

Identification of clinical risk factors of atrial fibrillation in congestive heart failure

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Abstract

Background: Factors associated with the development of atrial fibrillation (AF) in general population have been described, but it is still unknown whether the same risk factors apply to heart failure (HF) patients. The aim of this study was to identify clinical factors related to various forms of AF in HF patients.

Methods: The clinical and echocardiographic characteristics were assessed in 155 HF patients: 50 with sinus rhythm, 52 with non-permanent AF, and 53 with permanent AF.

Results: Multivariate logistic regression analysis showed that the increase in the NYHA class was an independent risk factor for both forms of AF. The occurrence of permanent AF in comparison to sinus rhythm group was independently associated with hs-C-reactive protein (CRP) elevation above 1 mg/dL (OR 1.87, 95% CI 1.05–3.35), left atrial dimension above 4 cm (OR 3.78, 95% CI 1.29–11.06) and tricuspid maximal pressure gradient elevation above 35 mm Hg (OR 5.01, 95% CI 1.38–18.27). The presence of coronary disease was independently associated with less frequent occurrence of permanent AF in comparison to sinus rhythm group (OR 0.21, 95% CI 0.06–0.67).

Conclusions: More advanced congestive HF was associated with presence of both types of AF. Non-ischemic etiology of HF and elevated CRP are independently associated with permanent AF compared to sinus rhythm. Left ventricular diastolic dysfunction indicators (increased tricuspid maximal pressure gradient and left atrial dimension) are independently associated with permanent AF. (Cardiol J 2013; 20, 4: 364–369)

Key words: heart failure, atrial fibrillation, echocardiography, C-reactive protein, coronary disease

Introduction

The advent of modern treatments in cardiology and the resulting survival benefit in industrialized countries have considerably increased the size of the population of patients suffering from congestive heart failure (CHF), estimated at over 15 million in the European Union [1].

Coronary artery disease (CAD), hypertension and tachyarrhythmia, usually in the form of atrial fibrillation (AF), are believed to be the most common causative factors of myocardial dysfunction [2–4]. The development of AF in CHF patients further exacerbates the signs and symptoms of HF, increases the risk of thromboembolic events and adversely affects the long-term prognosis [3].

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While factors associated with the development of AF in the general population of patients have been identified [5], it remains unclear whether the same risk factors apply to the population of patients suffering from CHF. The known causes of AF in patients with CHF include rapidly progressive conditions, such as hyperthyroidism, electrolyte imbalance, acute myocardial ischemia, alcohol abuse and heart surgery [3]. Maisel and Stevenson [6] reported an increased incidence of AF with increasing severity of CHF, as assessed using the New York Heart Association (NYHA) functional classification. It has not been established whether there is an independent association between AF and the increasing severity of CHF assessed using the NYHA classification or between AF and CHF assessed by echocardiographic parameters. Studies in patients without HF describe an association of AF with markers of inflammation [7, 8]. In the case of AF in patients with CHF this association has not yet been elucidated [9].

Identification of factors associated with the development and persistence of cardiac arrhythmias is of important prognostic significance and may play a role in therapy if these factors can be modified.

The aim of the study was to identify factors associated with various forms of AF in the population of patients with CHF.

Methods

This was a cross-sectional study investigating a population of patients with CHF. The study was approved by the local ethics committee. All the patients met the European Society of Cardiology (ESC) diagnostic criteria of CHF [3]. Patients with acute (up to 3 months duration) and chronic inflammatory diseases, hyperthyroidism, hemodynamically significant valvular disease, NYHA class IV CHF, or cancer were excluded from the study. The study population consisted of patients referred to the Cardiology Clinic by 41 general practitioners over a period of 15 months. Consecutive patients were assigned to one of the following 3 groups: the sinus rhythm (SR) group, the non-permanent AF (npAF) group (3 patients with paroxysmal and 49 with persistent AF) or to the permanent AF (pAF) group. The ESC classification of AF was followed [5].

We assessed the baseline demographic and clinical characteristics of the study patients. The severity of CHF was established in accordance with the NYHA functional classification. The diagnosis of hypertension was based on the history or measurements of blood pressure values in accordance

with the ESH/ESC guidelines [10]. The diagnosis of CAD was established in patients with a history of ST-elevation myocardial infarction or based on an angiographically confirmed significant narrowing of an epicardial coronary artery. The diagnoses of diabetes mellitus and metabolic syndrome were established in accordance with the International Diabetes Federation criteria [11]. Conduction abnormalities in the form of bundle branch blocks or atrioventricular block were diagnosed by ECG and/or based on a history of a pacemaker implantation. Laboratory and echocardiographic assessments were ordered during the first study visit. The patients underwent transthoracic echocardiography performed with GE Vingmed System FIVE using the standard 2.5–5.0 MHz probe. The methods of the study have been reported previously [9].

