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Clinical Value of Left Atrial Appendage Flow for Prediction of Long-Term Sinus Rhythm Maintenance in Patients With Nonvalvular Atrial Fibrillation

Emanuele Antonielli, MD,* Alfredo Pizzuti, MD,† Attila Pálinkás, MD,‡ Mattia Tanga, MD,* Noèmi Gruber, MD,‡ Claudio Michelassi, BSc,§ Albert Varga, MD,‡ Alessandro Bonzano, MD,† Nicola Gandolfo, MD,† László Halmai, MD,‡ Antonia Bassignana, MD,* Muhammad Babar Imran, MD,§ Fabrizio Delnevo, MD,† Miklós Csanády, MD,‡ Eugenio Picano, MD, PhD§

Savigliano, Torino and Pisa, Italy; and Szeged, Hungary

OBJECTIVES This study evaluated the role of various clinical and echocardiographic parameters, including the left atrial appendage (LAA) anterograde flow velocity, for prediction of the long-term preservation of sinus rhythm (SR) in patients with successful cardioversion (CV) of nonvalvular atrial fibrillation (AF).

BACKGROUND Echocardiographic parameters for assessing long-term SR maintenance after successful CV of nonvalvular AF are not accurately defined.

METHODS Clinical, transthoracic echocardiographic and transesophageal echocardiographic (TEE) data—measured in AF lasting >48 h—of 186 consecutive patients (116 men, mean age: 65 ± 9 years) with successful CV (electrical or pharmacologic) were analyzed for assessment of one-year maintenance of SR.

RESULTS At one-year follow-up, 91 of 186 (49%) patients who underwent successful CV continued to have SR. Mean LAA peak emptying flow velocity was higher in patients remaining in SR for one year than in those with AF relapse (41.7 ± 20.2 cm/s vs. 27.7 ± 17.0 cm/s; $p < 0.001$). On multivariate logistic regression analysis, only the mean LAA peak emptying velocity >40 cm/s ($p = 0.0001$; χ^2: 23.9, odds ratio [OR] = 5.2, confidence interval [CI] 95% = 2.7 to 10.1) and the use of preventive antiarrhythmic drug treatment ($p = 0.0398$; χ^2: 4.2; OR = 2.0, CI 95% = 1.0 to 3.8) predicted the continuous preservation of SR during one year, outperforming other univariate predictors such as absence of left atrial spontaneous echocardiographic contrast during TEE, the left atrial parasternal diameter <44 mm, left ventricular ejection fraction >46% and AF duration <1 week before CV. The negative and positive predictive values of the mean LAA peak emptying velocity >40 cm/s for assessing preservation of SR were 66% (CI 95% = 56.9 to 74.2) and 73% (CI 95% = 62.4 to 83.3), respectively.

CONCLUSIONS In TEE-guided management of nonvalvular AF, high LAA flow velocity identifies patients with greater likelihood to remain in SR for one year after successful CV. Low LAA velocity is of limited value in identifying patients who will relapse into AF. (J Am Coll Cardiol 2002;39:1443–9) © 2002 by the American College of Cardiology Foundation

Atrial fibrillation (AF), one of the most common rhythm abnormalities of the heart, is associated with substantial morbidity. Potential benefits of restoring and maintaining sinus rhythm (SR) include elimination of arrhythmic symptoms, improved rate control and hemodynamics and reduced susceptibility to thromboembolic complications. There are several proposed clinical and echocardiographic predictors of arrhythmia recurrence in patients with successful cardioversion (CV) of AF. Long-term maintenance of SR is more likely in patients with shorter AF duration, smaller left atrial (LA) size, preserved left ventricular (LV) function and absence of mitral valve disease (1,2). However, the predictive value of these parameters for assessment of long-term preservation of SR is far from the optimal (3,4). It would be important to stratify the patients to tailor their treatment (i.e., the CV and preventive antiarrhythmic drug treatment).

