Persistent atrial fibrillation as a prognostic factor of outcome in patients with advanced heart failure

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Abstract

Introduction: Chronic heart failure (CHF) is associated with high morbidity and mortality and is diagnosed more and more frequently. Fifteen to 30% of patients with systolic CHF develop atrial fibrillation (AF).

Aim: To establish whether persistent AF was an independent predictor of mortality, and had a predictive value with respect to late clinical outcomes in patients with systolic CHF.

Methods: Analysis comprised 120 men with systolic CHF. In 35 (58%) patients CHF was the result of ischaemic heart disease and in 25 (42%) - idiopathic dilated cardiomyopathy (DCM). Presence or absence of AF was a criterion of patients' subsequent division into two subgroups. Sixty patients with AF were assigned to the AF group. The control group involved 60 individuals with CHF and sinus rhythm (SR) on enrolment. Mean follow-up time was 36 months.

Results: Overall 59 (49%) patients died during 3-year follow-up, including 33 (56%) in the AF group. Deaths were noted more often in CHF patients with underlying ischaemic heart disease than DCM (66% *vs* 34%). This difference reached statistical significance in the AF group (72% *vs* 28%, p<0.001). Moreover, patients with AF more often complained of palpitations (p<0.01), had worse exercise capacity (p<0.01) as well as more frequently presented complex ventricular arrhythmia (p<0.01). The rate of hospital readmission was also higher (p<0.02). In univariate as well as multivariate analysis, AF was not found to be an independent predictor of mortality. Factors with a potential impact on adverse prognosis were concomitant complex ventricular arrhythmias (p=0.01), diabetes (0.04) and reduced exercise capacity (p<0.01).

Conclusions: Persistent AF is not an independent risk factor of death in patients with advanced systolic CHF. However, it has an unfavourable impact on functional status. Concomitant complex ventricular arrhythmias and reduced exercise capacity worsen prognosis in this group of patients.

Key words: chronic heart failure, atrial fibrillation, prognosis

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Introduction

Chronic heart failure (CHF) is associated with high morbidity and mortality, and is being diagnosed increasingly frequently in the aging European population. In the adult population it affects 0.4 to 2% of individuals. Incidence of CHF increases after the age of 65 years to 8–10% [1, 2]. The predominant underlying pathologies are ischaemic heart disease and arterial hypertension. Despite advances in both medical management and invasive treatment, CHF, particularly end-stage disease, is still associated with unfavourable prognosis. It is estimated that 30 to 40% of patients die within one year of diagnosis, and 60 to 70% do not survive 5 years [3-5].

Fifteen to 30% of patients with CHF develop atrial fibrillation (AF). It is thought that its prevalence rises gradually as age and failure degree increase [6]. However, it is not clear whether the presence of AF worsens the prognosis. The ongoing AF-CHF trial, scheduled to be completed in 2006, should find answers to many questions [7].

The purpose of this study was to establish whether persistent AF in patients with systolic CHF was an

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independent risk factor of mortality and how it affected clinical status and prognosis.

Methods

Patients

Analysis comprised 120 consecutive men admitted to the Department of Cardiology, Medical University in Białystok because of advanced CHF (functional NYHA classes III and IV accompanied by EF <30%). The examined group of patients involved 73 patients with CHF due to coronary artery disease (history of at least one myocardial infarction in all patients) and 47 patients meeting criteria of idiopathic dilated cardiomyopathy (DCM). Diagnosis of systolic CHF was established based on clinical history, signs and symptoms. Patients were enrolled in the study in the period of haemodynamic stabilisation; type II diabetes was diagnosed prior to enrolment. Patients received combined pharmacotherapy according to the recent guidelines of the European Society of Cardiology as well as the American Heart Association [8]. Patients with haemodynamically significant heart defects and two individuals found initially in sinus rhythm who developed AF during follow-up were excluded from the study. Presence or absence of AF was the criterion of division into two subgroups. The AF group involved 60 patients with systolic CHF and AF. The control group comprised 60 patients with CHF and sinus rhythm (SR).

