Does atrial fibrillation in elderly patients with chronic heart failure limit the efficacy of carvedilol? Suggestions from an observational study

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Atrial fibrillation; Carvedilol; Elderly; Heart failure.

Background. **No clinical investigation provided any information about a possible influence of atrial fibrillation on the response to beta-blocker therapy in elderly patients with chronic heart failure (CHF). The aim of this study was to observe carvedilol effects in a cohort of patients > 70 years of age with CHF due to left ventricular dysfunction and with chronic atrial fibrillation.**

Methods. **An observational, 12-month prospective clinical and echocardiographic study was carried out on 240 patients > 70 years of age with heart failure due to systolic dysfunction, 64 of whom with atrial fibrillation.**

Results. **After 1 year of beta-blocker treatment, patients with atrial fibrillation and those in sinus rhythm showed similar benefits, in terms of symptomatic improvement (ΔNYHA -0.44 if atrial fibrillation vs -0.57 if sinus rhythm, p = NS), reduction of events (death + hospitalizations -38 vs -15%), recovery of cardiac function (left ventricular ejection fraction Δ +8.8 vs +9.4%, p = NS; left ventricular end-diastolic volume Δ -17.2 vs -12.5 ml, p = NS), and reduction in mitral regurgitation (Δ -042 vs -0.57, p = NS). No difference was found between the two study groups regarding left ventricular end-diastolic volume reduction (12% in atrial fibrillation patients and 18% in sinus rhythm patients, p = NS) and prevalence of the "reverse remodeling" phenomenon (22 and 21%, respectively, p = NS).**

Conclusions. **In CHF patients > 70 years of age, beta-adrenergic blockade was shown to be equally effective in improving symptoms and left ventricular geometry and function in patients with atrial fibrillation or in sinus rhythm, without any adjunctive sign of long-term clinical deterioration.**

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It is well known that beta-blockers are useful in patients with chronic heart failure (CHF), in that they improve left ventricular function and reduce deaths from heart failure and hospital admissions[1-4]. These favorable effects have recently been observed even in elderly CHF patients[5], who are subjects of a recently concluded, not yet published, randomized trial[6].

Atrial fibrillation is present in about a quarter of CHF patients[7-12] and seems to be a risk factor for significant morbidity[13-16]. Retrospective analysis of the US Carvedilol Trial and other studies showed that the benefits of beta-blockers seen in randomized trials (improvement of left ventricular ejection fraction [LVEF], physical global assessment, symptoms and exercise capacity, and, probably, reduction in the combined endpoint of CHF hospitalizations and death) extend to patients with atrial fibrillation[17,18]. However, the mean age of patients involved in these studies was 60 years, thus data on elderly CHF patients with atrial fibrillation are lacking.

The aim of this observational study was to evaluate the effects of carvedilol therapy on the clinical status and left ventricular remodeling process in a cohort of patients > 70 years of age with CHF due to left ventricular dysfunction and with chronic atrial fibrillation.

Methods

Two hundred and forty CHF patients (151 males, 89 females, mean age 76 ± 5.7 years, range 70-99 years) with an echocardiographically measured LVEF of 29.6 ± 7.3% (range 10-39%) were consecutively recruited by four heart failure clinics into a

12-month prospective study and their data collected into a single database. Sixty-four patients had permanent chronic atrial fibrillation (27%), 24 of whom were females. Thirty-nine out of the 64 patients were treated with carvedilol, while 25 subjects had contraindications to such treatment. In fact, chronic obstructive pulmonary disease limited the carvedilol prescription in 12 cases, low heart rate or blood pressure in 10 cases, and severe peripheral arteriopathy in 3 cases.

