6 ± 6.1	p<0.01
LA diameter > 47 mm (%)	136 (33%)	97 (30%)	39 (49%)	p<0.01
% LVEF	54.3 ± 12,7	54.9 ± 12.8	52.1 ± 12,0	p = 0.077
LV EDD (mm)	54.1 ± 7.4	53.6 ± 7.3	55.9 ± 7.6	p<0.05
LV EDD > 58 mm (%)	116 (28%)	85 (26%)	31 (39%)	p<0.01
IVS thickness (mm)	10.9 ± 1.9	11.0 ± 1.9	11.0 ± 1.8	ns
LVPW thickness (mm)	10.3 ± 1.4	10.3 ± 1.5	10.3 ± 1.4	ns
Transesophageal echocardiographic variables				
Presence of left atrial SEC (%)	233 (57%)	178 (54%)	55 (69%)	p<0.05
Degree of mitral valve regurgitation (%)				
absent or mild	334 (82%)	273 (83%)	61 (76%)	
medium	53 (13%)	39 (12%)	14 (18%)	ns
severe	21 (5%)	16 (5%)	5 (6%)	
LAA peak anterograde flow (cm/sec)	30.6 ± 17.2	32.4 ± 23.5	23.5 ± 13.6	p<0.001
LAA peak anterograde flow < 31 cm/sec (%)	244 (60%)	178 (54%)	66 (83%)	p<0.001

LA = left atrium; LVEF = left ventricular ejection fraction; LVPW = left ventricular posterior wall; IVS = interventricular septum; LV EDD = left ventricular end-diastolic diameter; SEC = spontaneous echo contrast; LAA = left atrial appendage; ns = non significant; p value demonstrates the level of significance between groups of successful and unsuccessful cardioversion

3.2.2. Cardioversion

All patients underwent either pharmacological (n = 84) or electric cardioversion (n = 324) attempt, decided on clinical basis by the physician in charge. Electric cardioversion was performed in the coronary care unit or electrophysiology laboratory after the induction of a anaesthesia (propofol 0.8 to 1.4 mg/kg) and an initial synchronized direct current shock at 150 J with anterior-lateral paddle position. If necessary, the procedure was repeated with 200, 300, and up to a maximum of 360 J. In no instance was endotracheal intubation necessary. Pharmacological cardioversion was attempted with intravenous propafenone (n = 30), oral quinidine sulphate in combination with metoprolol if a high ventricular rate was present (n = 25), intravenous and/or oral amiodarone (n = 21) and flecainide (n = 8). All patients underwent permanent electrocardiographic monitoring during the cardioversion procedure. Continuous electrocardiographic monitoring was performed after successful restoration of sinus rhythm for 24 hours to assess maintenance of sinus rhythm. Successful cardioversion was defined as a stable sinus rhythm lasting for at least 1 day after successful conversion (63). All patient had appropriate anticoagulation level at the time point of cardioversion attempt – including those with short duration of atrial fibrillation, who were treated by intravenous heparin and subsequent oral anticoagulation therapy. Oral anticoagulation was prolonged for 4 weeks after successful restoration of sinus rhythm and continuously maintained in those with failure of cardioversion

3.3. Prediction of long-term sinus rhythm maintenance by left atrial appendage flow velocities in patients with nonvalvular atrial fibrillation

3.3.1. Study group

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 the above mentioned four cardiology centers. 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. The patient's demographic and clinical characteristics are shown in table 3.

Table 3. Clinical and echocardiograhic variables in patients with successful cardioversion of nonvalvular atrial fibrillation and 1-year follow-up (n=186)

Clinical variables	all patients n=186	SR maintenance n=91	AF relapse n=95	p value
Mean age (years)	65.1 ± 9.9	64.6 ± 10.7	65.4 ± 9.1	ns
Male sex (%)	116 (62%)	60 (66%)	56 (59%)	ns
Diabetes (%)	13 (7%)	5 (5%)	8 (8%)	ns
Hypertension (%)	119 (64%)	57 (63%)	62 (65%)	ns
Ischemic heart disease (%)	24 (13%)	11 (12%)	13 (14%)	ns
prior myocardial infarction (%)	14 (8%)	5 (6%)	9 (9%)	ns
atrial fibrillation duration (days)	36 ± 62	33 ± 39	39 ± 56	p<0.01
antiarrhythmic drug use during follow-up	66 (35%)	39 (43%)	27 (28%)	p<0.05
Transthoracic echocardiographic variables				
LA diameter (mm)	44.2 ± 6.2	43.0 ± 5.9	45.4 ± 6.3	p<0.01
LV EF (%)	54.6 ± 11.9	55.7 ± 10.9	53.5 ± 12.7	ns
LV EDD (mm)	53.2 ± 6.5	52.9 ± 6.7	53.4 ± 6.4	ns
LV mass (grams)	222.4 ± 59.3	216.9 ± 57.6	227.5 ± 60.8	ns
Transesophageal echocardiographic variables				
presence of left atrial SEC (%)	87 (47%)	34 (37%)	53 (56%)	p<0.05
degree of mitral valve regurgitation (%)				
absent or mild	155 (83%)	81 (89%)	74 (78%)	
medium	23 (12%)	6 (7%)	17 (18%)	ns
severe	8 (4%)	4 (4%)	4 (4%)	
mean LAA peak anterograde flow (cm/sec)	34.6 ± 19.9	41.7 ± 20.3	27.7 ± 17.0	p<0.001

LA = left atrium; LVEF = left ventricular ejection fraction; LV = left ventricular; EDD = end-diastolic diameter; SEC = spontaneous echo contrast; LAA = left atrial appendage; ns = non significant; p value demonstrates the level of significance between groups of SR maintenance and AF relapse

3.3.2. Follow-up

Patients were followed 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).

3.4. Echocardiographic studies

All transthoracic and transesophageal echocardiographic studies were performed in atrial fibrillation with a commercially available ultrasonographic systems. Transesophageal echocardiography was performed with bi- or multiplane probes with a 5.0 or 7.0 MHz transducer.

The following transthoracic echocardiographic measurements were taken by parasternal long-axis view from 2-D targeted M-mode tracings according to the recommendations of the American Society of Echocardiography (64): left atrial diameter, left ventricular end-diastolic diameter, left ventricular mass, ejection fraction (according to the Quinones formula). Two dimensional biplane area-length method was used for ejection fraction calculation in patients with previous infarction. All transthoracic echocardiographic indices were measured offline, using the integrated software of the echocardiographic equipment and were calculated as the average of 5 consecutive cardiac cycles.

Following the transthoracic echocardiography and after a 6 hour fasting period all patients underwent transesophageal echocardiographic examination. During the transesophageal echocardiography images were analyzed on-line by an experienced observer for the presence of intracardiac thrombus. In order to view the maximal size and to obtain the highest resolution of the left atrial appendage the most appropriate section was used for the analysis. The gain was continuously adjusted to ensure the best possible visualization and to

avoid noise artifact. A thrombus was considered to be present when a well-circumscribed echodense intracavitary mass that was acoustically distinct from the underlying endocardium was detected. Videotape and/or digitally stored images were subsequently analyzed off-line for the presence of left atrial SEC and mitral valve regurgitation grade by two independent observers, unaware of the patients' history. Spontaneous echo contrast was defined as an intracavitary swirling smokelike echo within the left atrium or left atrial appendage (65). Mitral regurgitation was qualitatively graded by color flow Doppler mapping as none, mild, moderate or severe on the basis of regurgitant jet area and spatial distribution of the regurgitant flow (66). Differences between observers were resolved by consensus; if observers could not agree, a third more experienced observer reviewed the study and his judgement was binding. Left atrial appendage velocity profiles were obtained by pulsed-wave Doppler interrogation 1 cm within the orifice of the left atrial appendage and analyzed off line from videotape or digitally stored unaware of the patients' history. Left atrial appendage peak emptying velocities were averaged with each RR interval over a minimum of 5 consecutive cardiac cycles (44, 51).

