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Combination therapy with carvedilol and amiodarone in patients with severe heart failure

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Abstract

Background: Carvedilol and at least in some studies, amiodarone have been shown to improve symptoms and prognosis of patients with heart failure. There are no reports on the outcome of combined treatment with both drugs on top of angiotensin-converting enzyme inhibitors (ACEI), diuretics and digitalis. *Methods and Results*: In 109 patients with severe heart failure submitted for heart transplantation at one single center between the years 1996 and 1998 [left ventricular ejection fraction (LVEF) $24.6 \pm 11\%$, 85% males, 52% idiopathic dilated cardiomyopathy (DCM), mean observation time 1.9 ± 0.4 years] a therapy with low-dose amiodarone (1000 mg/week) plus titrated doses of carvedilol (target 50 mg/day) was instituted. In addition, patients received a prophylactic dual chamber pacemaker (PM) in order to protect from bradycardia and for continuous holter monitoring. The devices were programed in back-up mode with a basal rate of 40 i.p.m. with a hysteresis of 25%. Significantly, more patients were in sinus rhythm after 1 year than at study entry (85% vs. 63%, $P < 0.01$). In 47 patients, under therapy over at least 1 year, the resting heart rate fell from 90 ± 19 to 59 ± 5 b.p.m. ($P < 0.001$). Ventricular premature contractions in 24-h holter ECGs were suppressed from 1.0 ± 3 to $0.1 \pm 0.3\%/24$ h ($P < 0.001$) as did numbers of tachycardias > 167 b.p.m. detected by the pacemaker (1.2 ± 2.8 episodes/patient/3 months vs. 0.3 ± 0.8 episodes/patient/3 months after 1 year ($P < 0.01$). The LVEF increased from 26 ± 10 to $39 \pm 13\%$ ($P < 0.001$). NYHA class improved from 3.17 ± 0.3 to 1.8 ± 0.6 ($P < 0.001$) as well as right heart catheterization data. From the total cohort, seven patients (6%) developed symptomatic documented bradycardic rhythm disturbances requiring reprograming of their pacemakers to DDD(R)/VVI(R) mode with higher basic rates. Two of these patients developed AV block, four sinu-atrial blocks or sinus bradycardia and one patient had bradycardic atrial fibrillation. During the observation period five patients died (3 sudden, 1 due to heart failure and 1 due to mesenteric infarction). Two patients had undergone heart transplants. The 1-year survival rate (Kaplan–Meier) without transplantation was 89%. Compared to historic control patients with amiodarone only ($n = 154$) or without either agent ($n = 283$) this rate was 64 and 57% ($P < 0.01$). *Conclusions*: Heart failure patients benefit

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AT1-AT, angiotensin 1 receptor antagonist; $aVDO_2$ (%), arterio-venous oxygen difference; Captoprileqi, captopril equivalent dose [dosage of ACEI or AT1-AT (mg) × (150/maximal recommended dosage of ACEI or AT1-AT (mg)]; CHF, congestive heart failure; CI ($l/min \times m^2$), cardiac index; DCM (%), dilated cardiomyopathy (primary) rate of patients in percent; FS, fractional shortening; HR, heart rate; i.p.m., impulses per minute; LAes (cm), left atrial end-systolic diameter; LVEDD (cm), left ventricular end-diastolic diameter; LVEF (%), left ventricular ejection fraction in percent; MAP (mmHg), mean arterial pressure; NYHA, New York heart association; LVSWI (pm), left ventricular stroke work index; PCP (mmHg), pulmonary capillary wedge pressure; PVR (dyn), pulmonic vascular resistance; RAP (mmHg), right atrial pressure; SD, sudden death; SVR (dyn), systemic vascular resistance; VPCs (%), ventricular premature contractions in percent per 24 h; VT (n), Ventricular tachycardia (three or more consecutive premature ventricular contractions) per 24 h

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from a combined therapy with carvedilol and amiodarone resulting in a markedly improved NYHA stage, an increase in LV ejection fraction, a stabilization of sinus rhythm, a significant reduction in heart rate, a delay of electrical signal conduction and a suppression of ventricular ectopies. Approximately 6% of patients under such a regime became pacemaker-dependent in the first year. Compared to historic controls prognosis was better and the need for heart transplantation was lower. The exact role of either agent in combination or alone should be clarified in larger randomized studies.

