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Atrial fibrillation as a prognostic factor in patients with systolic heart failure

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Abstract

Background: *Atrial fibrillation (AF) decreases left ventricular stroke volume, impaires the mechanical function of heart valves, and disturbes neurohumoral activity of the miocardium. This study evaluated the influence of AF on clinical presentation and long-term follow-up of the patients with systolic heart failure.*

Methods: *A retrospective analysis of the data on clinical presentation of 152 patients (38 women and 114 men) with systolic heart failure (EF < 40%) was performed. The following parameters were compared between patients with and without AF: heart rate and presence of LBBB, several echocardiographic parameters (EF, LVEDV, size of LA, LVEDd, LVESd), oxygen consumption per minute, and frequency of end-point's (death, stroke, rehospitalization, CABG) during mean 936-day follow-up.*

Results: *The 53 (35%) AF patients in comparison with 99 non-AF were characterized by: lower exercise performance (VO_2 max = 10.9* vs. *17.2 ml/kg/min), greater diameter of the left atrium (49.9* vs. *45.9 mm) and decreased end-diastolic volume (LVEDV = 159.5* vs. *183.7 ml), less frequent occurrence of LBBB (7.5%* vs. *13.0%), higher overall mortality (28.3%* vs. *17.1%), and more frequent rehospitalizations (15%* vs. *8%). In patients with persistent AF (40%) with HR < 75/min the mortality was 29% and was statistically significantly lower than in patients with HR > 75/min in whom it was 54%.*

Conclusions: *Atrial fibrillation in patients with systolic heart failure is a disadvantageous, but not independent risk factor. In patients with persistent atrial fibrillation the control of heart rate < 75/min was associated with significant decrease in mortality.* (Folia Cardiol. 2006; 13: 503–510)

Key words: atrial fibrillation, systolic heart failure, ejection fraction, exercise efficiency

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Introduction

Atrial fibrillation (AF) is a common form of arrhythmia. It is found in over 5% of people above 69 years of age and in 10% of the population above 80 years of age [1]. It is usually associated with the presence of organic heart disease, not uncommonly being one of the complications of arterial hypertension. Among other deseases where atrial fibrillation comes very often for is rheumatic disease, valvular heart disease, myocardial infarction, hyperthyreosis, pericarditis and myocarditis, alcohol intoxication, dyselectrolitaemia, and ecclampsia. The AF is observed in 10% of patients with systolic heart failure (SHF) with NYHA class II and in 50% of class IV patients [2].

The assessment of the clinical significance of atrial fibrillation in patients with systolic was the subject of prior research. Both in healthy and in

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damaged myocardium the function of left ventricle was deteriorated in patients with diagnosed AF [3]. It is a result of loss of synchronization of the contraction of the myocardium, worsening of contractile function of the atria, disturbance in excretion of neurohormonal factors and dysfunction of the valves. The loss of synchronic mechanical function of the atria results in a decrease of stroke volume of the left ventricle even up to 30% [4], and an inadequate response of the ventricles may result in development of cardiomyopathy (so called tachyarrhythmia-induced cardiomyopathy) [5]. It results in decreased parameters of exercise performance in patients with atrial fibrillation and systolic heart failure comparing to patients with SHF and sinus rhythm [6]. This is of vital importance for the progression of functional failure of the myocardium, what may result in worse prognosis of the patients with systolic heart failure. However, there are discrepancies in available literature regarding the influence of atrial fibrillation on the long-term follow-up (including mortality) in patients with diagnosed SHF [7].

The aim of this study was to compare the clinical presentation of patients with systolic heart failure and concomitant paroxysmal or persistent atrial fibrillation with patients with systolic heart failure and sinus rhythm, considering especially:

— echocardiographic evaluation of left ventricular parameters (EF, LVEDV, LVEDd, LVESd) and maximal oxygen consumption per minute (VO_2 max) in spiroergometric test;
— the frequency of thromboembolic events;
— the significance of the control of heart rhythm < 75/min in therapy of persistent AF in patients with systolic heart failure;
— the overall long-term prognosis.