In recent years, transesophageal echocardiography (TEE) has emerged as an accepted tool to guide management of patients with AF by screening for left atrial appendage (LAA) thrombi and allowing earlier CV (5,6). Furthermore, the assessment of thrombembolic risk by measurement of LAA velocities during TEE in AF has become widely accepted (7–9). Recent studies have suggested that long-term SR maintenance may be predicted by evaluating LAA velocities before CV (10,11). However, this finding has been challenged by other reports (4), and the conclusions are weakened by the small sample size and heterogeneous patient population of the available studies. To clarify the long-term prognostic value of the LAA anterograde flow velocities, we evaluated, in a prospective, four-center, international study design, 193 consecutive patients with non-

From the *Divisione di Cardiologia, Ospedale SS. Annunziata, Savigliano, Italy; †Divisione di Cardiologia, Ospedale Mauriziano, Umberto I, Torino, Italy; ‡Second Department of Medicine and Cardiology Center, Albert Szent-Györgyi Medical Faculty, University of Sciences, Szeged, Hungary; and §National Research Council, Consiglio Nazionale delle Ricerche, Institute of Clinical Physiology, Pisa, Italy. Dr. Pálinkás was supported by the educational grant "Eötvös" of the Hungarian government.

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Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
CV = cardioversion
ECG = electrocardiogram
LA = left atrial
LAA = left atrial appendage
LV = left ventricular
OR = odds ratio
ROC = receiver-operating characteristic
SR = sinus rhythm
TEE = transesophageal echocardiography/echocardiographic
TTE = transthoracic echocardiography/echocardiographic

valvular AF lasting <1 year in whom the SR was successfully restored by either electric or pharmacologic CV.

METHODS

Study group. We prospectively studied 193 patients with successful CV (electrical [n = 147] or pharmacologic [n = 46]) of nonvalvular AF lasting >48 h and < 1 year. Studies were done at 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 January 1998 and February 2000. Clinical data including the duration of AF were read from the patient's record and obtained by an interview with the patient, their attending physician and their home practitioner. Duration of AF was determined by careful examination of the patient's medical record, by questioning the patient and by reviewing all previous electrocardiograms (ECGs) available. Exclusion criteria were: duration of AF of >1 year, unknown duration of AF, presence of prosthetic valve, pericarditis, pericardial effusion, acute myocarditis, acute myocardial infarction, chronic obstructive lung disease, pulmonary embolism, congenital heart disease, recent heart surgery, latent or manifest hyperthyroidism, permanent pacemaker treatment, sick sinus syndrome, presence of atrial thrombus found by TEE and organic valvular heart disease (aortic stenosis and regurgitation, mitral and tricuspidal stenosis, mitral valve insufficiency of valvular origin). Mitral valve regurgitation due to mitral annular dilation was not included in the exclusion criteria. Of the 193 patients studied, 80 (41%) had a history of a previous episode of AF. All the enrolled patients underwent a one-year follow-up program for assessment of SR maintenance.

Echocardiography. Transthoracic echocardiography (TTE) and TEE were performed 24 h before the CV attempt with commercially available ultrasonographic systems (Hewlett-Packard Sonos 2500 and 5500, Acuson XP125 and Sequoia; ATL HDI 9, Andover, Massachusetts). The TEE was performed with bi- or multiplane probes with a 5- or 7-MHz transducer. The following TTE measurements were taken by parasternal long-axis view from two-dimensional targeted M-mode tracings according to the recommendations of the American Society of Echocardiography (12): LA diameter, LV end-diastolic and end-systolic diameter, LV septal and posterior end-diastolic wall thickness, ejection fraction (according to the Quinones formula). The two-dimensional biplane area-length method was used for ejection fraction calculation in patients with previous infarction. All TTE indices were measured off-line, using the integrated software of the echocardiographic equipment, and were calculated as the average of five consecutive cardiac cycles.

Following the TTE and after a 6-h fasting period, all patients underwent TEE examination. During the TEE, images were analyzed on-line by an experienced observer for the presence of intracardiac thrombus. To view the maximal size and to obtain the highest resolution of the LAA, the most appropriate section was always 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 (13). Patients demonstrating intracardiac thrombus during TEE were excluded from the study.