Echocardiography

All patients enrolled into this study underwent baseline transthoracic echocardiography. Parameters were measured according to the guidelines of the American Heart Association [9]. The following parameters were analysed: left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left atrial diameter in short axis view (LA sax) and visually assessed ejection fraction (EF).

Arrhythmia

Presence of arrhythmia was analysed based on standard ECG recordings and 24-hour Holter monitoring. For the purpose of this study, only simple and complex ventricular arrhythmias were distinguished. Type, number of arrhythmia episodes and their total duration were evaluated.

Exercise capacity

Exercise capacity was assessed by means of treadmill exercise test according to the modified Bruce protocol and 6-minute walking test. The response of heart rate and blood pressure to exercise load was recorded. A significant reduction in exercise capacity was diagnosed if maximum exercise load was <4 METS and walking distance <300 m [10].

Follow-up

Follow-up examinations were repeated every 6 months. They comprised clinical assessment and a number of hospital readmissions. All deaths were registered and their causes analysed. Mean follow-up time was 36 months.

Statistical analysis

Statistical analysis of studied parameters was performed based on mean values and their standard deviations for continuous variables, and on numbers and their ratios (expressed as percentages) for categorical variables. A value of P less than 0.05 was considered significant. Comparison of parameters between consecutive follow-up examinations within one group as well as between two groups was performed by means of Student's t-test. Multivariate regression analysis in Cox's proportional risk model was employed for evaluation of impact of the examined group variables on survival [11]. Analysis of Kaplan-Meier survival curves was carried out using statistical software package S-Plus 2000. Computer software Statistica for Windows version 6.0 (StatSoft, Inc., USA) was employed for analysis of variance. The study protocol was approved by the local Ethics Committee.

Results

Detailed patient characteristics are outlined in Table I. Patients in both groups were similar in terms of basic demographic data, CHF aetiology and previous medical management (Table I). Exceptions were β-blockers prescribed more often in the SR group and digitalis and/or anticoagulants in the AF group.

Mortality analysis

During 36-month follow-up 59 (49%) patients died; 33 (56%) in the AF group and 26 (43%) in the SR group. The difference in mortality between the groups was not statistically significant (Figure 1). Causes of death were as follows: 29 (49%) patients died because of sudden cardiac death and 30 because of progressive pump failure. In the study population, deaths were more frequent in patients with ischaemic heart disease underlying systolic CHF than in DCM patients (66% *vs* 34%). In the AF group, the difference in mortality reached statistical significance (72% *vs* 28%; p<0.001, respectively).

Analysis of clinical status and prognosis

The two groups did not differ with respect to complaints and clinical symptoms, except for

Table I. Patient characteristics

	SR group N=60	AF group N=60	P
1. Age (years)	61±9	60±9	NS
2. Gender	M	M	NS
3. Ischaemic aetiology			
(with concomitant arterial hypertension)	21 (35%)	20 (33%)	
(without concomitant arterial hypertension)	17 (28%)	15 (25%)	
Idiopathic cardiomyopathy	22 (37%)	25 (42%)	NS
4. Risk factors			
Diabetes	20 (33%)	15 (25%)	NS
Hypercholesterolaemia (>200 mg/dL)	18 (30%)	11 (18%)	NS
Smoking	46 (77%)	45 (75%)	NS
Alcohol (>50 g/day)	28 (47%)	27 (45%)	NS
5. Functional status			
NYHA III	37 (62%)	41 (68%)	NS
NYHA IV	23 (38%)	19 (32%)	NS
6. EF (%)	24±3.8	22±3.5	NS
7. Creatinine (mg/dL)	1.05±0.2	1.1±0.2	NS
8. Haemoglobin (mg/dL)	12.8±1.3	12.5±1.2	NS
9. Medications used			
Diuretics	60 (100%)	58 (97%)	NS
ACE-I	60 (100%)	59 (98%)	NS
β-blockers	60 (100%)	55 (92%)	<0.05
Digitalis	23 (38%)	58 (97%)	<0.001
Amiodarone	29 (48%)	29 (48%)	NS
Anticoagulants	0	60 (100%)	
Antiplatelet drugs	15 (25%)	24 (40%)	NS