Methods

Study population

There were 152 patients included in this study (38 females and 114 males), aged 31 to 98 (mean age was 65 years) hospitalized in the Department of Coronary Heart Disease CMUJ between June 1997 and May 2002 with diagnosed systolic heart failure (EF < 40%). The cases of left ventricular failure in course of: acute myocardial infarction, acute metabolic and endocrinologic disorders and patients with diagnosed valvular heart disease were excluded from the study.

From the qualified patients two groups were formed:

— group I — patients with persistent or paroxysmal atrial fibrillation confirmed by electrocardiography — 53 patients: 14 women (aged 59 to 88) and 39 men (aged 56 to 98); mean age was 69 years;
— group II — patients without history of atrial fibrillation — 99 patients: 24 women (aged 44 to 86) and 75 men (aged 31 to 85); mean age was 62 years.

In group I, paroxysmal (self-limiting) or persistent atrial fibrillation was diagnosed. The diagnosis and classification was based on ACC/AHA/ESC guidelines from 2001 [8]. Initially, in every patient the following parameters were analysed.

Clinical, ECG, and imaging variables

The following tests' results and clinical data were obtained in studied patients:

1. Electrocardiography at rest, including:
— presence of left bundle branch block (LBBB), possibly 2-bundle block;
— rate of the ventricles (when persistent AF was present).
2. Echocardiography, especially including:
— left ventricular ejection fraction (EF, %);
— end-diastolic (LVEDd) and end-systolic (LVESd) diameter of the left ventricle [mm];
— end-diastolic volume of the left ventricle (LVEDV) [ml].

All the measurements were performed using the same echocardiographic equipment (ACUSON).

3. Excercise performance was measured through maximal minute oxygen consumption in spiroergometric test (VO_2 max in ml/kg/min) — calculated according to Naughton protocol, restricted by occurrence of clinical signs or lack of increase in oxygen consumption.
4. Presence of arterial hypertension.

Clinical endpoints

Information on the frequency of following procedures or events was acquired in both groups:

— implantation of a pacemaker.
— performing coronary arterial by-pass grafting (CABG) or heart transplantation;
— re-hospitalization for cardiac causes during period of observation;
— occurrence of cerebral embolism in course of disease;
— death (main end-point).

The period of observation was 342 to 2315 days; mean period of observation was 936 days.

The analysis of the data referring to the follow-up period was performed based on the information from a survey conducted among the patients and their families. Patients consented to participate in the study.

Statistical analysis

In statistical analysis the following tests were used: Chi Square Pearson test, Chi Square Yates test, as shown above with Fisher correction for small groups, T-Student test and U-Mann-Whitney test. The association between studied variables and mortality was evaluated using univariate and multivariate logistic regression.

Results

Clinical characteristics and ECG and ECHO findings

Atrial fibrillation in the examined patients (either paroxysmal or persistent) occurred in 53 subjects (35%). It was observed most often in patients with NYHA class IV patients (58%). In class II NYHA patients AF was found in 33% of patients, and in class III patients in 29% (Table 1).

In group of patients with AF, 18 patients (34%) had NYHA class II, class III was found in 22 patients (41.5%), class IV in 13 patients (24.5%). In group II (without AF), NYHA class II was found in 34 patients (34.3%), class III in 54 patients (54.5%), and 11 patients (11.1%) class IV. The causes of heart failure were similar in both groups, however in the AF group there were more cases of unknown or questionable etiology (9.4% *vs.* 3.1%). Age and percentage of men and women in both groups was not different between those groups (Table 2).

Table 1. Prevalence of atrial fibrillation in relationship to the NYHA class.

NYHA class	Number of patients	Occurrence of atrial fibrillation
II	52	17 (33%)
III	76	22 (29%)
IV	24	14 (58%)

The SHF patients with AF had clinical signs of advanced heart failure (NYHA IV) more often when compared to patients with sinus rhythm (24.5% *vs.* 11.1%). The AF patients did not differ from patients with sinus rhythm regarding frequency of hypertension (66% *vs.* 55%, respectively).

In the analysis of left ventricular function, the EF in the AF patients (EF = 33.9%) was lower than

Table 2. Baseline characteristics of patients with (group I) and without (group II) atrial fibrillation (AF).