Keywords: Amiodarone; Carvedilol; Heart failure; Sudden death; Heart transplantation

1. Introduction

As heart transplantation (HTx) as a definite cure for cardiac failure is greatly limited by the shortage of donor organs [1], improvements in medical therapy are urgently needed, especially in patients with the most severely compromised ventricular function [2]. Many of these heart transplant candidates die while on the waiting list, which is steadily increasing [3]. The combination of ACEI, beta-blockers and spironolactone have reduced mortality due to progressive heart failure and sudden death by 50% or more [4–8]. The control of sudden death becomes increasingly important, as it accounts for approximately half of the deaths in heart failure patients [9]. A further shift to sudden death rather than death from pump failure is observed when hemodynamic therapy is more and more improved [10]. Although shown to be effective in at least some heart failure subgroups [11], due to economic problems the prophylactic implantation of implantable cardioverter defibrillators (ICDs) is restricted to selected patients. Prophylactic medical anti-arrhythmic therapy therefore, remains the only possible approach for the majority of the patients [12]. Studies with class I agents (i.e. 'CAST') showed their pro-arrhythmic effects, worsening the prognosis instead of being beneficial [13]. Amiodarone, an anti-arrhythmic drug without negative inotropic action, is well tolerated in heart failure. Its ability to increase coronary blood flow and to reduce systemic vascular resistance [14] are desired side effects. Little pro-arrhythmia makes amiodarone safe even in patients with known torsade des pointes tachycardias [15]. Some reports have shown an increase of the ejection fraction under amiodarone therapy [16,17]. In the randomized placebo-controlled GESICA trial [18], overall prognosis improved by 28% due to a likewise reduction of pump failure and sudden death. In the CHF-STAT study — greatly different from the GESICA trial regarding dosage, underlying aetiologies of cardiomyopathies and disease severity [19] — these results were not confirmed. Subgroup analysis of this study however, and a *meta*-analysis of a total of 13 randomized trials show that amiodarone indeed proved beneficial on the prognosis of approximately a 13% relative risk reduction per year [20]. Similar to CHF-STAT, the EMIAT study did not show an overall protective effect of amiodarone [21], but subgroup analysis reveals a marked prognostic advantage in the cohort of patients with additional beta-blocker therapy [22].

Based on these data we hypothesized that a combination of β-blockers (carvedilol) and amiodarone have synergistic beneficial effects. As no systematic information on the effects of the combined use of both in heart failure is available [23], we initiated a pilot study to investigate clinical, hemodynamic and electrophysiologic characteristics under combined β-blocker and amiodarone therapy. Because of reports describing severe bradycardias under a combination of beta-blockers and amiodarone [24] and reports of a substantial rate of bradyarrhythmic arrests in candidates for heart transplantation [25], pacemakers were implanted prophylactically in every patient.

2. Methods

2.1. Patient selection

We recruited consecutive ambulatory patients who were admitted to our institution as candidates for heart transplantation in the years 1996–1998. Control patients were ambulatory candidates for heart transplantation submitted in the former years (1986–1996). Non-compliance or loss of follow-up ($n = 27$), emergency situations ($n = 57$) and the presence of an ICD ($n = 24$) were exclusion criteria for this study. Exclusion and inclusion criteria did not change over time, as described in detail [10]. Due to low numbers, patients under adjunctive carvedilol therapy only ($n = 16$) were also excluded from analysis. A total of 560 patients were eligible for this study. In approximately half of the patients, end-stage coronary artery disease was the underlying cause for heart failure. The other half suffered from DCM (Table 1). Three different therapeutic modalities were used over time: (a) from 1986 to 1992 neither amiodarone, nor β-blocker ($n = 283$); (b) amiodarone treatment ($n = 154$) during 1993–1996 in all patients without contraindications when positive results of the GESICA trial became

Table 1
Entry characteristics of CHF patients in whom the combination of amiodarone plus carvedilol (ACall = all patients, ACsub = subset of patients from ACall with complete 1 year follow-up) was initiated compared to patients under amiodarone only (A) or without carvedilol or amiodarone (no AC)