3.5. Statistical analysis

All data are expressed as means ± standard deviation. In the intergroup comparison of clinical and echocardiographic continuous variables the statistical significance was assessed by unpaired Student t-test or Mann Whitney U test. Comparison of proportions was performed using chi-square analysis or Fisher exact as appropriate. Pearson tests were used to assess the correlation of continuous variables with left atrial appendage peak emptying velocity. Test of linear association between variables were made with multiple regression techniques.

Receiver-operating characteristic (ROC) analysis was used to determine optimal cut-off values of continuous variables for prediction of cardioversion success and 1 year sinus rhythm preservation. The ROC curve represents the relationship between sensitivity and specificity, by plotting true-positive rate (sensitivity) against the false-positive rate (specificity) as the cut-off level of the model varies. The best cut-off value was defined as the point with the highest sum of sensitivity and specificity. The area under the ROC curve was used to quantify the ability of the mean left atrial appendage emptying velocity to predict success of cardioversion and 1-year sinus rhythm maintenance accurately.

Univariate and multivariate logistic regression models (toward forward stepwise procedure) were used to control for all possible confounding factors and to assess interaction between variables for assessment of success of cardioverion and 1-year sinus rhythm maintenance. The univariate and multivariate odds ratios (OR) and their corresponding 95% confidence intervals (CI) are given. All tests were 2-sided, and a p value <0.05 was considered significant. All analysis was performed by an SPSS 9.0 software package.

4. RESULTS

4.1. Clinical and echocardiographic correlates of left atrial appendage flow

Demographic, clinical and echocardiographic data of the study subjects are shown in table 1. Peak left atrial flow anterograde velocities between 20 and 30 cm/sec were detected most frequently in the study population. One hundred and ninety seven patients (71%) had a peak left atrial appendage emptying flow < 40 cm/sec.

4.1.1. 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 (table 4). 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 (Table 4). Appendage velocities were markedly reduced in both groups of patients (17.4 ± 10.7 and 20.3 ± 14.9 cm/sec, respectively). Duration of atrial fibrillation was correlated inversely with the left atrial appendage emptying velocity ($r = -0.43$, $p < 0.001$) (Fig. 5). The mean of the peak left atrial appendage anterograde flow velocity of patients with relatively short duration (< 1 week) was in the normal range (42 ± 21 cm/sec), while this value was moderately reduced (30 ± 18 cm/sec) in patients who had an arrhythmia duration >1 week and <1 month. The appendage flow velocity was markedly reduced in those who had an atrial fibrillation duration > 1 month and < 6 months or longer than 6 months (22 ± 11 and 18 ± 8 cm/sec, respectively). Age was not significantly related to the appendage flow velocities ($r = 0.003$, $p = 0.96$).

Table 4. Left atrial appendage emptying velocity on various subgroup of patients defined by clinical and echocardiographic variables (n = 277)

Clinical variables	**Peak left atrial appendage emptying velocities (mean ± SD; cm/sec)**	**p value**
gender		
male	31.6 ± 19.9	ns
female	29.9 ± 16.7	
diabetes		
present	29.2 ± 16.1	ns
absent	31.1 ± 18.9	
hypertension		
present	32.7 ± 18.4	ns
absent	28.3 ± 19.1	
idiopathic dilated cardiomyopathy		
present	17.4 ± 10.7	<0.001
absent	32.9 ± 18.9	
rheumatic mitral valve stenosis		
present	20.3 ± 14.9	<0.05
absent	31.4 ± 18.8	
epicardial coronary stenosis		
present	30.6 ± 16.9	ns
absent	30.9 ± 19.1	
prior myocardial infarct		
present	28.7 ± 19.7	ns
absent	31.1 ± 18.7	
Echocardiographic variables		
left atrial appendage thrombus		
present	14.6 ± 10.2	<0.001
absent	32.2 ± 18.7	
left atrial appendage spontaneous echo contrast		
absent	45.8 ± 18.3	<0.001
mild	27.9 ± 11.9	
medium	18.8 ± 10.1	
severe	15.1 ± 18.8	
degree of mitral valve regurgitation		
absent or mild	32.5 ± 19.6	<0.05
medium	24.8 ± 14.1	
severe	22.2 ± 8.4	

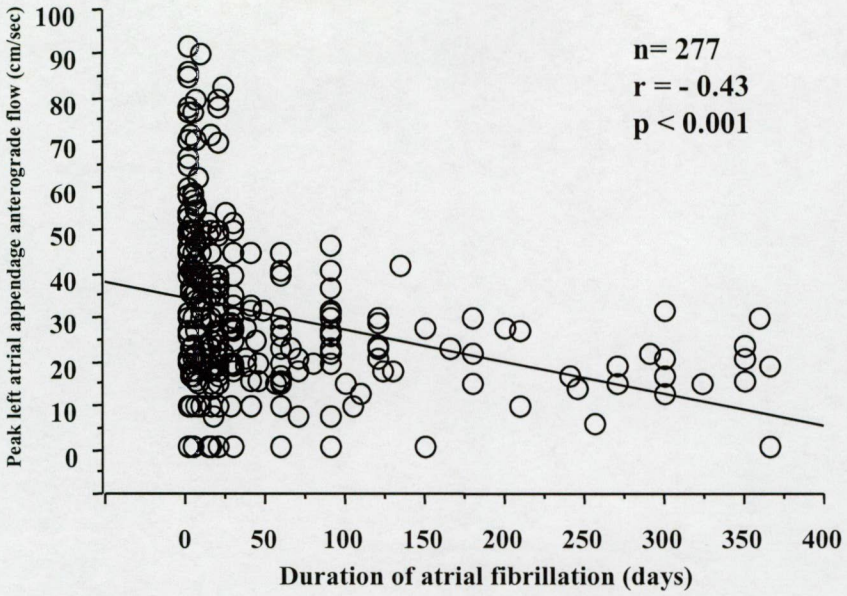

Figure 5. Relation of peak left atrial contraction velocity with duration of atrial fibrillation

4.1.2. 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 ± 10.2 vs 32.2 ± 18.7 cm/sec, $p<0.001$) (Fig. 6). 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 left atrial appendage 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 ± 13.1 vs 45.8 ± 18.3 cm/sec; $p<0.001$). Increasing grades of left atrial appendage SEC and mitral valve regurgitation were associated with decreasing peak left atrial appendage velocities (Table 4 and Fig. 7). Left atrial appendage velocities were inversely correlated with the left atrial dimension ($r = -0.326$, $p<0.001$) and left ventricular end-diastolic diameter ($r = - 0.148$, $p<0.05$) (Fig. 8 and 9). Positive correlation was found between left ventricular ejection fraction and the left atrial appendage emptying velocities ($r = 0.328$, $p<0.001$) (Fig. 10). Left ventricular mass was not related to the appendage flow velocities ($r = -0.09$, $p = 0.124$).