The results are presented as frequency values or calculated mean values for the analyzed groups of patients.

Preliminary statistical analysis of the study parameters allowed us to determine whether the percentage of patients within a particular class of a given parameter is independent of the group of patients classified on the basis of the presence and type of AF and whether the mean values of a given parameter in individual groups are similar or significantly different.

The distribution of hs-C-reactive protein (CRP) levels was not normal, hence the natural logarithm of the hs-CRP levels (ln CRP) was used for further analyses.

The mean values in the groups were compared using parametric tests (the t-Student or Cochrane-Cox tests) or the non-parametric U Mann-Whitney test.

Some continuous variables were transformed into dichotomized variables using their upper limits of normal as threshold values. Patients with left ventricular ejection fraction (LVEF) values below 45% made up Class 1, while the remaining patients made up Class 2. Patients with the maximum pressure gradient across the tricuspid valve (tMxPG) values below 35 mm Hg made up Class 1, while the remaining patients made up Class 2. The remaining variables were categorized as follows: NYHA functional classes were categorized in 3 classes; hs-CRP levels in 3 classes (≤ 1.00 mg/L, 1.01–3.00 mg/L and > 3.00 mg/L) [12, 13]; left atrial (LA) dimension in 3 classes (≤ 4 cm, 4.01–5.00 cm and > 5.00 cm) [9].

Univariate logistic regression analysis was used to determine which of the analyzed variables were significantly associated with the particular

Table 1. Patients characteristics.

Analyzed parameters	Patient groups by type of arrhythmia					P**
	SR	Non-permanent AF		Permanent AF		
	N = 53	N = 52	P*	N = 50	P*	
Age	72.2 ± 9.2	76.2 ± 10.0	0.038	74.5 ± 9.9	NS	NS
Male	37 (69.8%)	34 (65.4%)	NS	30 (60.0%)	NS	NS
Hypertension	40 (75.5%)	39 (75.0%)	NS	38 (76.0%)	NS	NS
Diabetes mellitus	48 (90.6%)	22 (42.3%)	< 0.001	11 (22.0%)	< 0.001	0.033
Coronary artery disease	34 (64.1%)	30 (57.7%)	NS	17 (34.0%)	0.003	0.017
Dilated cardiomyopathy	3 (5.7%)	3 (5.8%)	NS	6 (12.0%)	NS	NS
Mitral insufficiency	4 (7.5%)	7 (13.5%)	NS	15 (30.0%)	0.005	NS
Systolic heart failure	32 (60.4%)	37 (71.2%)	NS	36 (72.0%)	NS	NS
NYHA class III	9 (17.0%)	22 (42.3%)	0.006	28 (56.0%)	< 0.001	NS
Peripheral edema	20 (37.7%)	26 (50.0%)	NS	29 (58.0%)	0.045	NS
Conduction abnormalities	24 (50.9%)	19 (36.5%)	NS	22 (44.0%)	NS	NS
BMI [kg/m ²]	28.6 ± 5.1	29.4 ± 5.0	NS	29.4 ± 6.5	NS	NS
Metabolic syndrome	24 (45.3%)	23 (44.2%)	NS	15 (30.0%)	NS	NS
ACEI	50 (94.3%)	50 (96.2%)	NS	44 (88.0%)	NS	0.014
ARB	0	0		6		
Beta-blocker	44 (83.0%)	46 (88.5%)	NS	45 (90.0%)	NS	NS
Statin	46 (86.8%)	45 (86.5%)	NS	28 (56.0%)	0.001	0.001
Spirolactone	34 (64.2%)	38 (73.1%)	NS	40 (80.0%)	NS	NS
Diuretics	35 (66.0%)	36 (69.2%)	NS	44 (88.0%)	0.010	0.022
Aspirin	45 (84.9%)	44 (84.6%)	NS	26 (52.0%)	0.001	0.001
Acenocoumarol	4 (7.5%)	24 (46.2%)	< 0.001	37 (74.0%)	< 0.001	0.005

*vs. SR, **non-permanent AF vs. permanent AF; SR — sinus rhythm; AF — atrial fibrillation; BMI — body mass index; ACEI — angiotensin-converting enzyme inhibitors; ARB — angiotensin receptor blockers

types of AF. The variables for which the significance level was below 0.10 were used as the baseline variables for multivariate logistic regression analysis. An optimal subset of variables was identified. The odds ratio was estimated from the following formula: $OR = OR_{AB} = S(X = A)/S(X = B) = P(Y = 1 | X = A)/P(Y = 1 | X = B)$, for $A > B$, where A and B referred to classes of the independent factor X.