Videotape and/or digitally stored images were subsequently analyzed off-line for the presence of LA spontaneous echocardiographic contrast and mitral valve regurgitation grade; this was done by two independent observers who were unaware of the patient's history. Spontaneous echocardiographic contrast was defined as an intracavitary swirling smokelike echo within the left atrium or LAA (14). 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 (15). Differences between observers were resolved by consensus; if observers could not agree, a third and more experienced observer reviewed the study and his judgment was binding. The LAA velocity profiles were obtained by pulsed-wave Doppler interrogation 1 cm within the orifice of the LAA and analyzed off-line from videotape or digitally stored images by a single observer (A. P.), who was unaware of the patient's history. The LAA peak emptying velocities were averaged with each RR-interval over a minimum of five consecutive cardiac cycles (16,17).

Follow-up. Patients were followed-up *regularly* every three months up to one year. Serial ECGs were recorded at each visit to document the maintenance of SR or recurrence of AF. In addition, referring physicians and patients were told to confirm suspected recurrences of AF by a 12-lead ECG. Initiation of preventive antiarrhythmic drug treatment during the follow-up was decided by the patient's referring physician on the basis of integrated clinical assessment, which included access to echocardiographic data. According

Table 1. Clinical and Echocardiographic Variables in Patients With Successful Cardioversion of Nonvalvular AF and One-Year Follow-Up (n = 186)

	All Patients (n = 186)	SR Maintenance (n = 91)	AF relapse (n = 95)	p Value
Clinical variables				
Mean age (yrs)	65.1 ± 9.9	64.6 ± 10.7	65.4 ± 9.1	NS
Male gender (%)	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	< 0.01
Antiarrhythmic drug use during follow-up	66 (35%)	39 (43%)	27 (28%)	< 0.05
Transthoracic echocardiographic variables				
LA diameter (mm)	44.2 ± 6.2	43.0 ± 5.9	45.4 ± 6.3	< 0.01
LV ejection fraction (%)	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 (g)	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%)	< 0.05
Degree of mitral valve regurgitation (%)				
Absent or mild	155 (83%)	81 (89%)	74 (78%)	NS
Medium	23 (12%)	6 (7%)	17 (18%)	
Severe	8 (4%)	4 (4%)	4 (4%)	
Mean LAA peak anterograde flow (cm/s)	34.6 ± 19.9	41.7 ± 20.3	27.7 ± 17.0	< 0.001

AF = atrial fibrillation; EDD = end-diastolic diameter; LA = left atrial; LAA = left atrial appendage; LV = left ventricular; SEC = spontaneous echo cardiographic contrast; SR = sinus rhythm.

to this, 72 of the 193 (37%) successfully converted patients were treated by preventive antiarrhythmic drugs during the follow-up period. Drug therapy for arrhythmia prevention was flecainide (n = 9), amiodarone (n = 19), sotalol (n = 2) and propafenone (n = 42).

Statistical analysis. All data are expressed as means ± SD. In the intergroup comparison of clinical and echocardiographic continuous variables between patients with SR preservation compared to AF relapse, the statistical significance was assessed by the unpaired Student *t* test. Comparison of proportions was performed using chi-square analysis or the Fisher exact test as appropriate. Receiver-operating characteristic (ROC) analysis was used to determine optimal cutoff values of continuous variables for prediction of one-year SR 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 cutoff level of the model varies. The best cutoff 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 LAA emptying velocity to predict the one-year SR 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 one-year SR maintenance. The univariate and multivariate odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) are given. All tests were two-sided, and a p value <0.05 was considered statistically significant. All analyses were performed by an SPSS 9.0 software package (SPSS Inc., Chicago, Illinois).

RESULTS

Follow-up. During the follow-up period, four patients died (two from noncardiac and two from cardiac causes), and three patients were lost for other reasons. The one-year follow-up was finally completed in 186 patients (94%), with successful CV of nonvalvular AF. At the end of the one-year period, 91 (49%) patients remained in SR and AF recurred in 95 (51%) patients. Patients' demographic and clinical characteristics are shown in Table 1.

Clinical parameters and maintenance of SR. There were no differences in age, gender and underlying diseases between patients with and without SR maintenance (Table 1). Patients who continued to have SR for one year had shorter AF duration before CV compared to those with AF relapse. On the basis of ROC analysis (Fig. 1), an AF duration of one week (present in 71 patients, 38%) provided the best separation between patients with and without SR maintenance (shorter in patients with SR preservation). Antiarrhythmic drug use was more frequent in patients who continued to have SR at one-year follow-up compared to those with AF relapse (Table 1).