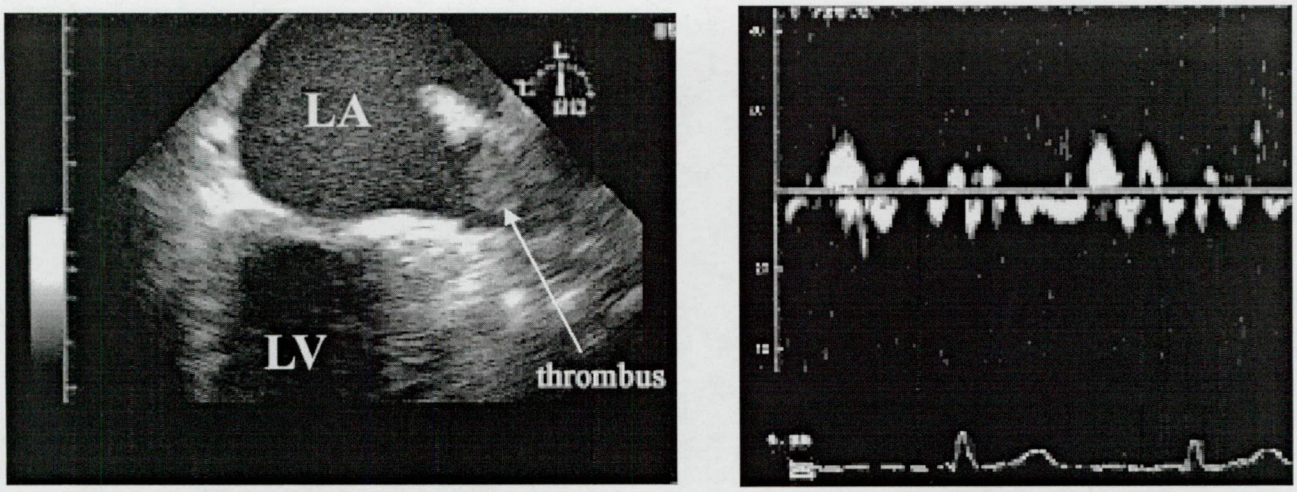

Figure 6. An example of a thrombus localised to the additional lobe of the left atrial appendage (left sided panel). On the right sided panel, a pulsed Doppler flow obtained in the appendage of the same patient showing low velocity profile (mean peak appendage flow is 16 cm/sec)

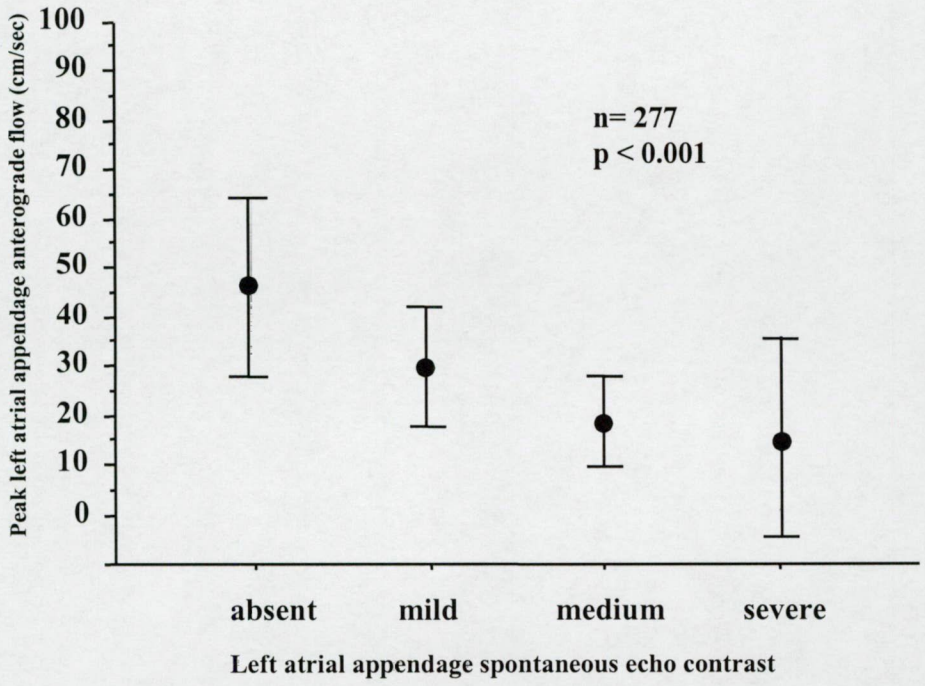

Figure 7. Mean peak left atrial appendage contraction flow velocity in patients with different grades of left atrial appendage SEC formation

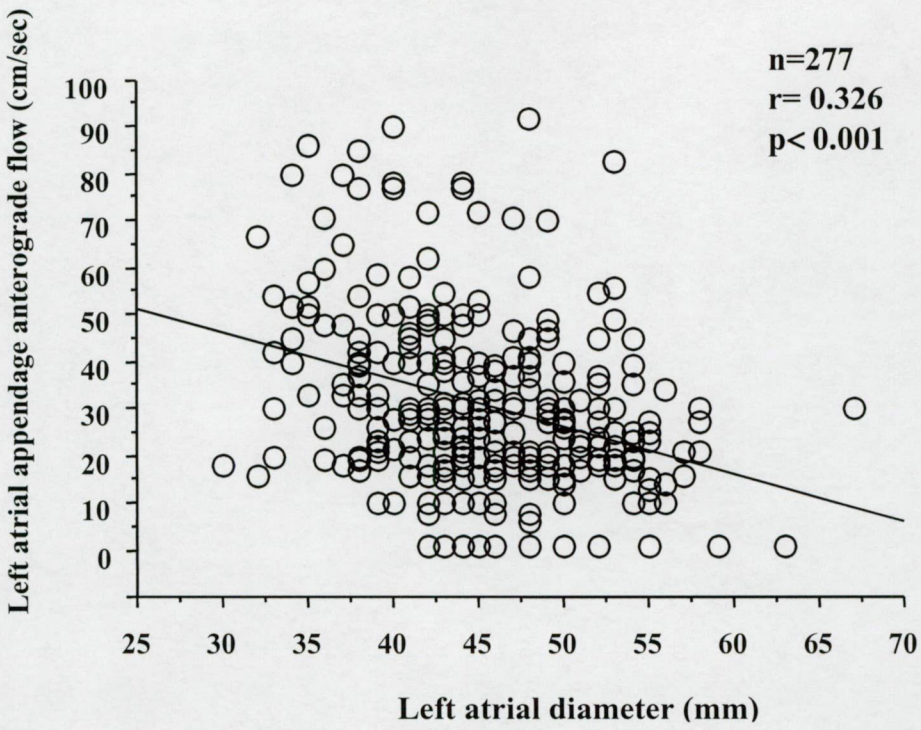

Figure 8. Relationship between left atrial appendage emptying velocities and left atrial parasternal diameter