Parameter	Group I (SHF with AF)	Group II (SHF without AF)	p
Number of patients	53 (35%)	99 (65.1%)	
Mean age (SD) years	69 (11.2)	62 (11.5)	NS
Number of women years	14 (26.4%)	24 (24.2%)	NS
Mean age of women (SD) years	71.86 (9.7)	63.25 (9.1)	NS
Number of men	39 (73.6%)	75 (75.7%)	NS
Mean age of men (SD) years	67.91 (11.7)	61.73 (12.2)	NS
NYHA class:			
II	18 (34%)	34 (34.3%)	NS
III	22 (41.5%)	54 (54.5%)	NS
IV	13 (24.5%)	11 (11.1%)	< 0.05
Heart failure etiology:			
ishaemic cardiomyopathy	27 (51%)	54 (54.4%)	NS
hypertrophic cardiomyopathy	21 (39.6%)	42 (42.4%)	NS
other*	5 (9.4%)	3 (3.1%)	< 0.05
Arterial hypertension	35 (66%)	54 (55%)	NS
VO_2 max [ml/kg/min]	10.9	17.2	< 0.05
Ejection fraction (%)	33.9	37.3	NS
End-diastolic diameter of the left ventricle [mm]	56.9	61.0	NS
End-systolic diameter of the left ventricle [mm]	42.1	46.9	NS
End-diastolic volume of the left ventricle [ml]	159.5	183.7	< 0.05
Left atrium diameter [ml]	49.9	45.9	< 0.05
Presence of the left bundle branch block	4 (7.5%)	13 (13%)	< 0.05

*Including etiologically unconfirmed, cardiomyopathies of questionable etiology; VO_2 max — maximal oxygen consumption per minute in spiroergometric test; SHF — systolic heart failure

Table 3. Endpoints during long-term follow up in the two groups.

Parameter	Group I (SHF with AF)	Group II (SHF without AF)	p
Pacemaker implantation	10 (18.8%)	14 (14%)	NS
Coronary arterial by-pass grafting	3 (5.6%)	9 (9%)	NS
Arterial hypertension + stroke	4 (11.5%)	6 (11.1%)	NS
Stroke	4 (7.5%)	8 (8%)	NS
Cardiac rehospitalizations	8 (15%)	8 (8%)	< 0.05
Mortality	15 (28.3%)	17 (17.1%)	< 0.05

SHF — systolic heart failure; AF — atrial fibrillation

the EF in non-AF patients (EF = 37.3%). Despite the marked tendency, those differences were statistically non-significant. There were no statistically significant differences in LVEDd (56.9 mm in AF patients *vs.* 61.0 mm in non-AF patients) and in LVESd (42.1 mm *vs.* 46.9 mm, respectively). However, when comparing to patients without AF, the diameter of the left atrium was greater (49.9 mm *vs.* 45.9 mm) and LVEDV was lower (159.5 ml *vs.* 183.7 ml) the AF patients.

In the spiroergometric test of the exercise efficacy of the myocardium, the oxygen consumption in AF patients was on the average 10.9 ml/kg/min, and was statistically significantly lower than the value reached in patients without history of AF episodes (17.2 ml/kg/min). In the ECG, in 7.5% (n = 4) of patients with AF the LBBB was found. In the non-AF patients, this conduction disorder occurred in 13% (n = 13) of patients ($p < 0.05$).

Clinical endpoints

The analysis of end-points (Table 3) showed that the patients with AF required more frequent hospitalizations for cardiac causes (in 15% of patients) when compared to patients without AF (8%). There were no significant differences stated between the AF and non-AF patients when considering the frequency of CABG, 5.6% *vs.* 9%, respectively; the frequency of stroke (with various neurological consequences): 7.5% *vs.* 8%; the number of pacemaker implantations: 18.8% *vs.* 14%.

In patients with concurrent AF and hypertension, a stroke episode occurred in 4 patients (11.5%). In patients with sinus rhythm and without hypertension same complications in the evaluated period occurred in 2 (4.5%) patients ($p < 0.05$).

The mortality in the AF group was 28.3% (n = 15). It was statistically significantly higher than mortality in the same period in patients with sinus rhythm (17.1%; n = 17).