	ACall	ACsub	A	no AC	$P < 0.05$
n	109	47	154	283	
Pacemakers (%)	100	100	9	6	A + C vs. oth.
Mean age (years)	54 ± 8	53 ± 9	54 ± 11	50 ± 12	no vs. A + C
Males (%)	85	87	90	83	ns
DCM (%)	52	48	47	49	ns
NYHA stage	3.1 ± 0.3	3.17 ± 0.3	3.2 ± 0.5	3.3 ± 0.5	ns
LVEF (%)	24.6 ± 11	26 ± 10	24.1 ± 12	21.4 ± 12	ns
Creatinine (mg/dl)	1.2 ± 0.3	1.2 ± 0.3	1.3 ± 0.6	1.4 ± 0.6	ns
Sodium (mmol/l)	137 ± 4	136 ± 4	137 ± 6	137 ± 5	ns
VPCs/24 h (%)	1.5 ± 4	1.1 ± 3	1.4 ± 3	0.9 ± 2	ns
VT/24 h (*n*)*	1.6 ± 1	1 ± 1	2.1 ± 3.4	2.1 ± 3.4	ns
Frusemide (mg/d)	118 ± 140	125 ± 83	127 ± 87	132 ± 67	ns
Captoprileqi (mg/d)	90 ± 45	84 ± 38	71 ± 31	54 ± 30	A + C vs. no
FS (%)	14.8 ± 4	12.8 ± 6	14.8 ± 6	15.5 ± 7	ns
LVEDD (cm)	7.0 ± 0.8	7.0 ± 0.7	6.9 ± 0.9	6.9 ± 1.2	ns
LAes (cm)	4.6 ± 0.7	4.6 ± 0.5	4.7 ± 0.7	4.6 ± 0.9	ns
Mitral regurg. (grade)	1.6 ± 1	1.4 ± 1	1.7 ± 0.8	1.7 ± 0.8	ns
Tricuspid regurg (grade)	0.8 ± 0.8	0.8 ± 0.8	0.9 ± 1	0.9 ± 1	ns
Roskamm stage	3.6 ± 0.7	3.7 ± 0.6	3.6 ± 0.7	3.3 ± 1	A + C vs. no
PCP (mmHg)	18 ± 7	16 ± 9	19 ± 9	19 ± 9	ns
RAP (mmHg)	6.5 ± 5	5.6 ± 5	7.5 ± 6	7.5 ± 5	ns
CI (l/min* m2)	2.2 ± 0.5	2.2 ± 0.5	2.2 ± 0.5	2.3 ± 0.6	ns
SVR (p* m/cm-5)	1409 ± 412	1473 ± 412	1477 ± 456	1454 ± 500	ns
PVR (p* m/cm-5)	216 ± 140	216 ± 140	229 ± 150	238 ± 194	ns
aVDO2 (vol%)	6.7 ± 1.7	6.3 ± 1.5	6.8 ± 1.7	6.7 ± 2	ns
LVSWI (pm)	24 ± 11	25 ± 10	24 ± 12	24 ± 13	ns
MAP (mmHg)	77 ± 12	77 ± 12	79 ± 13	81 ± 14	no vs. oth.
HR/min	89 ± 16	90 ± 19	86 ± 16	87 ± 16	ns

available [18]; and (c) additional carvedilol (not tolerated $n = 14$, tolerated in $n = 109$), thereafter. After informed consent the latter group also received prophylactic dual chamber pacemakers programed in an inhibited mode (VVI 40, hysteresis 30 for three cycles). The rate of pacemakers was low in the control groups (6% in the group without anti-arrhythmics and 9% in the amiodarone-only group). The protocol including prophylactic pacemaker implants was approved by the Hamburg Ethic Committee.

2.2. Evaluation and management

The medical therapy was intensified individually in all groups in a similar way, according to the results of repeated right heart catheterization studies [10]. Measurements were usually taken 2 h after intake of the chronic medication to assess the efficacy of the current therapy. The protocol was ambulatory for all patients. According to filling pressures (target RA pressure < 4 mmHg, target PCP < 15 mmHg), diuretic and vasodilator therapy was adjusted, mainly by adding xipamide (mean daily dose of 16 ± 7 mg), molsidomine (mean daily dose of 28 ± 12 mg) and/or nitrates (mean daily dose of 64 ± 22 mg). Spironolactone (mean daily dose of 34 ± 18 mg) was given whenever renal function and potassium levels remained within tolerable margins. In all patients ACEI were up-titrated to the highest tolerable dose (target systolic blood pressure ≤ 100 mmHg). For comparison of the groups we defined a captopril equivalent dose as the final dose of ACEI or AT1-AT (mg) $\times$ [150/maximal recommended dose of ACEI or AT1-AT (mg)]. We used the following maximal recommended daily dosages as noted in the patients brochure: captopril 150 mg; enalapril 40 mg; fosinopril 40 mg; quinalapril 40 mg; ramipril 10 mg; and losartan 100 mg. We saw a general indication for digitalis glycosides which was given as digitoxin (mean daily dose of 0.065 ± 0.01 mg). We used a relatively low digitoxin dose due to known increases of digitoxin plasma levels and concomitant amiodarone therapy [26]. Accordingly, digitoxin plasma levels measured 12 months after evaluation were within the therapeutic range (19 ± 9 ng/ml). Eighty-nine percent of the patients received phenprocoumon to prevent embolic events, without any bleeding complications (target International Normalized Ratio 2–3). Blood coagulation tests were done repeatedly at least every week during the stabilization phase, because of a reduced