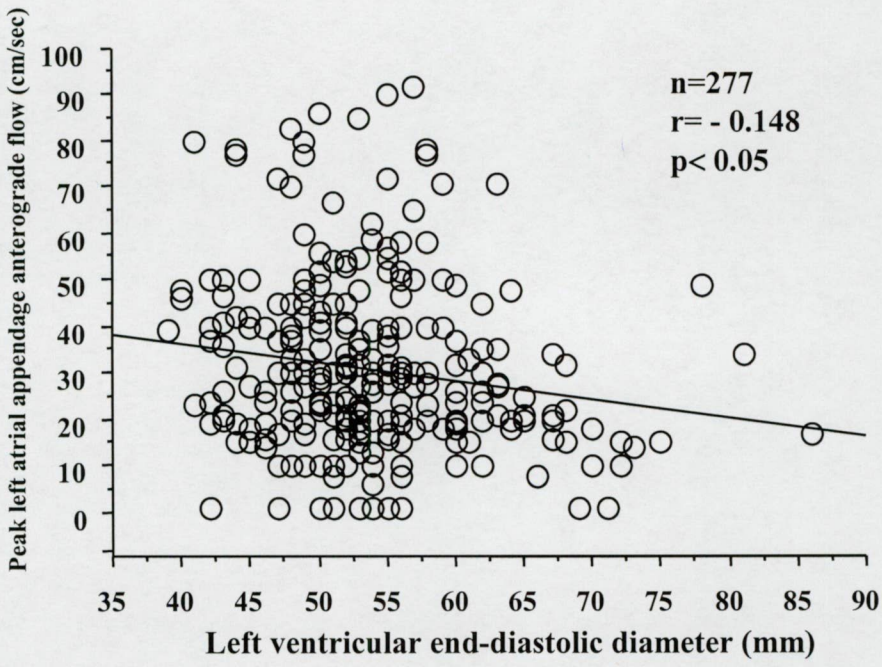

Figure 9. Relationship between left atrial appendage anterograde velocities and left ventricular end-diastolic diameter

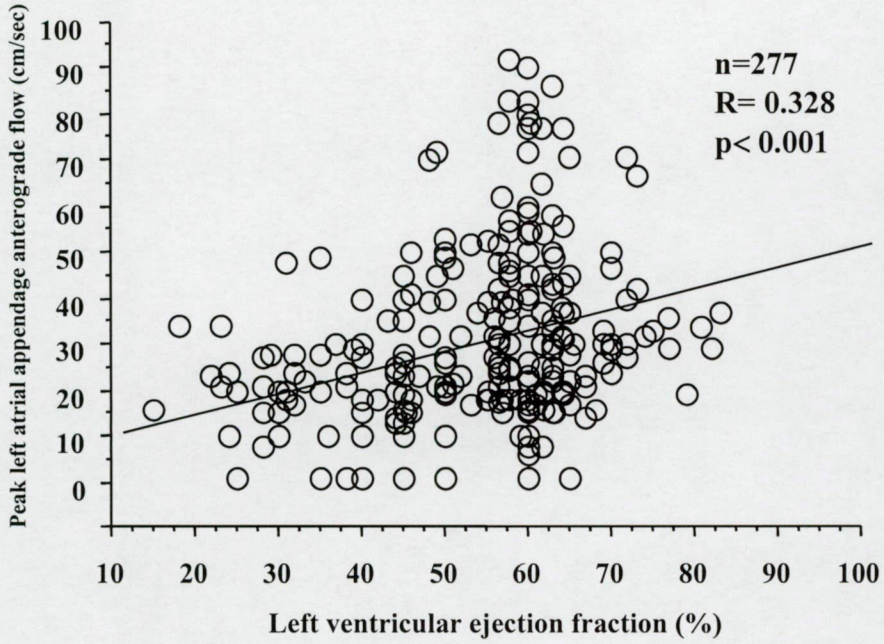

Figure 10. Relationship between left atrial appendage anterograde velocities and left ventricular ejection fraction

4.1.3. Independent correlates of left atrial appendage flow in atrial fibrillation

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

4.2 Prediction of cardioversion success by left atrial appendage flow velocities

4.2.1. 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%) with

an average of 2.5 shocks (range 1-4) and cumulative 552 ± 314 J energy dose, while during pharmacological cardioversion attempt 62 of 84 patients (74%) converted to sinus rhythm. There were no important side effects during either pharmacological or electric cardioversion attempt.

4.2.2. Clinical parameters and cardioversion success

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

4.2.3. 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 (Table 2). On the basis of a ROC analysis, 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 left atrial appendage 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 (Table 2). Typical examples of high and low flow velocity profiles of the left atrial appendage in atrial fibrillation, obtained by pulsed Doppler during transesophageal echocardiography in patients with and without successful cardioversion are shown in figure 11 and 12, respectively. According to the ROC analysis, a mean left atrial appendage peak anterograde flow velocity > 31 cm/sec provided the best separation between patients with and without cardioversion success (Table 2).

4.2.4. Prediction of cardioversion success by integrated clinical, transthoracic and transesophageal echocardiographic variables

Univariate logistic regression analysis revealed that the mean left atrial appendage 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 (Table 2). By multivariate logistic regression analysis, 3 parameters proved to be independent predictors of cardioversion success: atrial fibrillation duration < 2 weeks, followed by the mean left atrial appendage peak anterograde velocity > 31 cm/sec and left atrial parasternal diameter < 47 mm (Table 5).

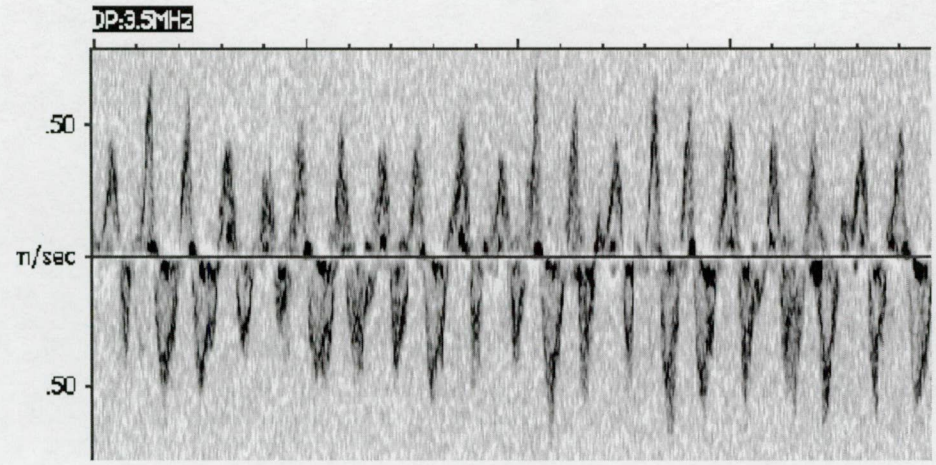

Figure 11. Pulsed Doppler tracing of the left atrial appendage obtained by transesophageal echocardiography in atrial fibrillation showing high peak emptying flow velocity signals in a patient with successful cardioversion. The mean left atrial appendage peak anterograde flow velocity was 52 cm/sec.

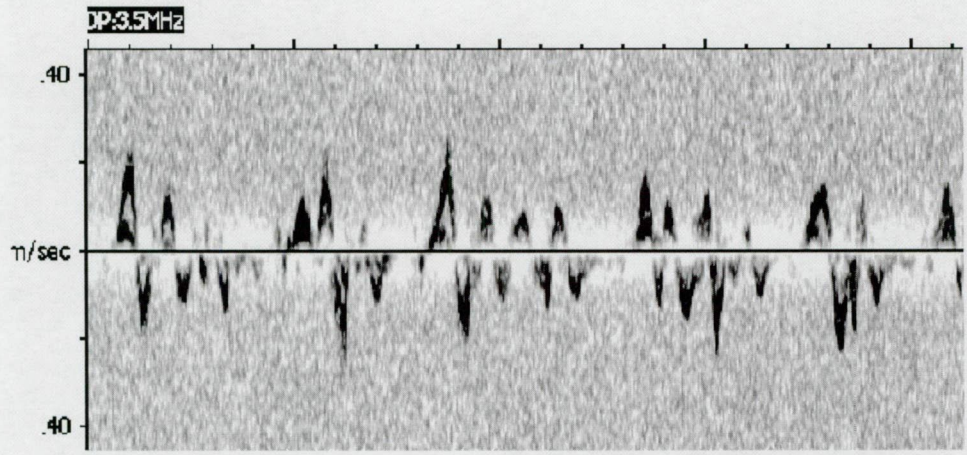

Figure 12. Pulsed Doppler tracing of the left atrial appendage obtained by transesophageal echocardiography in atrial fibrillation showing low peak emptying flow velocity signals in a patient with unsuccessful cardioversion. The mean peak left atrial appendage anterograde velocity was 26 cm/sec.