Type of atrial fibrillation: persistent *vs.* paroxysmal

Among group I patients, clinically persistent atrial fibrillation was identified in 21 patients (39.6%), aged from 56 to 98 (4 women, 17 men; mean age 64 years). In analysis of the level of systolic insufficiency of those patients we found, that 3 patients (14.3%) had clinical signs of NYHA class II, 13 patients (62%) — NYHA class III, and 5 subjects (23.7%) — NYHA class IV. Paroxysmal atrial fibrillation occurred in 32 patients (10 women, 22 men) aged 54 to 84 (mean age 72 years). In NYHA class II there were 16 patients (50%), in 8 in each in both class III and IV groups (25%). A detailed analysis is shown in Table 4.

Patients with persistent AF had higher ejection fraction (EF = 38.4%) in echocardiographic evaluation than patients with paroxysmal AF (EF = 36.6%). However, this difference was statistically non-significant. Also in such parameters as LVEDd (57.7 mm in the group with persistent AF *vs.* 56.9 mm for patients with paroxysmal AF), LVESd (43.2 mm *vs.* 41.1 mm, respectively) and LVEDV (162.8 ml *vs.* 155.9 ml) there were no significant differences. However, in patients with persistent AF the left atrial diameter was significantly greater (54.3 mm) in comparison with its dimensions in patients with paroxysmal AF (45.7 mm).

The patients with persistent AF were also characterized by a lower exercise performance (VO_2 max = 8.2 ml/kg/min) when compared to patients with paroxysmal AF (VO_2 max = 11.8 ml/kg/min; $p < 0.05$).

In the analysed ECG, beside the records of AF there was LBBB found in 2 (9.5%) patients with persistent and in 2 (6.25%) patients with paroxysmal AF (p = non-significant).

The pacemaker implantation procedure was performed in 5 (23.8%) of patients with persistent

Table 4. Comparison of patients with persistent and paroxysmal atrial fibrillation (AF) — basic characteristic

Parameter	Persistent AF	Paroxysmal AF	p
Number of patients	21 (39.6%)	32 (60.4%)	
Number of women	4 (19%)	10 (31%)	< 0.05
Number of men	17 (81%)	22 (69%)	< 0.05
Mean age (SD) years	64.47 (12.6)	72.31 (9.0)	NS
Mean age of women (SD) years	69.5 (7.1)	72.8 (10.8)	NS
Mean age of men (SD) years	63.29 (13.5)	72.8 (8.3)	NS
NYHA class:			
II	3 (14.3%)	16 (50%)	< 0.05
III	13 (62%)	8 (25%)	< 0.05
IV	5 (23.7%)	8 (25%)	NS
VO_2 max [ml/kg/min]	8.2	11.8	< 0.05
Ejection fraction (%)	38.4	36.6	NS
Diastolic diameter of left ventricular [mm]	57.7	56.9	NS
Systolic diameter of left ventricular [mm]	43.2	41.1	NS
End-diastolic volume of the left ventricle [ml]	162.8	155.9	NS
Left atrium diameter [mm]	54.3	45.7	< 0.05
Presence of the left bundle branch block	2 (9.5%)	2 (6.25%)	NS
Arterial hypertension	14 (66.6%)	21 (65.6%)	NS

AF and in 5 (15.6%) with paroxysmal AF. During the period of observation, the CABG was performed in 2 (9.5%) patients with persistent and in 1 (3.1%) patient with paroxysmal atrial fibrillation. In both cases, those differences were statistically significant.

Two patients with persistent AF (9.5%) underwent a stroke; in the same period of time this complication occurred in two patients (6.3%) with paroxysmal AF. Every patient who had a stroke, had also arterial hypertension. Those differences were statistically insignificant, however we can speak of a tendency to higher occurrence of strokes in patients with persistent AF.

During the period of observation, three (14.3%) patients with persistent AF and five patients (15.6%) with paroxysmal AF were rehospitalised (at least once) for cardiac causes. The frequency of those incidents did not distinguish statistically both subgroups.

During the period of observation, there was a significantly higher mortality of patients with persistent AF: 42.9% (n = 9) comparing to patients with paroxysmal AF: 18.8% (n = 6).