Table II. Incidence of clinical symptoms, reduction in exercise capacity and arrhythmias in both study groups

	AF group	SR group	P
Dyspnoea	33 (55%)	26 (43%)	NS
Anginal pain	17 (28%)	8 (13%)	NS
Syncope	8 (13%)	9 (15%)	NS
Peripheral oedema	33 (55%)	26 (43%)	NS
Palpitations	33 (55%)	10 (17%)	0.001
6-minute walking test [m]	353±129	397±125	0.001
Complex ventricular rhythm disturbances	23(38%)	14(23%)	0.001

palpitations, which were more frequent in patients with AF (Table II).

Functional status assessed by means of 6-minute walking test was worse in the AF group. Moreover, in this group more episodes of complex ventricular arrhythmia were noted (Table II).

Patients with persistent AF were readmitted to hospital more frequently during 3-year follow-up as compared to the SR group. The reasons for rehospitalisation were worsening of heart failure or arrhythmia (Figure 2).

Univariate and multivariate analysis of the risk of mortality included the following parameters: risk factors, clinical data, electrocardiographic data (AF and complex ventricular arrhythmias) and exercise capacity. In univariate analysis only diabetes, complex ventricular arrhythmia and reduced exercise capacity were found to be associated with higher risk of death (Table III). In multivariate analysis the following

Table III. Results of univariate analysis - predictors of death

	OR	95% CI	P
Walking distance ≤300 m	13.07	5.43–31.44	0.001
Exercise capacity <4 METS	4.70	1.81–12.22	0.009
Complex ventricular arrhythmias	3.25	1.52–6.93	0.002
Diabetes	2.30	1.01–5.22	0.04

Table IV. Results of multivariate analysis - predictors of death

	OR	95% CI	P
Distance ≤300 m	14.65	5.72–37.50	0.001
Complex ventricular arrhythmias	3.48	1.36–8.91	0.01

independent risk factors of death were found: reduced exercise capacity and complex ventricular arrhythmia (Table IV).

Discussion

Atrial fibrillation itself may lead to CHF, particularly in the case of fast ventricular response. Because of several atrial reentry circuits, it may cause specific damage to left ventricular myocardium called tachycardiomyopathy [12]. Atrial fibrillation is also a factor accelerating arrhythmia maintenance; thus the statement "atrial fibrillation begets atrial fibrillation" was formed [13]. It was observed that sinus node cells underwent remodelling (electrical remodelling) similarly to atrial myocardium [14]. Thus, many data indicate that AF itself may have an adverse impact on CHF progression and consequently on mortality.

Although SR maintenance seems to be advantageous especially in patients with end-stage CHF, there is still no consensus whether such management is life-saving or just improves the quality of life [15].

Patients with persistent AF usually complain of annoying symptoms such as palpitations, dyspnoea and fatigue [15]. Chronic heart failure is accompanied by similar symptoms. Such symptoms were seen at the same rate in both examined groups except for palpitations, which were noted significantly more frequently in the AF group.

Walking test is the simplest and cheapest examination that provides preliminary assessment of functional status. It may be a useful supplement to clinical evaluation of patients with CHF, which was also employed in this study protocol. A higher degree of exercise capacity impairment in the AF group than in subjects with sinus rhythm was found.