Table 5. Univariate and multivariate predictors of successful cardioversion outcome

Univariate predictors	p value	Chi-square	OR (95 % CI)
left ventricular end-diastolic diameter < 58 mm	p = 0.0236	5.1	1.8 (1.1-3.0)
absence of left atrial SEC during TEE	p = 0.0201	5.4	1.9 (1.1-3.1)
left ventricular ejection fraction > 56 %	p = 0.0029	8.8	2.1 (1.3-3.5)
left atrial diameter < 47 mm	p = 0.0013	10.3	2.3 (1.4-3.7)
atrial fibrillation duration < 2 weeks	p = 0.0001	15.6	6.6 (2.6-16.7)
mean peak anterograde LAA flow velocity > 31 cm/sec	p = 0.0001	19.2	4.0 (2.1-7.4)
Multivariate predictors			
left atrial diameter < 47 mm	p = 0.0093	6.8	2.0 (1.2-3.4)
mean peak anterograde LAA flow velocity > 31 cm/sec	p = 0.0013	10.4	2.8 (1.5-5.4)
atrial fibrillation duration < 2 weeks	p = 0.0011	10.6	4.9 (1.9-12.7)

SEC = spontaneous echocontrast; TEE = transesophageal echocardiography LAA = left atrial appendage

4.3. Prediction of long-term sinus rhythm maintenance by left atrial appendage flow velocities

4.3.1. 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. The patient's demographic and clinical characteristics are shown in table 3.

4.3.2. 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 (Table 3). 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 (present in 71 patients, 38%) 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 (Table 3).

4.3.3. 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 (Table 3). On the basis of the ROC analysis (Fig 13), 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 left atrial appendage 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 (Table 3). According to the ROC analysis derived mean left atrial appendage anterograde flow velocity cut-off of 40 cm/sec, 70 patients (38 %) had higher mean left atrial appendage peak anterograde velocity than 40 cm/sec.

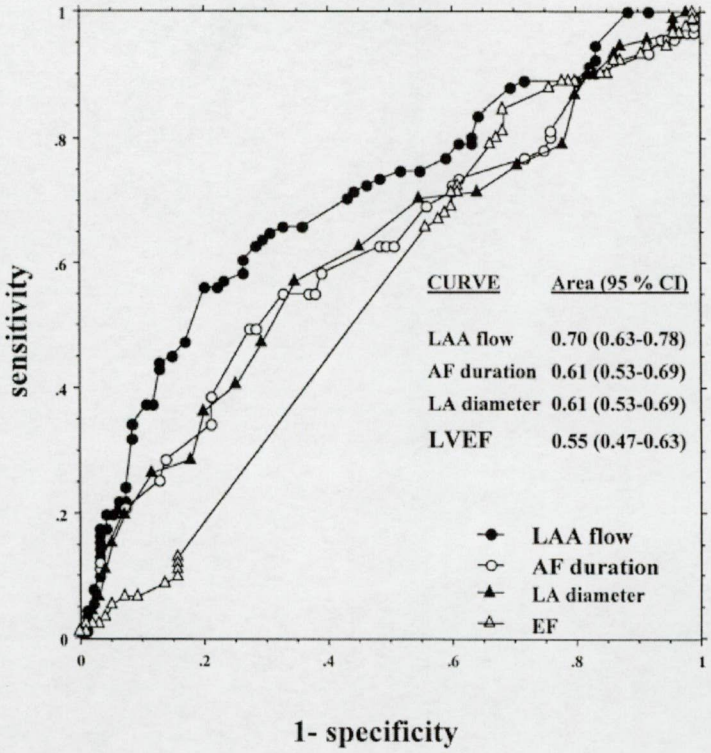

Figure 13. Receiver-operating curves of left atrial appendage (LAA) flow, atrial fibrillation (AF) duration, left atrial (LA) diameter and left ventricular ejection (LVEF) fraction for prediction of 1-year maintenance of sinus rhythm.

4.3.4. Prediction of long-term maintenance of sinus rhythm by integrated clinical and echocardiographic variables

Univariate logistic regression analysis revealed that mean left atrial appendage 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 left atrial appendage 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, $p<0.05$) (Table 6).

Table 6. Univariate and multivariate predictors of 1-year maintenance of sinus rhythm

Univariate predictors	p value	Chi-square	OR (95 % CI)
Preventive antiarrhythmic drug use during follow-up	p<0.05	4.2	1.9 (1.0-3.5)
Absence of left atrial SEC during TEE	p<0.05	6.3	2.1 (1.2-3.8)
Left ventricular ejection fraction > 46 %	p<0.05	6.5	2,5 (1.2-5.2)
Left atrial diameter < 44 mm	p<0.01	9.3	2,5 (1.4-4.5)
Atrial fibrillation duration < 1 week	p<0.01	9.4	2,6 (1.4-4.8)
Mean peak anterograde LAA flow velocity > 40 cm/sec	p<0.0001	24	5,1 (2.7-9.8)
Multivariate predictors			
Preventive antiarrhythmic drug use during follow-up	p<0.05	4.2	2.0 (1.0-3.8)
Mean peak anterograde LAA flow velocity > 40 cm/sec	p<0.0001	23.9	5.2 (2.7-10.1)

SEC = spontaneous echo contrast; TEE = transesophageal echocardiography; LAA = left atrial appendage

5. GENERAL DISCUSSION

5.1. Correlates of left atrial appendage flow in patients with atrial fibrillation

This study defines the significant correlates of the left atrial appendage 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 left atrial appendage flow in a large cohort of patients with atrial fibrillation. In this multivariate analysis left atrial appendage SEC, idiopathic dilated cardiomyopathy, presence of left atrial appendage thrombus and duration of atrial fibrillation composed the best predictive model for left atrial appendage emptying flow velocity.

Association between left atrial appendage flow, spontanous 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 (67). Previous experimental studies have reported qualitative increase in blood echogenicity with the onset of blood stasis (68).

From the clinical point-of-view the association of SEC with low flow states - such as mitral valve stenosis - known to predispose to intracardiac thrombus formation (69). 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, Fatkin et al. demonstrated a close relationship between the emptying flow of the appendage, its SEC and thrombus formation (70). 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 left atrial appendage 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 left atrial appendage 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 and there is certain inter-observer variability. In contrast, the measurement of appendage flow is more objective and highly reproducible (24, 28). Our observation is concordant with those of previous studies demonstrating an association between reduced flow velocities of the appendage and future systemic embolic events (50, 60).

Relationship between other variables and left atrial appendage flow

No data are available in the literature regarding the effect of different grades of mitral valve regurgitation on the mechanical function of the left appendage in atrial fibrillation. Our study demonstrates for the first time that increasing grades of mitral regurgitation is - albeit weakly - associated with decreasing left atrial appendage 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 left atrial appendage contractile function, mitral regurgitation has an overall protective effect against thrombembolism by prevention of blood stasis (71, 72).