Carvedilol was used together with angiotensin-converting enzyme inhibitors or sartans, spironolactone and digoxin (if not contraindicated) and started at a low dose of 3.125 mg twice daily and then progressively doubled in order to reach the target dosage of 50 mg/day or symptoms and signs indicative of "effective" beta-blockade (defined as clinical stability on fixed diuretic dosage, heart rate and systolic blood pressure comprised between 60-70 b/min and 100-120 mmHg, respectively). Four patients were intolerant to carvedilol (worsening heart failure in 2, severe bradycardia in 2). Six patients died before the completion of the follow-up period (1 on and 5 off carvedilol therapy). Thus, clinical effects of 1 year of carvedilol therapy in elderly patients with atrial fibrillation were assessed in 34 patients and compared with those in patients without atrial fibrillation. Clinical and echocardiographic variables were recorded before and after 12 months of carvedilol therapy in all survivors. Standard transthoracic echocardiographic studies were systematically performed by expert cardiologists at baseline and at the end of the follow-up using a Megas Esaote Biomedica machine (Florence, Italy) equipped with a 2.5 to 3.5 MHz annular-array transducer. Left ventricular volumes and LVEF were computed from apical 2- and 4-chamber views by the area-length method and mitral regurgitation was diagnosed by color Doppler and quantified using a 1-4+ grading system. Details of the reproducibility of echocardiographic measurements detected in patients with heart failure from our laboratory have been previously reported[19].

In this study we used the NYHA functional classification as measure of the functional status, and the left ventricular end-diastolic volume (LVEDV), LVEF (normal if ≥ 50%) and the degree of mitral regurgitation as markers of the left ventricular remodeling process. Patients were defined as "improved" when a reduction of at least one NYHA functional class associated with an increase in LVEF > 10 points % were documented from baseline to 1-year evaluation. The left ventricular reverse remodeling phenomenon was recognized in case LVEDV decreased > 24 ml/m^2 from baseline to the end of follow-up (> 2 SD of the mean)[19].

Statistical analysis. The differences in continuous variables between groups were assessed by an analysis of variance (ANOVA/MANOVA); *post-hoc* comparisons were analyzed by the Scheffé test. Differences in categorical variables were tested by χ^2 tests. Multivariate analysis was used to evaluate the independent predictors of clinical improvement and left ventricular reverse remodeling. Statistical significance was set at $p < 0.05$ for all analyses.

Results

The clinical characteristics of all patients and comparisons between patients with atrial fibrillation and in sinus rhythm are reported in table I.

Valvular disease was more frequent among patients with atrial fibrillation.

Contraindications to carvedilol were present in similar percentages among patients with atrial fibrillation (39%) and among those in sinus rhythm (31%). In the latter group, chronic obstructive pulmonary disease represented the main contraindication in 28, bradycardia or hypotension in 15, and peripheral vascular disease (with or without diabetes) in 11 patients.

There were no differences in the tested characteristics between atrial fibrillation patients treated or not by carvedilol. The same was true for sinus rhythm patients. Moreover, apart from a slightly higher LVEF and, obviously, their heart rhythm, atrial fibrillation patients treated with carvedilol did not differ from sinus rhythm patients. As regards concomitant treatment, as expected digoxin was more often prescribed in atrial fibrillation patients. Dosages of furosemide were higher among patients not treated with carvedilol, especially if they had atrial fibrillation.

After 1 year of beta-blocker treatment, patients with atrial fibrillation and those in sinus rhythm showed similar benefits, in terms of symptomatic improvement and recovery of cardiac function (Table II). Of note, the dose of carvedilol was significantly higher in atrial fibrillation patients (perhaps because of the ventricular response control) but the dosages of furosemide had not been increased further. The portion of atrial fibrillation patients who could be defined "improved" at the final 1-year evaluation was 22%. This behavior was recognized in a similar percentage of counterparts with sinus rhythm (28%, p = NS). Compared to the latter, our elders with atrial fibrillation had a similar relevant decrease of the degree of mitral regurgitation over time (Table II). Concordantly, no difference was found between the two study groups in terms of LVEDV reduction and prevalence of the reverse remodeling phenomenon (22 and 21%, respectively, p = NS).

At a multivariate analysis where atrial rhythm together with age, sex, Charlson score, systolic blood pressure, diabetes mellitus, duration of symptoms and etiology of CHF, basal NYHA class, LVEF, mitral regurgitation and LVEDV were considered, the duration of symptoms (< 6 months) emerged as the only independent predictor both of clinical improvement (odds ratio 7.3, confidence interval 19.1-2.7, $p < 0.0001$) and left ventricular reverse remodeling process (odds ratio 3.3, confidence interval 8.3-1.3, p = 0.01).

Table I. Comparison between atrial fibrillation and sinus rhythm elderly patients treated and not treated with carvedilol.