A significance level of 0.05 was adopted to verify the statistical hypotheses. The statistical analysis was performed using Statistica 6.0 PL.

Results

Baseline characteristics of the 3 study groups and the results of the statistical tests to verify the significant differences between the groups are presented in Table 1. Although the patients in the npAF group were older than the patients in the remaining 2 groups, the difference was statistically significant only vs. the SR group ($p = 0.038$). CAD was significantly more common in the SR and the npAF groups than in the pAF

group ($p = 0.03$ and $p = 0.017$, respectively). The highest percentage of patients with diabetes mellitus was identified in the SR group ($p < 0.001$ for both comparisons). This percentage decreased with increasing severity of AF. The prevalence of haemodynamically significant mitral insufficiency and peripheral edema was significantly higher in the pAF group vs. the SR group ($p = 0.005$ and $p = 0.045$, respectively). The prevalence of NYHA class III HF was significantly higher in the npAF and pAF groups than in the SR group ($p = 0.06$ and $p < 0.001$, respectively). Table 1 presents also the details of the pharmacological treatment in the study groups. The differences in pharmacotherapy resulted from the underlying cause and severity of CHF and from the presence of AF. The exception was the treatment with angiotensin-converting enzyme inhibitors, which was less common in the npAF group than in the pAF group as a result of the more frequent use of angiotensin receptor blockers in the pAF group (6 patients).

The results of laboratory and echocardiographic assessments in the study groups are summar-

Table 2. Comparison of laboratory and echocardiographic parameters between the study groups.

Analyzed parameters	SR	Non-permanent AF		Permanent AF		P**
	N = 53	N = 52	P*	N = 50	P*	
hs-CRP [mg/L]	4.27 ± 11.2	8.81 ± 27.3		8.84 ± 11.6		
ln hs-CRP	0.67 ± 1.11	1.13 ± 1.27	0.052	1.56 ± 1.20	< 0.001	NS
Fibrinogen [mg/dL]	361.4 ± 79.6	355.5 ± 65.6	NS	398.0 ± 87.2	0.021	0.007
Hemoglobin [g/dL]	14.0 ± 1.5	13.4 ± 1.7	NS	13.9 ± 1.6	NS	NS
MCV [μm^3]	91.4 ± 4.0	91.6 ± 5.6	NS	91.2 ± 6.1	NS	NS
Platelets [$\times 10^3/\text{mL}$]	194.5 ± 55.8	182.3 ± 52.1	NS	186.1 ± 63.5	NS	NS
WBC ($\times 10^3/\text{mL}$)	7.6 ± 2.0	7.4 ± 2.0	NS	7.3 ± 2.1	NS	NS
Serum creatinine [mg/dL]	0.99 ± 0.39	1.10 ± 0.57	NS	1.12 ± 0.30	0.010	NS
Na ⁺ [mmol/L]	139.5 ± 2.8	140.7 ± 3.4	0.025	140.3 ± 3.1	NS	NS
K ⁺ [mmol/L]	4.33 ± 0.41	4.48 ± 0.40	NS	4.39 ± 0.47	NS	NS
Glucose [mg/dL]	106.1 ± 25.1	109.4 ± 33.9	NS	103.7 ± 32.8	NS	NS
Total cholesterol [mg/dL]	177.6 ± 45.2	158.5 ± 34.7	0.036	163.9 ± 47.3	NS	NS
Triglycerides [mg/dL]	137.6 ± 82.3	119.7 ± 70.1	NS	121.8 ± 70.1	NS	NS
HDL-cholesterol [mg/dL]	54.2 ± 14.7	50.7 ± 16.0	NS	51.9 ± 16.5	NS	NS
LDL-cholesterol [mg/dL]	95.9 ± 43.0	83.8 ± 32.6	NS	87.7 ± 40.0	NS	NS
LA [cm]	4.40 ± 0.58	4.56 ± 0.81	NS	5.20 ± 0.77	< 0.001	< 0.001
LV [cm]	5.90 ± 1.03	5.86 ± 0.98	NS	5.85 ± 1.08	NS	NS
LVEF [%]	45.7 ± 13.8	42.1 ± 12.7	NS	43.7 ± 14.1	NS	NS
RV [cm]	2.62 ± 0.40	2.49 ± 0.52	NS	2.80 ± 0.58	NS	0.004
tMxPG [mm Hg]	16.9 ± 17.7	18.6 ± 15.0	NS	36.2 ± 17.4	< 0.001	< 0.001