Controversial data are available in the medical literature considering the association between left atrial appendage flow and left atrial and ventricular size and left ventricular systolic function (26, 28, 46, 52, 53). The relatively large sample allowed us to demonstrate that the left atrial appendage emptying flow 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 (52, 73). 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 left atrial appendage 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 (27, 74, 75). This reduced left atrial appendage contractile function may explain why these aforementioned clinical conditions are predictors of left atrial appendage thrombus formation and systemic thromboembolism in atrial fibrillation (76, 77, 78).

Similarly, as reported in a previous study the duration of atrial fibrillation in our study showed an inverse correlation with left atrial appendage emptying flow (44). 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 left atrial appendage, 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) (29). 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 left atrial appendage function supports a diagnosis of appendage thrombus, whereas normal function suggests an alternative diagnosis.

Although patients with atrial fibrillation can be stratified according to intra-appendage thrombus formation and systemic thromboembolic risk by pulsed Doppler assessment of left atrial appendage velocity profile, the clinical impact of this risk stratification on anticoagulant therapy has not been established yet.

5.2. Prediction of short and long-term success of cardioversion by left atrial appendage flow velocities in patients with atrial fibrillation

5.2.1. Prediction of cardioversion success by left atrial appendage flow velocities in patients with atrial fibrillation

Our study demonstrated that measurement of the left atrial appendage emptying velocity profile by TEE before cardioversion in patients with nonvalvular atrial fibrillation provides valuable additional information for prediction of cardioversion success.

Comparison with previous studies

Previous studies have already demonstrated that the left atrial appendage velocity is related to the left atrial size (70, 79) and the duration of atrial fibrillation (44), 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 left atrial appendage function before cardioversion, although this was not a uniform observation (44, 51, 53, 61). Mitusch et al. reported transesophageal echocardiography data from 93 patients with nonvalvular atrial fibrillation (44). They found a significant difference in left atrial appendage 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 left atrial appendage 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 left atrial appendage 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 (51). On the contrary, in a study of 82 patients with atrial fibrillation < 6 months duration, Perez et al. found no relationship between left atrial appendage flow velocities and outcome of the cardioversion (53). 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 left atrial appendage velocity values between successful and unsuccessful cardioversion groups, but the left atrial appendage flow velocities tended to be higher in patients who converted to sinus rhythm (61). Similarly, as reported in previous studies, we also found that the duration of atrial fibrillation is a predictor of successful conversion (44, 51). 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 (4, 44, 61). 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 left atrial appendage peak emptying velocity has independent and additive prognostic value over other clinical and echocardiographic predictors (80).

5.2.2. Prediction of 1-year maintenance of sinus rhythm by left atrial appendage flow velocities in patients with atrial fibrillation

Our study demonstrated that measurement of the left atrial appendage 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 left atrial appendage velocity is related to the left atrial size (79) and the duration of atrial fibrillaton (44), all of which are predictors of long-term sinus rhythm maintenance. However, conflicting and scarce data exist on the usefulness of left atrial appendage flow to predict long-term preservation of sinus rhythm (53, 61, 62). 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 left atrial appendage 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 left atrial appendage flow (81).

5.2.3. 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 left atrial appendage and in the left atrium (chamber dilatation, loss of myofibrils, fragmentation of sarcoplasmatic reticulum and marked collagen formation) (16, 21, 82, 83). 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 (84, 85). Loss of contractile elements of left atrial appendage may result in its reduced mechanical function which could be expressed in low left atrial appendage flow velocities profile. However, according to our knowledge, there is no published data in the literature studying the direct link between left atrial appendage flow and histopathological changes in the appendage in patients with nonvalvular atrial fibrillation.

6. CONCLUSIONS

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

We defined several correlates of the left atrial appendage anterograde flow velocity in a large cohort of patients with atrial fibrillation. Spontaneous echo contrast and thrombus formation within the left atrial appendage, 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 left atrial appendage 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 left atrial appendage velocity pattern can be considered as a valuable marker of left atrial appendage clot formation.

We reported for the first time that increasing grades of mitral regurgitation is - albeit weakly - associated with decreasing left atrial appendage 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 left atrial appendage 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. left atrial appendage flow), can be of use in predicting 1-year outcome of successful cardioversion.

7. REFERENCES

1. Feinberg WM, Blackshear JL, Laupacis A et al. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. Arch Intern Med 1995; 155: 469-73
2. Atrial fibrillation: current understandings and research imperatives. The National Heart, Lung, and Blood Institute Working Group on Atrial Fibrillation. J Am Coll Cardiol 1993; 22: 1830-4
3. Falk RH. Etiology and complications of atrial fibrillation: insights from pathology studies. Am J Cardiol 1998; 82:10N-17N
4. Chugh SS, Blackshear JL, Shen WK et al. Epidemiology and natural history of atrial fibrillation: clinical implications. J Am Coll Cardiol 2001; 37: 371-8
5. Benjamin EJ, Levy D, Vaziri SM et al. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA 1994; 271: 840-4
6. Kannel WB, Abbott RD, Savage DD et al. Epidemiologic features of chronic atrial fibrillation: the Framingham study. N Engl J Med 1982; 306: 1018-22
7. Gajewski J, Singer RB. Mortality in an insured population with atrial fibrillation. JAMA 1981; 245: 1540-4
8. Gersch BJ. The epidemiology of atrial fibrillation and flutter. In: DiMarco JP, Prystowsky EN, editors. Atrial arrhythmias: State of the art. Armonk, New York: Futura Publishing, 1995: 1-22
9. Kubac G, Mallowany L. Functional capacity of patients with atrial fibrillation and controlled heart rate before and after cardioversion. Can J Cardiol 1992; 8: 941-946
10. Benjamin EJ, Wolf PA, D'Agostino RB et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998, 98: 946-52
11. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. Arch Intern Med 1987; 147: 1561-4
12. Cairns JA, Connolly SJ. Nonrheumatic atrial fibrillation. Risk of stroke and role of antithrombotic therapy. Circulation 1991; 84: 469-81
13. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg 1996; 61: 755-9

14. Aschenberg W, Schluter M, Kremer P et al. transesophageal two-dimensional echocardiography for the detection of left atrial appendage thrombus J Am Coll Cardiol 1986; 7: 163-166
15. Veinot JP, Harrity PJ, Gentile F. et al. Anatomy of the normal left atrial appendage: a quantitative study of age-related changes in 500 autopsy hearts: implications for echocardiographic examination. Circulation 1997; 96: 3112-5
16. Ernst G, Stollberger C, Abzieher F et al. Morphology of the left atrial appendage. Anat Rec 1995; 242: 553-61
17. Hoit BD, Shao Y, Tsai LM et al. Altered left atrial compliance after atrial appendectomy. Influence on left atrial and ventricular filling. Circ Res 1993; 72: 167-75
18. Davies CA , Rembert JC, Greenfield JC. Complience of left atrium with and without left atrial appendage Am J Physiol 1990; 259: H1006-8
19. Kappagoda CT, Linden RJ, Snow HM. The effect on heart rate of distending the atrial appendage in dogs. J Physiol 1972; 225: 705-19
20. Chapeau C, Gutkowska J, Schiller PW et al. Localization of immunoreactive synthetic atrial natriuretic factor (ANF) in the heart of various animal species. J Histochem Cytochem 1985; 33: 541-50
21. Shirani J, Alaeddini J. Structural remodelling of the left atrial appendage in patients with chronic non-valvular atrial fibrillation: Implications for thrombus formation, systemic embolism, and assessment by transesophageal echocardiography. Cardiovasc Pathol 2000; 9: 95-101
22. Fuster V, Rydén LE, Asinger RW et al. ACC/AHA/ESC Guidelines for the management of patients with atrial fibrillation: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation) Developed in Collaboration With the North American Society of Pacing and Electrophysiology Circulation 2001; 104: 2118-2150
23. Ono M, Asanuma T, Tanabe K et al. Improved visualization of the left atrial appendage by transthoracic 2-dimensional tissue harmonic compared with fundamental echocardiographic imaging. J Am Soc Echocardiogr 1998; 11: 1044-9