demand of anticoagulants under amiodarone co-therapy [27]. Amiodarone was started in all patients immediately after the first evaluation with a loading dose of 600 mg/day over 2 weeks and 1000 mg/week, thereafter. The mean dose of amiodarone was 1182 ± 364 mg/week. Thyroid hormone levels were repeatedly controlled. Eighteen patients did not receive or did not tolerate amiodarone (8 due to pre-existing hyperthyroidism, 6 due to hyperthyroidism under therapy, 1 due to gastrointestinal intolerance, 1 due to dermatological problems, 1 due to ocular problems and 1 due to cholestatic hepatitis). When patients were in a stable condition (no increase in diuretics or signs of worsening in the previous 14 days), carvedilol was given initially in low doses starting with 1.56 mg bid, increasing this dosage every 14 days if tolerated, with a target dose of 25 mg bid. Fourteen patients did not tolerate carvedilol due to side effects (hypotension and dizziness $n = 7$, dyspnoea $n = 2$, angina pectoris $n = 1$, psoriasis $n = 1$, allergic dermatitis $n = 1$, depression $n = 1$ and worsening of symptoms from peripheral arterial occlusive disease $n = 1$). The mean dose of carvedilol was 35.7 ± 17 mg/day. Carvedilol was started 2–4 weeks after initial presentation. Pacemaker implantation with right atrial and right ventricular leads was scheduled during the first 4 weeks of observation and was performed with standard techniques via cephalic or subclavian veins. The pacemaker implantation usually overlaps with the up-titration phase of carvedilol. As pulse generators CHORUS RM 7034 (ELA Medical, Paris, France) were used, loaded with a program to detect and store bradycardic and/or tachycardic rhythm disturbances [28]. The upper rate limit for the detection of VT was set at 167 b.p.m. for more than three consecutive cardiac cycles to exclude most of supraventricular tachycardias. Correspondingly, the lower rate limit for the detection of bradycardias was set at 30 b.p.m. for more than three cardiac cycles to exclude physiologic sinus bradycardias.

Mortality due to the pacemaker implantation was zero. Two reoperations for ventricular and atrial lead dislodgements were necessary. The pacemakers were programed in VVI 40 hysteresis 30 back-up mode unless reprograming to a higher rate was indicated due to symptomatic bradycardia. Three-monthly follow-up investigations included right heart catheterization, physical examination, routine lab, chest X-ray (evaluation of cardiothoracic ratio), echocardiography (fractional shortening and end-diastolic left ventricular diameter, valve function), resting ECG at a paper speed of 100 mm/s (measurement of PQ time and QRS width) and Holter-ECG recordings with analysis of ventricular premature contractions (VPCs). Ventricular tachycardia in holters was defined as three or more consecutive ventricular beats. Pacemakers were interrogated and stored marker chains were analyzed. Wenckebach point was measured in AAI mode (highest atrial pacing rate with regular conduction to the ventricle). Left ventricular ejection fraction at baseline was measured by analysis of the right anterior oblique view (RAO) at left heart catheterization in the case this investigation was done within the last 3 months (53% of patients) or was calculated from the baseline echocardiography. Ejection fraction at months 3 and 12 was determined by radionuclid-ventriculography with re-injected Technetium-labeled erythrocytes. A good correlation has been shown between radionuclid-ventriculography and the LV angiogram [29]. Exercise capacity measurements were not done. Only patients not responding to an intensification of medical therapy were processed to HTx. The same team of cardiologists was responsible over the whole study period so that patient management remained similar over time. Clinical events (death, mode of death, HTx) were noted prospectively in EXCEL work sheets. Sudden death (SD) was defined as death within 1 h of symptoms without premonitory symptoms during a clinically stable period of at least 1 week; death after a period of deterioration in signs and symptoms of CHF, despite maximal treatment, was classified as resulting from progressive CHF.