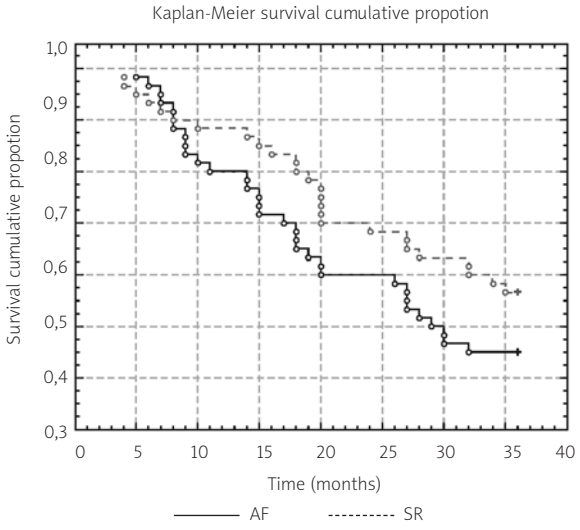

Figure 1. Survival curves in groups of patients with atrial fibrillation (AF) and sinus rhythm (SR)

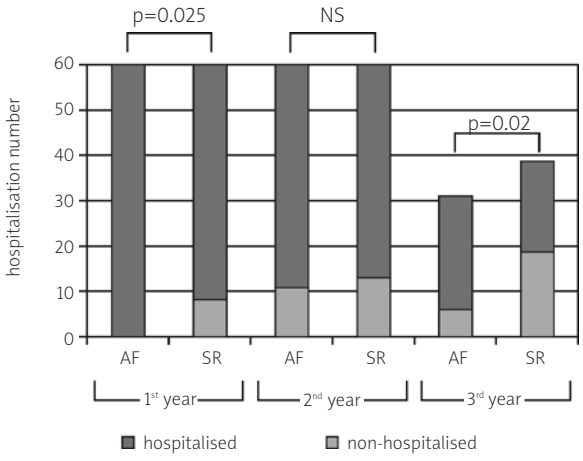

Figure 2. Rate of rehospitalisation in both groups during 3-year follow-up

The predictive value of ventricular arrhythmia has been the subject of several investigations. Most commonly these arrhythmias have re-entry nature and accompany CHF. They are considered to be responsible for sudden cardiac death in as many as 50% of patients. The frequency of ventricular arrhythmia, particularly ventricular tachycardia, is associated with the degree of left ventricular myocardial damage. In the mid-1980s Meinertz et al. [16] published the results of 11-month follow-up of 74 patients with DCM. They stressed the importance of ventricular tachycardia as a risk factor responsible for sudden cardiac death. Four years later, the same research team confirmed the correlation between sudden cardiac death and complex ventricular arrhythmias. In our study herein we also found, both in univariate and multivariate analysis, that complex ventricular rhythm arrhythmias were independent prognostic factors.

High morbidity in patients with CHF results in more frequent hospital admissions [17]. It was also seen in our group of patients. In 3-year follow-up, patients with persistent AF were more frequently rehospitalised.

Results of the recently published Euro Heart Survey on Atrial Fibrillation clearly showed that coexistence of AF in patients with CHF markedly worsens prognosis [15]. Patients with diagnosed CHF who developed AF during the course of the disease formed, as in our studied population, a different group of patients. Opinions regarding the predictive value of AF in CHF patients are not consistent. The SOLVD trial found AF to be an independent risk factor of death in CHF patients [18]. These findings were subsequently confirmed by Middlekauff et al. [5] in a retrospective analysis of 390 patients with CHF and AF. Unlike in the SOLVD trial, the predominant reason for mortality in the latter study was sudden cardiac death. In the PRIME II programme, during 2-year follow-up, in the AF group 60% of patients died, compared to only 42% in the group of patients with SR. Meanwhile, in the report by Keogh et al. [19] in patients with end-stage CHF and similar duration of follow-up, AF was not found to increase mortality. It was shown in V-HEFT I and II studies that both overall mortality and incidence of sudden cardiac death in patients with AF and in SR were similar [20]. In the multicentre MERIT-HF trial, sudden cardiac deaths dominated in patients in functional NYHA classes II and III (64% *vs* 59%). In the end-stage heart failure group (functional NYHA class IV) the predominant cause of death was progressive pump failure (56%) rather than sudden death (33%) [21]. In our study, 3-year mortality was high – approximately half of patients enrolled in the study died during the follow-up. This was caused by the worsening of CHF and sudden cardiac death in similar proportions. Although our study was not a cohort one, the mortality rate approximates those found in large population studies [1, 2, 22]. The mortality rate was higher in the group with persistent AF, but the difference was not significant and AF was not found to be an independent risk factor of death in either univariate or multivariate analysis.