A significantly higher mortality in patients with persistent atrial fibrillation (54%) was observed when heart rate was > 75/min. In patients with persistent AF, in whom the heart rate in ECG was < 75/min, the mortality was 28.6% (Table 5).

In the performed univariate and multivariate analyses only age > 60 years, ejection fraction of the left ventricle below 30% and hypertension were independent prognostic risk factors for predicting mortality in the examined group of patients with systolic heart failure. Atrial fibrillation did not reach significance in neither univariate nor multivariate model (Table 6, 7).

Discussion

The risk of cardiac arrhythmias, including atrial fibrillation, increases with age. This arrhythmia may result in a decrease of hemodynamic parameters of heart function by impairing the filling phase of the ventricles, valvular function, as well as secretion of mediators that disturb the neurohormonal stimulation of the myocardium [9–12].

Older age influences significantly an impairment of heart function as a result of various changes undergoing in the myocardiocytes, what is manifested clinically by features of it's insufficiency. It has been found in the present study that in NYHA class IV patients atrial fibrillation occurred in more than half of the patients (58%). In the NYHA class II patients, atrial fibrillation occurred in 34% of patients. That is more frequent than in previous study [2].

From the analysed echocardiographic parameters only the diameter of the left atrium and LVDEV

Table 5. Comparison of patients with persistent and paroxysmal atrial fibrillation (AF) — long-term follow-up results

Parameter	Persistent AF	Paroxysmal AF	p
Pacemaker implantation	5 (23.8%)	5 (15.6%)	< 0.05
Coronary arterial by-pass grafting	2 (9.5%)	1 (3.1%)	< 0.05
Atrial hypertension + stroke	2 (14.3%)	2 (9.5%)	NS
Stroke	2 (9.5%)	2 (6.3%)	NS
Cardiological rehospitalization	3 (14.3%)	5 (15.6%)	NS
Mortality among patients with HR < 75	3 (28.6%)		
Mortality of patients with HR > 75	6 (54%)		
Mortality	9 (42.9%)	6 (18.8%)	< 0.05

VO_2 max — maximal oxygen consumption per minute in spiroergometric test; HR — heart rate in min

Table 6. Prognostic significance of studied parameters for predicting the risk of death in patients with systolic heart failure in univariate analysis.

Parameter	Odds ratio	95% confidence interval	p
Age (years)	1.08	1.03–1.13	0.001
Age > 60 years	5.84	1.92–17.81	0.002
NYHA functional class	1.61	0.93–2.77	0.085
Atrial fibrillation	1.56	0.71–3.41	0.261
LVEF	0.98	0.94–1.03	0.512
LVEF< 30%	3.16	1.41–7.1	0.005
Diabetes	0.87	0.35–2.14	0.757
Left bundle branch block	0.85	0.26–2.78	0.789
CABG in anamnesis	0.8	0.16–4.02	0.788
Past myocardial infarction	0.78	0.35–1.73	0.541
Arterial hypertension	0.55	0.25–0.89	0.041
Past stroke	0.19	0.02–1.55	0.119

LVEF — left ventricular ejection fraction; CABG — coronary arterial by-pass grafting

Table 7. Independent risk factors of death in the examined patients with systolic heart failure — multivariate analysis.

Parameters	Odds ratio	95% confidence interval	p
Age > 60 years	9.16	2.73–30.75	< 0.0005
Left ventricular ejection fraction < 30%	3.57	1.46–8.73	< 0.01
Arterial hypertension	0.29	0.12–0.72	< 0.01

distinguished significantly the patients with AF from the patients with sinus rhythm. Those changes may be explained by dilation of mechanically insufficient atria (LA diameter) and shortening of the ventricle filling period when heart evolutions came quickly one after another (LVEDV). The expected difference between ejection fraction in both groups did not reach statistical significance, however in the AF patients its values were lower.

Based on oxygen consumption in the spiroergometric test, we observed a lower functional performance in patients with concurrent AF in comparison with patients with sinus rhythm. The values of VO_2 max were lower by 27% in AF patients. This corresponds with our hypothesis and with previous research [13].