3. Statistical analysis

Differences in the results of clinical and hemodynamic data were checked for significance by means of Student's *t*-test for matched pairs. Non-parametric data were checked for significance by Wilcoxon test. All data were expressed as mean ± S.D. Survival rate was calculated by Kaplan-Meier analysis, and differences between groups were tested for significance by multivariance analysis (bonferroni correction) and the log-rank test (Winstat 3.1, Kalmia Inc and SPSS for Windows 6.1).

4. Results

The patients characteristics are described in Table 1. There were no major differences between the groups, except a lower mean captopril equivalent dosage in the historic cohort of patients without amiodarone and beta-blockers. The following results were drawn from patients tolerating the combination therapy of amiodarone and carvedilol and reached at least 1 year follow-up (Table 2): Significantly more patients were in sinus rhythm after 1 year than at study entry ($n = 40$, 85% of the cohort vs. $n = 30$, 63% of the cohort, $P < 0.01$). Resting and mean 24-h heart rate fell during the first follow-up year from

90 ± 19 to 59 ± 5 b.p.m. and from 86 ± 10 to 69 ± 8 b.p.m. (Fig. 1, $P < 0.001$ for all time points vs. entry). The Wenckebach point was lowered (Table 2). QRS width and PQ conduction time increased (Table 2). To exclude a drug overdose as a reason for bradycardias we determined serum amiodarone and digitoxin levels in all patients at months 3 and 12. Mean serum amiodarone level was 0.98 ± 0.4 ng/ml mean serum desmethylamiodarone level was 0.7 ± 0.3 ng/ml (just below the therapeutic range) and mean serum digitoxin level at month 12 was 19 ± 9 ng/ml (within the therapeutic range). Ventricular ectopic beats were suppressed in 24-h holter ECGs from 1.1 ± 3 to $0.1 \pm 0.3\%/24$ h (Fig. 2, $P < 0.01$ for all time points vs. entry). This suppression was accompanied by a reduced rate of ventricular tachycardias in the PM memory from 1.2 ± 2.8 to 0.3 ± 0.8 episodes/patient/3 months (Table 2). The LVEF increased from 26 ± 10 to $32 \pm 13\%$ after 3 months and to $39 \pm 13\%$ after 1 year (Table 2, Fig. 3, $P < 0.001$, for all time points vs. entry) and NYHA stage of the patients decreased from 3.17 ± 0.3 to 1.8 ± 0.6 (Fig. 4, $P < 0.001$ for all time points vs. entry). Marked improvements were seen in echocardiographic assessment, such as an increase of fractional shortening (FS), a decrease of left ventricular end-diastolic diameter (LVEDD) and left atrial end-systolic diameter (LAes). The cardiothoracic ratio fell from 0.57 ± 0.1 to 0.49 ± 0.1 after 1 year ($P < 0.01$). Hemodynamic data, such as pulmonary capillary wedge pressure (PCP, right atrial pressure (RAP), cardiac index (CI), systemic vascular resistance (SVR), pulmonal vascular resistance (PVR), left ventricular stroke work index (LVSWI), also improved. Mean arterial pressures showed no significant changes over time. More patients ($n = 85$) up to now reached a 3-month follow-up. However, their results were not significantly different from those reaching 1 year and therefore, were not shown. Seven (6%) of the patients developed symptomatic bradycardic rhythm disturbances requiring reprograming of the pacemaker to a higher rate and/or to DDD(R)/VVIR mode. Two of these patients developed AV block, four had sinu-atrial blocks and/or sinus-bradycardia < 40/min. One patient developed bradyarrhythmic atrial fibrillation. During an observation period of 1.9 ± 0.4 years 5 patients died (3 sudden, 1 CHF death and 1 mesenteric infarct). Two patients received a donor heart. The survival rate without transplantation is shown in Fig. 5 comparing patients on amiodarone, on

Table 2
Changes in clinical, hemodynamic and electrocardiographic parameters in a subset of 47 patients (ACsub) under combined carvedilol/amiodarone therapy reaching a 1-year follow-up (characteristics see Table 1)[a]