Limitations of the study

An obvious limitation of our study is the relatively small number of examined patients. This is likely to affect the findings of both univariate and multivariate analysis of mortality. Our study involved only male individuals. Such preselection resulted from our efforts to eliminate any gender impact on the final results. On the other hand, the natural course of CHF differs in women [23]. Moreover, we assessed only systolic type of CHF, which is different to the diastolic one in terms of clinical course.

Conclusions

1. Persistent atrial fibrillation is not an independent predictor of clinical outcome in patients with advanced, systolic heart failure. However, it has an unfavourable impact on clinical status.
2. Concomitant complex ventricular arrhythmias and reduced exercise capacity worsen prognosis in this group of patients.

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Utrwalone migotanie przedsionków jako czynnik rokowniczy u chorych z zaawansowaną niewydolnością serca

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Streszczenie

Wstęp: Niewydolność serca jest chorobą o wysokiej chorobowości i śmiertelności, rozpoznawaną coraz częściej. U 15–30% chorych ze skurczową niewydolnością serca (HF) współistnieje migotanie przedsionków (AF).

Cel: Ustalenie, czy utrwalone AF jest niezależnym czynnikiem ryzyka zgonu oraz czy ma wpływ na stan kliniczny i rokowanie u chorych ze skurczową HF.

Metoda: Analizą objęto 120 mężczyzn ze skurczową HF. U 35 (58%) chorych jej podłożem była choroba niedokrwienna serca, a u 25 (42%) kardiomiopatia rozstrzeniowa. Obecność względnie brak AF stanowiły kryterium podziału chorych na 2 grupy. Do grupy AF zaliczono 60 chorych z HF i AF. Do grupy kontrolnej 60 osób z HF i rytmem zatokowym (SR). Średni czas obserwacji wynosił 36 mies.

Wyniki: Po 3 latach zmarło ogółem 59 (49%) pacjentów, z tego 33 (56%) w grupie z AF. Zgony występowały częściej u pacjentów, u których podłożem była choroba niedokrwienna serca (66% *vs* 34%). W grupie AF różnica ta osiągnęła istotność statystyczną (72% *vs* 28%, p<0,001). Ponadto chorzy z AF częściej skarżyli się na kołatania serca (p<0,01), mieli gorszą tolerancję wysiłku (p<0,01). Istotnie częściej występowały też złożone, komorowe zaburzenia rytmu serca (p<0,01). Byli też częściej hospitalizowani (p<0,02). W analizie jedno- i wieloczynnikowej nie wykazano, aby AF stanowiło niezależny czynnik ryzyka zgonu. Czynnikami obciążającymi rokowanie było współistnienie złożonych komorowych zaburzeń rytmu (p=0,01), cukrzycy (0,04) oraz ograniczonej tolerancji wysiłku (p<0,01).

Wnioski: Utrwalone AF nie stanowi niezależnego czynnika ryzyka zgonu u pacjentów z zaawansowaną skurczową HF. Ma jednak niekorzystny wpływ na stan kliniczny. Współistnienie złożonych komorowych zaburzeń rytmu, ograniczona tolerancja wysiłku pogarszają rokowanie w grupie chorych z HF.

Słowa kluczowe: niewydolność serca, migotanie przedsionków, rokowanie

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