*vs. SR, **non-permanent AF vs. permanent AF; SR — sinus rhythm; AF — atrial fibrillation; CRP — C-reactive protein; MCV — mean corpuscular volume; LA — left atrium; LV — left ventricle; RV — right ventricle; LVEF — left ventricular ejection fraction; tMxPG — tricuspid maximal pressure gradient

zed in Table 2. The mean hs-CRP levels (ln CRP) were higher in the npAF and pAF groups than in the SR group ($p = 0.052$ and $p < 0.001$, respectively). The pAF group was also characterized by a significantly higher fibrinogen levels compared to the other 2 groups ($p = 0.021$ and $p = 0.007$, respectively) and by a significantly higher serum creatinine levels compared to the SR group ($p = 0.010$). Sodium levels were significantly higher ($p = 0.025$) and total cholesterol significantly lower ($p = 0.036$) in the npAF group, compared to the SR group. There were no significant differences in LVEF between the npAF or pAF groups and the SR group. LA dimension was significantly higher in the pAF group ($p < 0.001$ and $p < 0.001$, respectively) as was tMxPG ($p < 0.001$ and $p < 0.001$, respectively). Right ventricular (RV) dimension was higher in the pAF group compared to the npAF group ($p = 0.004$).

The parameters showing a statistically significant association with the presence of arrhythmia on univariate logistic regression analysis were: diabetes mellitus, CAD, NYHA class of CHF, the levels of hs-CRP, fibrinogen, serum creatinine and sodium, and LA dimension, RV dimension and tMxPG. The

parameters for which the significance level did not exceed 0.10 were the baseline parameters for multivariate logistic regression analysis, which allowed us to identify an optimal subset of factors of which the most important ones may be treated as variables independently associated with a particular type of AF.

The final results of the multivariate logistic regression analysis for the above types of AF are summarized in Table 3.

The optimal subset of parameters describing the likelihood of npAF included: NYHA class of CHF, hs-CRP levels and LA dimension, treated as the classified variables. The increase in the severity of CHF, as assessed by the NYHA functional class, was the only variable independently associated with npAF.

In addition, the optimal subset of independent variables described by the likelihood of pAF also included: confirmed CAD and elevated tMxPG. The multivariate logistic regression analysis revealed that elevated hs-CRP, NYHA class increase, LA enlargement and tMxPG increase above 35 mm Hg were independently associated with pAF, whereas CAD was independently associated with reduced odds of pAF after multivariable adjustment.

Table 3. Multivariable analysis; optimal subsets of independent variables.

Independent variables X Factors (number of classes)	Regression coefficients	P	OR**		95% CI***	
			One class change	Range changes	One class change	Range changes
III A – Y*: AF (1 — non-permanent AF; 0 — sinus rhythm)						
Intercept	-2.701					
NYHA (3 classes)	1.243	0.001	3.47	12.01	1.70–7.08	2.88–50.15
hs-CRP (3 classes)	0.123	NS	1.14	1.45	0.74–1.72	0.41–5.12
LA (3 classes)	0.297	NS	1.35	1.81	0.68–2.66	0.46–7.09
III B – Y*: AF (1 — permanent AF; 0 — sinus rhythm)						
Intercept	-7.747					
CAD	-1.582	0.008	0.21		0.06–0.67	
NYHA (3 classes)	1.508	0.004	4.52	20.40	1.61–12.70	2.57–161.38
hs-CRP (3 classes)	0.755	0.033	1.87	6.56	1.05–3.35	1.14–37.68
LA (3 classes)	1.484	0.014	3.78	14.28	1.29–11.06	1.67–122.36
tMxPG	1.719	0.013	5.01		1.38–18.27	
III C – Y*: AF (1 — permanent AF; 0 — non-permanent AF)						
Intercept	-2.52					
CAD	-0.865	0.061	0.42		0.17–1.05	
hs-CRP (3 classes)	0.491	NS	1.63	4.37	0.97–2.76	0.91–21.08
LA (3 classes)	1.135	0.003	2.9	8.41	1.42–5.92	2.02–35.03
tMxPG	1.411	0.004	4.1		1.54–10.89	

*Dichotomized variable Y describing the type of atrial fibrillation (1 — success; 0 — failure); **Odds ratio (OR) for the change in the value of the independent variable; ***95% confidence interval for OR; AF — atrial fibrillation; CAD — coronary artery disease; tMxPG — tricuspid maximal pressure gradient; LA — left atrium

OR = $OR_{A>B} = P(Y=1 | X=A) / P(Y=1 | X=B)$, A>B -> number of classes of variable X

Factors significantly and independently associated with pAF, when the failure was npAF, turned out to be: increased LA dimension and elevated tMxPG above 35 mm Hg.