Echocardiographic parameters and maintenance of SR. On the basis of TTE parameters, patients without AF relapse had lower LA parasternal diameter. Left ventricular ejection fraction tended to be higher in those patients who continued to have SR for one year, whereas LV wall thickness and end-diastolic diameter were not related to the long-term maintenance of SR (Table 1). On the basis of the ROC analysis (Fig. 1), cutoff values of an LA diameter <44 mm and an LV ejection fraction $>46\%$ provided the

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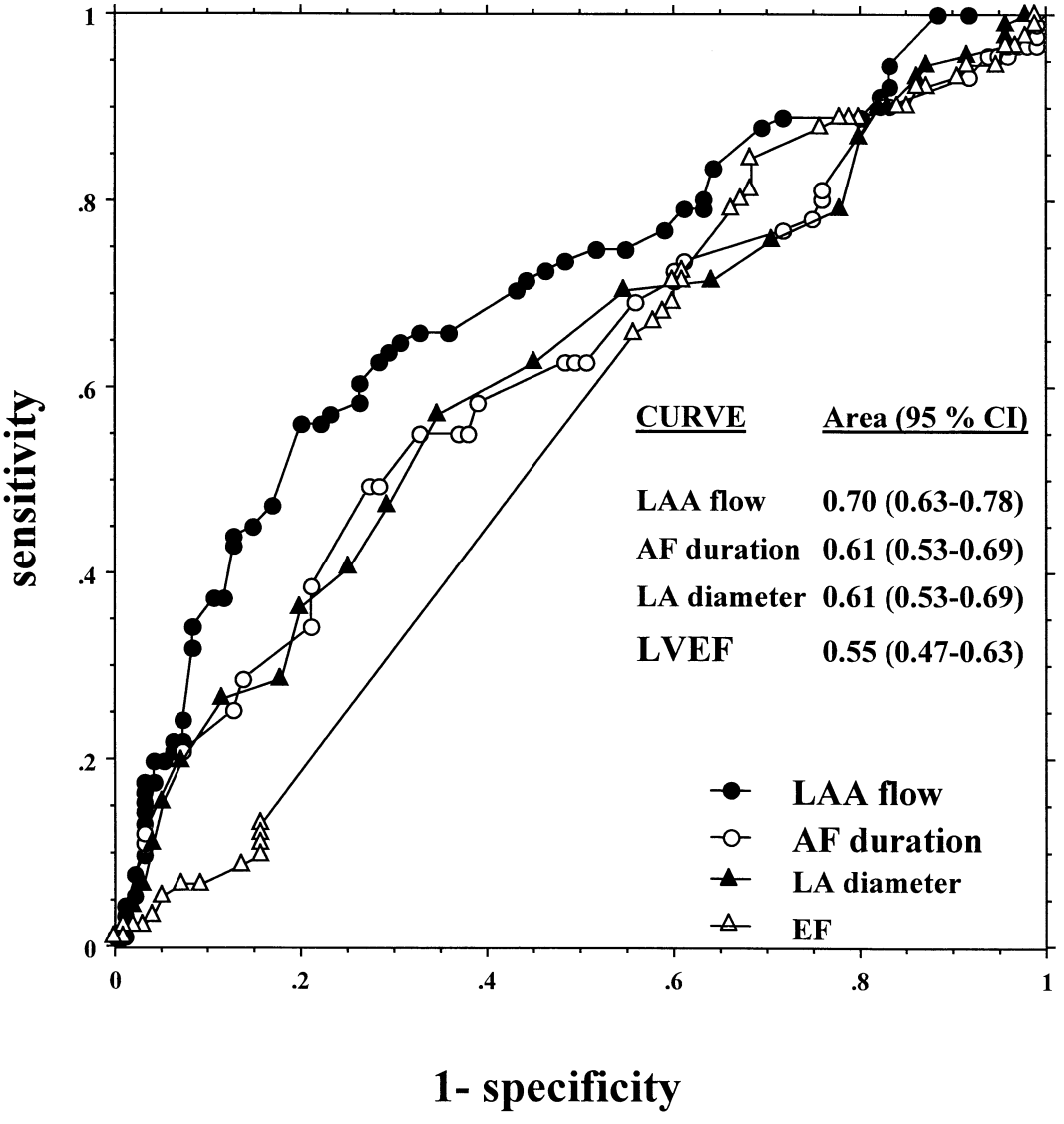