24. Agmon Y, Khandheria BK, Gentile F, Seward JB. Echocardiographic assessment of the left atrial appendage. J Am Coll Cardiol 1999; 34: 1867-77
25. Ito T, Suwa M, Hirota Y et al. Influence of left atrial function on Doppler transmitral and pulmonary venous flow patterns in dilated and hypertrophic cardiomyopathy: evaluation of left atrial appendage function by transesophageal echocardiography. Am Heart J 1996; 131: 122-30
26. Fatkin D, Feneley MP. Patterns of Doppler-measured blood flow velocity in the normal and fibrillating human left atrial appendage. Am Heart J 1996; 132: 995-1003
27. Hwang JJ, Li YH, Lin JM et al. Left atrial appendage function determined by transesophageal echocardiography in patients with rheumatic mitral valve disease Cardiology 1994; 85: 121-8
28. Pollick C, Taylor D. Assessment of left atrial appendage function by transesophageal echocardiography. Implications for the development of thrombus. Circulation 1991; 84: 223-31
29. Seward JB, Khandheria BK, Oh JK et al. Critical appraisal of transesophageal echocardiography: limitations, pitfalls, and complications. J·Am Soc Echocardiogr 1992; 5: 288-305
30. Herzog E, Scherid M. Bifid left atrial appendage with thrombus: source of embolism. J Am Soc Echocardiogr. 1998; 11: 910-5
31. Manning WJ, Weintraub RM, Waksmonski CA et al. Accuracy of transesophageal echocardiography for identifying left atrial thrombi: a prospectice, intraoperative study. Ann Intern Med 1995; 123: 817-22
32. Kortz RA, Delemarre BJ, van Dantzig JM. et al. Left atrial appendage blood flow determined by transesophageal echocardiography in healthy subjects. Am J Cardiol 1993; 71: 976-981
33. Tabata T, Oki T and Fukuda N et al. Influence of aging on left atrial appendage flow velocity patterns in normal subjects. J Am Soc Echocardiogr 1996; 9: 274-280
34. Pálinkás A, Jambrik Z, Varga A, Forster T, Csanády M. A bal pitvari fülcse echocardiographiás vizsgálatának klinikai jelentősége Orv Hetil, 2003; 104:23-29
35. Ito T, Suwa M, Otake Y et al. Assessment of left atrial appendage function after cardioversion of atrial fibrillation: relation to left atrial mechanical function. Am Heart J 1998; 135: 1020-1026

36. Grimm RA, Leung DY, Black IW et al. Left atrial appendage "stunning" after spontaneous conversion of atrial fibrillation demonstrated by transesophageal Doppler echocardiography. Am Heart J 1995; 130: 174-176
37. Harjai K, Mobarek S, Abi-Samra F et al. Mechanical dysfunction of the left atrium and the left atrial appendage following cardioversion of atrial fibrillation and its relation to total electrical energy used for cardioversion. Am J Cardiol 1998; 81: 1125-9
38. Noda T, Arakawa M, Miwa H et al. Effects of heart rate on flow velocity of the left atrial appendage in patients with nonvalvular atrial fibrillation. Clin Cardiol 1996;19:295-300
39. Gonzalez-Torrecilla E, Garcia-Fernandez MA, Perez-David E et al. Predictors of left atrial spontaneous echo contrast and thrombi in patients with mitral stenosis and atrial fibrillation. Am J Cardiol 2000; 86: 529-34
40. Bollmann A, Binias KH, Grothues F et al. Left atrial appendage flow in atrial fibrillation. Relationship with pulmonary venous flow and ECG fibrillatory wave. Chest 2001; 119: 485-492
41. Daoud EG, Marcovitz P, Knight BP et al. Short-term effect of atrial fibrillation on atrial contractile function in humans. Circulation 1999; 99: 3024-7
42. Garcia-Fernandez MA, Torrecilla EG, San Roman D et al. Left atrial appendage Doppler flow patterns: implications on thrombus formation. Am Heart J 1992; 124: 955-61
43. Akosah KO, Funai JT, Porter TR et al. Left atrial appendage contractile function in atrial fibrillation: influence of heart rate and cardioversion to sinus rhythm. Chest 1995; 107: 690-696
44. Mitusch R, Garbe M, Schmucker G et al. Relation of left atrial appendage function to the duration and reversibility of nonvalvular atrial fibrillation. Am J Cardiol 1995; 75: 944-7
45. Mugge A, Kuhn H, Nikutta P et al. Assessment of left atrial appendage function by biplane transesophageal echocardiography in patients with nonrheumatic atrial fibrillation: identification of a subgroup of patients at increased embolic risk. J Am Coll Cardiol 1994; 23: 599-607
46. Jue J, Winslow T, Fazio G et al. Pulsed Doppler characterization of left atrial appendage flow. J Am Soc Echocardiogr 1993; 6: 237-244
47. Pozzoli M, Febo O, Torbicki A et al. Left atrial appendage dysfunction: a cause of thrombosis? Evidence by transesophageal echocardiography-Doppler studies. J Am Soc Echocardiogr 1991; 4: 435-441

48. Li YH, Lai LP, Shyu KG et al. Clinical implication of left atrial appendage function: its influence on thrombus formation. Int J Cardiol 1994; 43: 61-6

49. Tsai LM, Chao TH, Chen JH. Association of follow-up change of left atrial appendage blood flow velocity with spontaneous echo contrast in nonrheumatic atrial fibrillation. Chest 2000; 117: 309-13

50. Kamp O, Verhorst PM, Welling RC et al. Importance of left atrial appendage flow as a predictor of thromboembolic events in patients with atrial fibrillation. Eur Heart J 1999; 20: 979-85

51. Tabata T, Oki T, Iuchi A et al. Evaluation of left atrial appendage function by measurement of changes in flow velocity patterns after electrical cardioversion in patients with isolated atrial fibrillation. Am J Cardiol 1997; 79: 615-20

52. Ito T, Suwa M, Kobashi A et al. Influence of altered loading conditions on left atrial appendage function in vivo. Am J Cardiol 1998; 81: 1056-59

53. Perez Y, Duval AM, Carville C et al. Is left atrial appendage flow a predictor for outcome of cardioversion of nonvalvular atrial fibrillation ? A transthoracic and transesophageal echocardiographic study. Am Heart J 1997; 134: 745-51

54. Goldman ME, Pearce LA, Hart RG et al. Pathophysiologic correlates of thromboembolism in nonvalvular atrial fibrillation: I. Reduced flow velocity in the left atrial appendage (The Stroke Prevention in Atrial Fibrillation [SPAF-III] study) J Am Soc Echocardiogr 1999; 12: 1080-7

55. Brodsky MA, Allen BJ, Capparelli EV et al. Factors determining maintenance of sinus rhythm after chronic atrial fibrillation with left atrial dilatation. Am J Cardiol 1989; 63: 1065-8