There was no increase in frequency of cerebral embolic complications in AF patients compared to

sinus rhythm patients found during follow-up. Perhaps it is a result of a relatively short period of observation, but also of a successful antithrombotic prevention. There has been a few large clinical trials conducted lately dedicated to occurrence of stroke in course of atrial fibrillation (AFFIRM, RACE, STAF). New, more exact biochemical markers of increased risk of neurological complications in AF patients are also searched for [14–17].

In the examined group of patients with SHF, the risk of embolic events was significantly higher when atrial fibrillation occurred (especially persistent) as well as when hypertension was present — in the non-AF and non-hypertension patients the ishaemic episodes in the central nervous system were less frequent.

Diagnosing persistent AF in patients with systolic heart failure proved to be an additional risk factor worsening the prognosis and impairing left ventricular function. Persistent AF was observed more often in patients with severe heart failure (NYHA class IV), what may be a result of the extent of myocardial damage (fibrosis), what has in consequence morphologic and electric remodelling of the myocardium [18]. In patients with persistent atrial fibrillation, as proved in the study, one may expect a need for more frequent hospitalizations, coronary arterial by-pass grafting operations and pacemaker implantation procedures. In this study it was proved that the prognosis of patients with concurrent atrial fibrillation is worse, however the predictive independence of this factor has not been proven. However, the predictive value and independence has been proven in case of previously acclaimed risk factors of death of the SHF patients: low ejection fraction of the left ventricle and older age. It seems to be suitable to consider the atrial fibrillation (according to observations of the overall population) a sign of changes occurring in the aging myocardium and as such, through the described mechanisms, contributes to progression of cardiac insufficiency, turning to be a marker of its dysfunction (increase in frequency of the occurrence of atrial fibrillation in higher NYHA classes). Although according to the presented results atrial fibrillation can be considered an "old people's sickness", it does not reduce the meaning of the fact that the occurrence of this arrhythmia is associated with worse prognosis.

It is interesting to find arterial hypertension as beneficial prognostic factor in patients with systolic heart failure. This apparently paradoxal observation may be explained perhaps by potentially greater hemodynamic reserves of patients with hypertension, and what is a consequence of this — a possibility for a more aggressive, full-dosed pharmacotherapy, as recommended in randomised clinical trials. This observation undoubtedly requires further studies.

In patients with persistent atrial fibrillation, regardless of a degree of heart failure it has been beneficial to maintain heart rate < 75/min. This result confirmes the validity of increasingly more often postulated possibility of pharmacological therapy of persistent and fixed AF [19] — at least in some patients [20].

The mutual dependence of factors determining the clinical presentation of patients with systolic heart failure and atrial fibrillation also seems to be interesting: on one hand, damaged myocardium predisposes to occurrence of arrhythmia, on the other hand atrial fibrillation through the described before mechanisms may result in heart failure ("tachyarrhythmia-induced cardiomyopathy" — this is perhaps the source of higher percentage of SHF of unknown etiology in patients with AF?). Both variants of the "vicious circle" of the sequence of events result in an identical clinical picture, what may cause difficulties in finding the initial cause of the illness [21].

It should be considered also that in the elderly population (majority of patients in this study) even 30–40% of AF incidents are asymptomatic, and only 1 per each 12 episodes of uncharacteristic palpitations in cardiac region is further diagnosed [22]. Perhaps, with a detailed clinical history, more frequent ECG, and 24-hour heart rhythm monitoring the role of this arrhythmia as a factor of heart failure progression would prove to be even more valuable.

Conclusions

1. Atrial fibrillation in patients with systolic heart failure is a disadvantageous, but not independent risk factor of outcome.
2. Atrial fibrillation is a common arrhythmia in patients with systolic heart failure (over 1/3 of patients examined), indicating advanced myocardial damage and decreasing cardiac function, especially in patients with persistent AF.
3. Patients with atrial fibrillation have more frequent cardiac hospitalizations than patients with sinus rhythm, and in case persistent AF was present required also a greater number of CABG and/or pacemakers implantations.
4. In patients with persistent atrial fibrillation the control of heart rate < 75/min was associated with significant decrease in mortality.

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