Figure 1. Receiver-operating curves of left atrial appendage (LAA) flow, atrial fibrillation (AF) duration, left atrial (LA) diameter and left ventricular ejection fraction (LVEF) for prediction of one-year maintenance of sinus rhythm. The area under the curve is given. CI = confidence interval.

best separation between patients with and without one-year SR maintenance. According to these cutoff points, 85 (46%) patients had an LA diameter of <44 mm and 142 (76%) patients had an ejection fraction of >46%. Transesophageal parameters could separate the two groups on the basis of the mean LAA peak anterograde flow (higher in patients with SR maintenance) and presence of LA spontaneous echocardiographic contrast (less frequent in patients with SR maintenance) whereas no difference could be observed when the degree of mitral valve regurgitation was considered (Table 1). According to the ROC analysis of derived mean LAA anterograde flow velocity cutoff of 40 cm/s, 70 patients (38%) had a mean LAA peak anterograde velocity higher than 40 cm/s. Typical examples of high and low velocity profiles of the LAA in AF, obtained by pulsed Doppler during TEE in patients with and without one-year maintenance of SR, are shown in Figures 2 and 3, respectively.

Prediction of long-term maintenance of SR by integrated clinical and echocardiographic variables. Univariate logistic regression analysis revealed that mean LAA peak anterograde flow velocity >40 cm/s was the strongest predictor of one-year SR maintenance followed by AF duration <1 week before CV, LA diameter <44 mm, LV ejection fraction >46%, absence of LA spontaneous echocardiographic contrast on TEE and use of preventive antiarrhythmic drug during follow-up. Using multivariate logistic regression analysis, only two parameters proved to be independent predictors of one-year preservation of SR: the mean LAA peak anterograde velocity >40 cm/s (OR = 5.2, CI 95% = 2.7 to 10.1; χ^2 23.9, $p < 0.0001$) and the use of preventive antiarrhythmic drug during follow-up (OR = 2.0, CI 95% = 1.0 to 3.8; χ^2 4.2, $p < 0.05$) (Table 2). The diagnostic values of the different clinical and echocardiographic parameters are presented in Table 3.

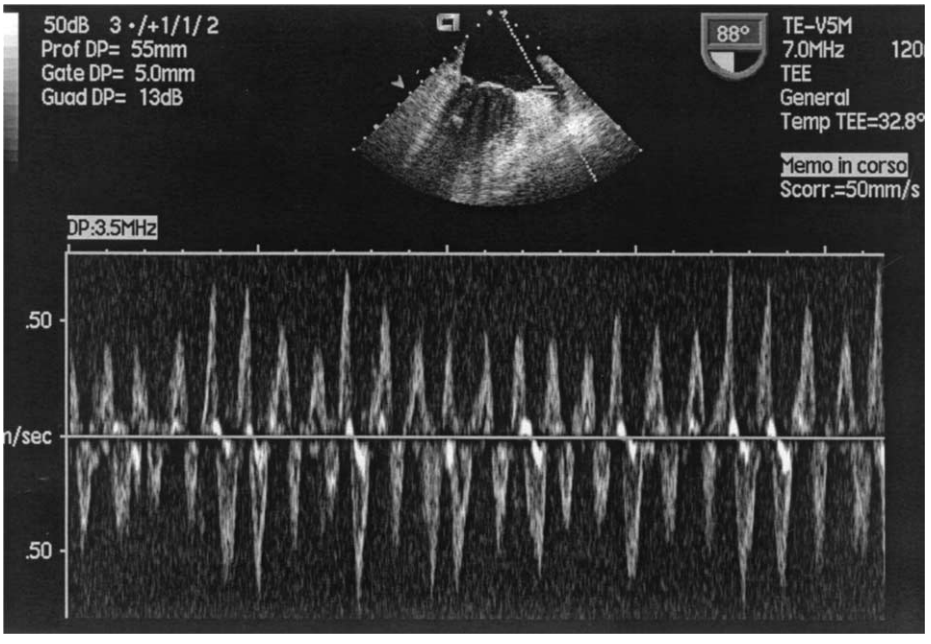

Figure 2. Pulsed Doppler tracing of the left atrial appendage (LAA) obtained by transesophageal echocardiography in atrial fibrillation showing high peak emptying flow velocity signals in a patient who preserved the sinus rhythm for one year. The mean LAA flow peak anterograde velocity was 52 cm/s.