	Atrial fibrillation		Sinus rhythm		F	p	p post-hoc
	Carvedilol	No carvedilol	Carvedilol	No carvedilol			
No. patients	39	25	122	54			
Age (years)	75.4 ± 5.7	78.1 ± 5.3	75.8 ± 5.3	76.2 ± 5.4	1.36	NS	
Females	13 (33%)	11 (44%)	51 (42%)	14 (26%)		NS	
Comorbidity Charlson index	2.1 ± 1.5	2.2 ± 1.3	2.1 ± 1.5	2.4 ± 1.5	0.66	NS	
LVEF (%)	31.4 ± 6.8	30.8 ± 7.7	28.7 ± 7.3	29.4 ± 7.4	1.7	NS	
NYHA class	2.7 ± 0.6	3.0 ± 0.6	2.7 ± 0.6	2.6 ± 0.6	2.9	NS	
Heart failure duration (months)	15.6 ± 20	20.2 ± 19	15.9 ± 20	21.6 ± 19	0.97	NS	
Drugs							
Spironolactone	15 (38%)	13 (52%)	63 (52%)	25 (46%)			
ACE-inhibitors	25 (64%)	15 (60%)	95 (78%)	54 (67%)			
AT-I inhibitors	9 (23%)	5 (20%)	21 (17%)	8 (15%)			
Digoxin	29 (74%)*	23 (92%)*	66 (54%)	32 (59%)			
Furosemide dosage (mg)	56 ± 64	80.8 ± 66**	37.6 ± 31	58.5 ± 78	5.07	0.002	0.04**
Etiology							
Ischemic	16 (41%)	7 (28%)§	72 (59%)	35 (65%)			
Valvular disease	6 (15%)§	8 (32%)§	7 (6%)	14 (7%)			
Hypertensive	6 (15%)	4 (16%)	17 (14%)	3 (5%)			
Carvedilol intolerance	4 (10%)		7 (6%)				
Death	1 (3%)	5 (20%)	16 (13%)	8 (15%)			

ACE = angiotensin-converting enzyme; AT-I = angiotensin I; LVEF = left ventricular ejection fraction. Only significant χ^2 are depicted. * digoxin percentage significantly higher in atrial fibrillation patients treated (p = 0.02) and not treated (p = 0.004) with carvedilol; ** valvular etiology significantly higher in atrial fibrillation patients treated (p = 0.0001) and not treated (p = 0.0001) with carvedilol; § ischemic etiology significantly lower (p = 0.0001) in atrial fibrillation patients not treated with carvedilol.

During the follow-up of the patients with atrial fibrillation, 10 of those on carvedilol were rehospitalized at least once (25%) as were 15 of those patients not receiving beta-blocker therapy (60%). The respective numbers for sinus rhythm patients were 31 (25%) and 26 (48%). Thus, combining 1-year death and hospitalizations, atrial fibrillation patients on carvedilol had a lower rate of events than did patients not receiving the beta-blocker (31 vs 69%, p = 0.003). This reduction in event rate is even greater than that seen in the sinus rhythm patients (41% in carvedilol-treated patients vs 56% in patients not given carvedilol, p = 0.0059).

Discussion

The effectiveness of beta-blocker therapy in CHF patients with atrial fibrillation is still controversial. Similar degrees of clinical and LVEF improvements in response to carvedilol were reported in patients with atrial fibrillation in a retrospective analysis of 45 patients in Arnold's study[20] as well as in the US Carvedilol Heart Failure Trials Program[17]. Moreover, in this latter trial, there was a trend (albeit not statistically significant) toward a reduction in the combined endpoint of death and heart failure hospitalization in the carvedilol group. However, when changes in LVEF after carvedilol treatment were measured by Schleman et al.[21], a significant negative correlation was found with the presence of atrial fibrillation, which also was associated with hospitalization after initiation of carvedilol therapy. Furthermore, conflicting results emerged by subgroup analyses of the CIBIS II and MERIT-HF trials regarding the effects of bisoprolol and metoprolol in reducing the risk of death and/or hospitalization in CHF patients with atrial fibrillation[22-24].