56. Henry WL, Morganroth J, Pearlman AS et al. Relation between echocardiographically determined left atrial size and atrial fibrillation. Circulation 1976; 53: 273-9

57. Flaker GC, Fletcher KA, Rothbart RM et al. Clinical and echocardiographic features of intermittent atrial fibrillation that predict recurrent atrial fibrillation. Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. Am J Cardiol 1995;76: 355-8

58. Dittrich HC, Erickson JS, Schneiderman T et al. Echocardiographic and clinical predictors for outcome of elective cardioversion of atrial fibrillation. Am J Cardiol 1989; 63: 193-7

59. Klein AL, Murray DR, Grimm RA. Role of transesophageal echocardiography-guided cardioversion of patients with atrial fibrillation J Am Coll Cardiol 2001; 37: 691-704

60. The Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography. Transesophageal echocardiographic correlates of thrombembolism in high risk patients with nonvalvular atrial fibrillation. Ann Int Med 1998; 128: 639-47
61. Verhorst PM, Kamp O, Welling RC et al. Transesophageal echocardiographic predictors for maintenance of sinus rhythm after electrical cardioversion of atrial fibrillation. Am J Cardiol 1997; 79: 1355-9
62. Omran H, Jung W, Schimpf R et al. Echocardiographic parameters for predicting maintenance of sinus rhythm after internal atrial defibrillation. Am J Cardiol 1998; 81: 1446-9
63. Singh S, Zoble RG, Yellen L et al.. Efficacy and safety of oral dofetilide in converting to and maintaining sinus rhythm in patients with chronic atrial fibrillation or atrial flutter: the symptomatic atrial fibrillation investigative research on dofetilide (SAFIRE-D) study. Circulation 2000; 102: 2385-90
64. Sahn DJ, DeMaria A, Kisslo J, Weyman A Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978; 58:1072-83
65. Daniel W, Nellensen U, Schröder et al. Left atrial spontanous echo contrast in mitral valve disease: an indicator for an increased thromboembolic risk. J Am Coll Cardiol 1988; 11: 1204-11
66. Yoshida K, Yoshikawa J, Yamaura Y et al. Assessment of mitral regurgitation by biplane transesophageal color Doppler flow mapping. Circulation 1990; 82: 1121-6.
67. Sigel B, Coelho JCU, Spigos DG et al. Ultrasonography of blood during stasis and coagulation. Invest Radiol 1981; 16: 71-6
68. de Kroon MG, Slager CJ, Gussenhoven WJ et al. Cyclic changes of blood echogenicity in high-frequency ultrasound. Ultrasound Med Biol 1991; 17: 723-8
69. Black IW, Hopkins AP, Lee LC et al. Left atrial spontaneous echo contrast: a clinical and echocardiographic analysis. J Am Coll Cardiol 1991; 18: 398-404
70. Fatkin D, Kelly R, Feneley M. Relations between left atrial appendage blood flow velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. J Am Coll Cardiol 1994; 23: 961-9

71. Gonzalez-Torrecilla E, Garcia-Fernandez MA, Perez-David E at al. Predictors of left atrial spontaneous echo contrast and thrombi in patients with mitral stenosis and atrial fibrillation. Am J Cardiol 2000; 86: 529-34
72. Blackshear JL, Pearce LA, Asinger RW et al. Mitral regurgitation associated with reduced thromboembolic events in high-risk patients with nonrheumatic atrial fibrillation. Stroke Prevention in Atrial Fibrillation Investigators. Am J Cardiol 1993; 72: 840-3
73. Hoit BD, Shao Y, Gabel MM. Influence of acutely altered loading conditions on left atrial appendage velocities. J Am Coll Cardiol 1994; 24: 1117-23
74. Chou HT, Wang TF. Left atrial appendage smoke-like echo in dilated cardiomyopathy: its clinical significance and relation to left atrial appendage function. Zhonghua Yi Xue Za Zhi 1993; 52: 222-8
75. Lin JM, Hsu KL, Hwang JJ et al. Influence of left ventricular diastole on left atrial appendage blood flow in patients with nonrheumatic atrial fibrillation. Cardiology 1997; 88: 563-8
76. Hinton RC, Kistler JP, Fallon JT et al.. Influence of etiology of atrial fibrillation on incidence of systemic embolism. Am J Cardiol 1977; 40: 509-13
77. Zabalgoitia M, Halperin JL, Pearce LA et al. Transesophageal echocardiographic correlates of clinical risk of thromboembolism in nonvalvular atrial fibrillation. Stroke Prevention in Atrial Fibrillation III Investigators. J Am Coll Cardiol 1998; 31: 1622-6
78. Siostrzonek P, Koppensteiner R, Gossinger H et al. Hemodynamic and hemorheologic determinants of left atrial spontaneous echo contrast and thrombus formation in patients with idiopathic dilated cardiomyopathy. Am Heart J 1993; 125 (2 Pt 1): 430-4
79. Li YH, Lai LP, Shyu KG et al. Clinical implications of left atrial appendage flow patterns in nonrheumatic atrial fibrillation. Chest 1994; 105: 748-52
80. Pálinkás A, Antonielli E, Picano E, Pizzuti A, Varga A, Nyúzó B, Alegret T, 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. Eur Heart J 2001; 22: 2201-8
81. Antonielli E, Pizzuti A, Pálinkás A et al. Clinical value of left atrial appendage flow for prediction of long-term sinus rhythm maintenance in patients with nonvalvular atrial fibrillation J Am Coll Cardiol 2002; 39: 1143-49

82. Davies MJ, Pomerance A Pathology of atrial fibrillation in man. Br Heart J 1972; 34: 520-5

83. Aime-Sempe C, Folliguet T, Rucker-Martin C. et al. Myocardial cell death in fibrillating and dilated human right atria. J Am Coll Cardiol 1999; 34: 1577-86

84. Pandozi C, Santini M. Update on atrial remodelling owing to rate; does atrial fibrillation always 'beget' atrial fibrillation? Eur Heart J 2001; 22: 541-53.

85. Douglas M, Zipes DP. Genesis of cardiac arrhythmias: Electrophysiological considerations. In Braunwald E, editor. Heart Disease. 6th edition. Philadelphia: WB Saunders, 2001. p 659-699

8. ACKNOWLEDGEMENT

First of all, I am deeply indebted to my advisor and supervisor **Dr. Eugenio Picano,** the Director of the Echocardiographic Laboratory of the Institute of Clinical Physiology, Pisa, Italy. His scientific curiosity, encouragement, and guidance throughout this work have been essential for this thesis.

I would like to express my sincere thanks to **Professor Miklós Csanády,** the previous Head of the 2nd Department of Medicine for his constant help and efforts in supporting my works and providing me with the facilities necessary to accomplish this thesis.

I am grateful to **Professor Tamás Forster,** the present head of the 2nd Department of Medicine for his guidance, encouragement, and untiring efforts in the supervision on these studies.

I express my sincere gratitude to **Dr. Albert Varga** for his tremendous support and suggestions relating to this thesis

I wish to thank to **Dr. Noemi Gruber** and **Dr. Bálint Nyúzó** for their professional help and assistance in providing the patients used in these investigations.

My thanks go to my **Colleagues** for the co-operative daily work.

Finally and above all I would like to thank to **my parents, my wife** and **my daughter** for their forbearance, and support throughout the duration of my work and my life.

9. ORIGINAL COMMUNICATIONS