DISCUSSION

Measurement of the LAA emptying velocity profile by TEE before CV in patients with nonvalvular AF provides important information for prediction of long-term SR maintenance.

Comparison with previous studies. Previous studies have already demonstrated that the LAA velocity is related to the LA size (18,19) and the duration of AF (8,16), all of which are predictors of long-term SR maintenance. However, conflicting and scarce data exist on the usefulness of LAA flow to predict long-term preservation of SR (4,10,11). 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 patients, whereas previous studies enrolled 38 to 75 patients); and 3) the strict

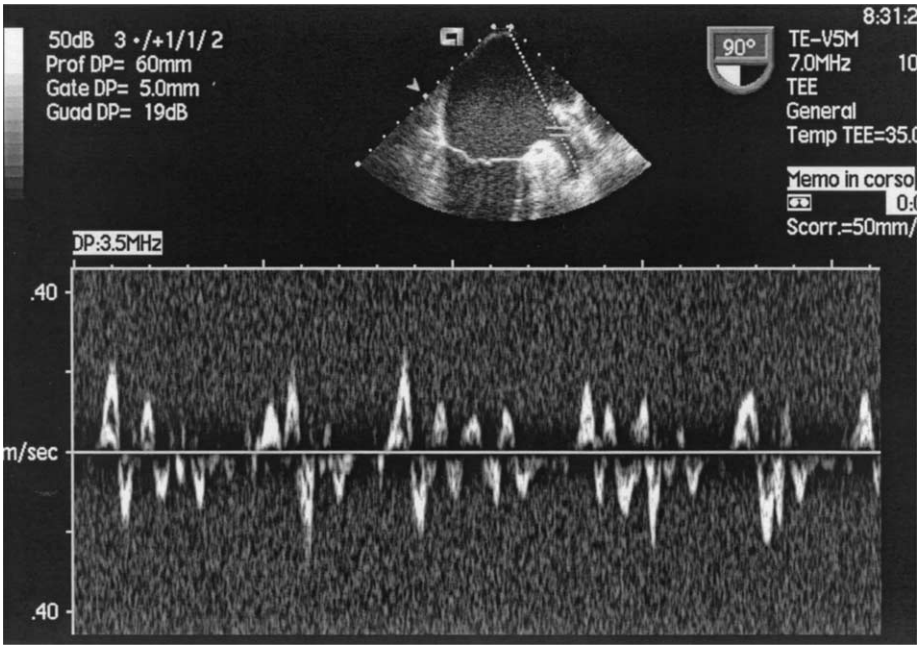

Figure 3. Pulsed Doppler tracing of the left atrial appendage (LAA) obtained by transesophageal echocardiography in atrial fibrillation (AF) showing low peak emptying flow velocity signals in a patient with AF relapse during the follow-up. The mean LAA peak anterograde velocity was 18 cm/s.

Table 2. Univariate and Multivariate Predictors of One-Year Maintenance of SR

	p Value	Chi-Square	OR (95% CI)
Univariate predictors			
Preventive antiarrhythmic drug use during follow-up	<0.05	4.2	1.9 (1.0–3.5)
Absence of left atrial SEC during TEE	<0.05	6.3	2.1 (1.2–3.8)
LV ejection fraction >46%	<0.05	6.5	2.5 (1.2–5.2)
LA diameter <44 mm	<0.01	9.3	2.5 (1.4–4.5)
AF duration <1 week	<0.01	9.4	2.6 (1.4–4.8)
Mean peak anterograde LAA flow velocity >40 cm/s	<0.0001	24	5.1 (2.7–9.8)
Multivariate predictors			
Preventive antiarrhythmic drug use during follow-up	<0.05	4.2	2.0 (1.0–3.8)
Mean peak anterograde LAA flow velocity >40 cm/s	<0.0001	23.9	5.2 (2.7–10.1)