Discussion

Although the CHF patients in both AF groups were older than those in the SR group, the difference was not independently associated with AF. A similar finding of the higher prevalence of AF among older patients was reported in the Euro-Heart Failure Survey [14]. We did not identify any association between the arrhythmia and hypertension, or increasing obesity, as assessed by body mass index, which are factors associated with AF in the general population [5]. The analysis of a large European population of patients with HF conducted by Rivero-Ayerza et al. [14] also demonstrated no significant differences in the prevalence of obesity and hypertension between patients with AF and patients with SR, which confirms our findings obtained in a relatively small randomly selected group of patients.

Diabetes mellitus and CAD are considered to be the factors that are associated with the development of AF in general population of patients [5]. In our group of patients with HF the prevalence of diabetes mellitus and CAD were the highest in the SR group and decreased with the severity of the arrhythmia. In a multivariate logistic regression analysis, the diagnosis of CAD was associated with about a 5-fold decrease in odds ratio for the development of pAF vs. the SR group. In this context, it is notable that Lee et al. [15], in the Framingham population with CHF, showed a significantly higher prevalence of AF in patients in whom CHF resulted from non-coronary causes. Similarly, Rivero-Ayerza et al. [14], in a population of patients with CHF, observed that CAD and diabetes mellitus were significantly less prevalent in patients with CHF and AF compared to the population of CHF patients with SR. Our study confirmed these findings and showed an independent association between CAD and the less common occurrence of pAF.

Univariate logistic regression analysis shows that both npAF and pAF are significantly associated

with elevated hs-CRP levels. In multivariate analysis, this association has only been confirmed for pAF. The higher was its value, the higher was the likelihood of developing AF. Chung et al. [8] were the first who reported the association between AF and increasing hs-CRP levels, relative to the severity of AF in patients without HF. In the case of patients with CHF, this association remains unclear. Shah et al. [16] demonstrated an association between serum hs-CRP and increasing LV end-diastolic pressure. Smith et al. [17] showed that the occurrence of AF was independently associated with elevated MR-proANP and hs-CRP. These findings suggest that hs-CRP elevation may be associated with increased vascular wall tension, which may explain its independent association with LA enlargement and hypertension in the group of patients with CHF [9].

We also observed that the prevalence of AF increases with the severity of CHF as assessed using the NYHA functional classification, which may result from the increasing predisposition to developing AF with increasing filling pressures in the atria and their enlargement [5, 6]. We confirmed this association and showed its independent nature. An increase of one NYHA class resulted in an almost 3.5-fold increase in odds ratio for developing npAF and a 4.5-fold increase in odds ratio for developing pAF.

The LA enlargement and the elevated tMxPG values we observed were independently associated with pAF. The higher were these parameters, the higher was the likelihood of developing this arrhythmia. An association between both of these parameters has been shown in the course of CHF. Berkowitz et al. [18] observed that the severity of pulmonary hypertension increased with the severity of LV diastolic dysfunction. It also has been shown that LA volume was depended on the severity of LV diastolic dysfunction [19]. These findings suggest that the disordered LV diastole significantly affects both these parameters. LVEF values did not affect the occurrence of AF in the study population. In a similar population of patients, Rivero-Ayerza et al. [14] also showed no differences in LVEF between patients with AF and patients without this arrhythmia. Straburzyńska-Migaj et al. [20] observed that in patients with systolic HF and SR, a considerably impaired LV diastolic function is independently associated with pulmonary hypertension. LA enlargement and elevated tMxPG may therefore indirectly indicate an association between LV diastolic dysfunction with pAF in the course of CHF both in patients with preserved and in patients with impaired LV systolic function.

Conclusions

More advanced CHF was associated with presence of both types of AF. Non-ischemic etiology of HF and elevated CRP are independently associated with permanent AF compared to SR. LV diastolic dysfunction indicators (increased tMxPG and LA dimension) are independently associated with permanent AF.

Conflict of interest: none declared

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