No clinical investigation provided any information about a possible influence of atrial fibrillation on the response to beta-blocker therapy in elderly patients with CHF. In this 1-year observational study, carvedilol was equally effective in improving symptoms and left ventricular systolic function in elderly patients with atrial fibrillation or in sinus rhythm, without any adjunctive sign of long-term clinical deterioration (i.e. there was no change in the dosage of loop diuretics, and there was a reduction in the combined endpoint of hospitalizations and death).

Considering the older age and the multiple comorbidities of our patients, the percentage of "clinical improvement" found in the subjects with atrial fibrillation (near a quarter of survivors) has to be considered particularly high. In our analysis atrial fibrillation *per se* did not influence the clinical effects of beta-blocker therapy, which exclusively depended, instead, on the duration of the cardiac syndrome. Similarly, the presence of atrial fibrillation in CHF elders receiving carvedilol did not reduce the likelihood of developing left ventricular reverse remodeling process, which was, once again, inversely related to the duration of heart failure symptoms. Our data confirm the analyses of Palazzuoli et al.[25] and Konstam et al.[26], who clearly showed in the recent past that left ventricular reverse

Table II. Carvedilol effects: 1-year follow-up. Comparison between atrial fibrillation and sinus rhythm elderly patients.

	Carvedilol									
	Atrial fibrillation (n=34)			Sinus rhythm (n=99)			Heart rhythm effect		Carvedilol effect	
	Basal	12 months	Δ	Basal	12 months	Δ	F	p	F	p
Age (years)	75.7 ± 5.7			75.3 ± 4.9			p = 0.63, NS			
Carvedilol dose (mg)	29.2 ± 16.5 (range 6.25 ÷ 62.5)			22.7 ± 14.8 (range 3.125 ÷ 50)			p = 0.03			
NYHA class	2.73 ± 0.67	2.29 ± 0.76	-0.44	2.64 ± 0.6	2.07 ± 0.59	-0.57	1.96	NS	55.5	< 0.0001
LVEF (%)	31.5 ± 6.1	40.3 ± 12	+8.8	28.7 ± 7.4	38.1 ± 10	+9.4	2.40	NS	78.2	< 0.0001
LVEDV (ml)	94.8 ± 41.5	77.6 ± 34.2	-17.2	101.8 ± 37	89.3 ± 35.8	-12.5	1.47	NS	31.9	< 0.0001
Mitral regurgitation	2 ± 0.8	1.58 ± 0.7	-0.42	1.75 ± 1	1.18 ± 0.99	-0.57	2.86	NS	18.5	< 0.0001
HR (b/min)	86.4 ± 15	72.5 ± 11	-13.9	75.8 ± 13	65.3 ± 9	-10.5	20.7	< 0.0001	53.7	< 0.0001
SBP (mmHg)	135 ± 21	126 ± 14	-9	132.4 ± 21	123.9 ± 20	-8.5	0.41	NS	12.8	0.0005
Furosemide dosage (mg)	53.7 ± 67	50.4 ± 49	-3.3	33.4 ± 28.5	28.8 ± 20	-4.6	8.9	0.003	2.29	NS

HR = heart rate; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; SBP = systolic blood pressure.

remodeling may take place in many elderly as well as in younger CHF patients.

An expected finding of our observation was that patients with atrial fibrillation, who had a slightly higher mean heart rate at baseline, required higher dosages of carvedilol than those with sinus rhythm specifically for the ventricular response control. It is worth noting, however, that the reductions in heart rate and systolic blood pressure were similar in both groups, irrespective of the dose prescribed at the end of follow-up. Further, unlike controlled clinical trials, only a minority of our patients achieved the "target dose" of 50 mg daily (given in a similar percentage of atrial fibrillation and sinus rhythm patients), and yet effects on the clinical status and left ventricular geometry were evident, suggesting that even low doses may be effective in elderly patients with CHF[7,8,27,28].

The originality of the present study lies in the combination of the two clinical variables such as age > 70 years and atrial fibrillation; its limits are that it is an observational and non-randomized study in a small sample of patients, with few clinical endpoints. Our experience suggests that the beneficial effects of carvedilol on the clinical status and left ventricular geometry and function are independent of cardiac rhythm even in elderly CHF patients with left ventricular systolic dysfunction. While waiting the results of subgroup analysis of the SENIORS trial, this information may reassure physicians who operate in the general setting that includes older patients with multiple comorbidities.

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