CI = confidence interval; OR = odds ratio; TEE = transesophageal echocardiography; other abbreviations as in Table 1.

selection criteria, which allowed us to exclude patients with valvular heart disease. The relatively large sample size enabled us to demonstrate that mean LAA peak emptying velocity has independent and additive prognostic value over other echocardiographic and clinical predictors, such as LA diameter, LA spontaneous echocardiographic contrast, ejection fraction and duration of AF whose prognostic value is totally eclipsed by LAA flow.

The possible link between LAA velocity and prediction of SR maintenance. In chronic nonvalvular AF, a time-related structural and histologic remodeling develops both in the LAA and in the left atrium (chamber dilation, loss of myofibrils, fragmentation of sarcoplasmatic reticulum and marked collagen formation) (20–25). These unfavorable degenerative changes may cause inhomogeneity of atrial repolarization, nonuniform anisotropy or slowing of conduction, and they are important components in the pathogenesis of AF (25,26). Loss of contractile elements of LAA may result in its reduced mechanical function, which could be expressed in low LAA flow velocities profile. However, according to our knowledge, there is no published data in the literature studying the direct link between LAA flow and histopathologic changes in the appendage in patients with nonvalvular AF.

Study limitations. The study population may appear heterogeneous with regard to the clinical parameters such as duration of AF, mode of CV, type of preventive antiarrhythmic therapy, but it corresponds to the variable clinical situations encountered in hospital practice. Therefore, the conclusions of this study can be reasonably applied to the general population of patients with nonvalvular AF of <1-year duration. It is important to note that the duration of follow-up influences the rate of preserved SR to some extent and may, therefore, affect the relationship between clinical parameters and outcome. Consequently, our conclusions are not necessarily valid for a longer follow-up period. Selection of patients for antiarrhythmic drug treatment may have introduced a potential bias that might have influenced the results to some extent. Nonetheless, the postcardioversion treatment was not randomized in our study the antiarrhythmic drug use were equally distributed in patients with high and low LAA flow.

Short, asymptomatic episodes of AF between the regular follow-up visits may have been missed in some patients, and this potential misclassification could have resulted in an underestimation of some difference.

The LAA areas were not assessed in our study; however, these measurements are inherently prone to substantial interobserver variability during both data registration and off-line analysis (8,27), possibly due to the complex three-dimensional anatomy of the LAA. In contrast, assessment of LAA function by Doppler echocardiography during TEE could be easily performed and it was reproducible and clinically highly relevant (7–9). The negative predictive value of LAA emptying flow velocity >40 cm/s for prediction of long-term SR preservation was relatively low, with a value of 66%. Thus, we do not know accurately whether a patient with low LAA flow velocity will relapse into AF within one year.

Conclusions. Our study showed that high LAA flow identifies those patients who will remain in SR for one year. Conversely, low LAA velocity is of limited value in identifying patients who will relapse into AF. In patients with nonvalvular AF, the same TEE-derived parameter often

Table 3. Diagnostic Value of Clinical and Echocardiographic Parameters for Assessment of Long-Term Maintenance of SR

	SENS (%)	SPEC (%)	PPV (%)	NPV (%)	ACC (%)
LAA peak emptying flow >40 cm/s	56	80	73	66	68
LA diameter <44 mm	57	65	61	61	61
AF duration <1 week	49	72	63	60	61
Absence of LA SEC during TEE	63	56	58	61	59
LVEF >46%	85	32	54	68	58

ACC = accuracy; LVEF = left ventricular ejection fraction; NPV = negative predictive value; PPV = positive predictive value; SENS = sensitivity; SPEC = specificity; other abbreviations as in Table 2.

used to assess the embolic risk and to predict the chances of acute success of CV (28) (i.e., LAA flow) can be of use in predicting one-year outcome of successful CV.

Reprint requests and correspondence: Dr. Eugenio Picano, Institute of Clinical Physiology, Pisa, CNR, Via Moruzzi, 1, 56100 Pisa, Italy. E-mail: picano@ifc.cnr.it.

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