	Pre	m3	m6	m9	m12
Sinus rhythm (%)	63	72	83	78	85
Resting heart rate (b.p.m.)	90 ± 19	72 ± 12	66 ± 10	65 ± 11	59 ± 5
Mean heart rate (b.p.m.)	86 ± 10	73 ± 14	72 ± 9	70 ± 7	69 ± 8
Wenckebach Point (i.p.m.)	111 ± 10	102 ± 14	104 ± 12	98 ± 17	100 ± 18
NYHA stage	3.17 ± 0.3	2.2 ± 0.5	2.0 ± 0.8	2.0 ± 0.7	1.8 ± 0.6
LVEF (%)	26 ± 10	32 ± 13	–	–	39 ± 13
FS (%)	12.8 ± 6	17 ± 6	21 ± 6	23 ± 6	27 ± 7
LVEDD (cm)	7.0 ± 0.7	6.7 ± 0.9	6.3 ± 0.9	6.4 ± 1	5.8 ± 0.9
LAes (cm)	4.6 ± 0.5	4.4 ± 0.7	4.0 ± 0.7	4.2 ± 0.7	4.1 ± 0.8
Mitral regurg. (°)	1.4 ± 1	1.3 ± 0.9	0.6 ± 0.9	0.7 ± 1.0	0.5 ± 0.7
Tricuspid regurg (°)	0.8 ± 0.8	0.5 ± 0.7	0.2 ± 0.4	0.4 ± 0.8	0.2 ± 0.3
Cardio-thoracic ratio	0.57 ± 0.1	0.53 ± 0.1	0.51 ± 0.1	0.52 ± 0.1	0.49 ± 0.1
Creatinine (mg/dl)	1.2 ± 0.3	1.3 ± 0.6	1.3 ± 0.4	1.3 ± 0.4	1.2 ± 0.4
Sodium (mmol/l)	136 ± 4	136 ± 6	137 ± 5	138 ± 6	136 ± 5
QRS width (ms)	128 ± 34	127 ± 26	129 ± 30	130 ± 34	138 ± 36
PQ time (ms)	198 ± 33	202 ± 37	206 ± 29	209 ± 28	214 ± 32
VPCs/24 h (%) (Holter)	1.1 ± 3	0.4 ± 0.9	0.3 ± 0.6	0.2 ± 0.5	0.1 ± 0.3
VT/24 h (n)* (Holter)	1 ± 1	0.4 ± 0.7	0.6 ± 1	0.3 ± 0.6	0.2 ± 0.4
Pauses/pt (f < 30 b.p.m.) (RAM)	3.1 ± 1.8	3.2 ± 1.6	4 ± 1.9	31 ± 22	21 ± 14
Tachy/pt (f > 167 b.p.m.) (RAM)	1.2 ± 2.8	0.5 ± 1.3	0.3 ± 0.7	0.2 ± 0.6	0.3 ± 0.8
Roskamm stage	3.7 ± 0.6	3.3 ± 1	–	–	2.9 ± 1
PCP (mmHg)	16 ± 9	7 ± 6	–	–	6 ± 6
RAP (mmHg)	5.6 ± 5	1.8 ± 4	–	–	2.2 ± 3
CI (l/min* m2)	2.2 ± 0.5	2.5 ± 0.6	–	–	2.5 ± 0.6
SVR (p* m/cm-5)	1473 ± 412	1373 ± 600	–	–	1200 ± 300
PVR (p* m/cm-5)	216 ± 140	200 ± 150	–	–	176 ± 150
LVSWI (pm)	25 ± 10	38 ± 13	–	–	38 ± 13
MAP (mmHg)	77 ± 12	74 ± 13	–	–	76 ± 13

[a]All values (except MAP) were significantly better than baseline values (P at least < 0.05).

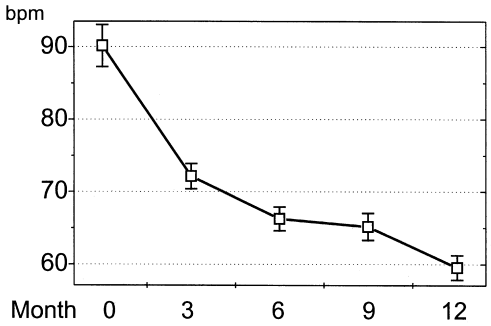


Fig. 1. Heart rate at rest (b.p.m.) in 47 CHF patients under combined amiodarone/carvedilol therapy. $P < 0.001$ month 0 vs. all other months.

carvedilol plus amiodarone or without any of these agents. Survival was best with both agents. To reduce selection bias, this analysis was done according to the intention to treat principle and includes patients not tolerating carvedilol. These were usually those with the more severe diseases. Sudden death rate is shown in Fig. 6. Similar to total survival a significant benefit was demonstrated for the group under combination therapy.

5. Discussion

Patients in our study were ambulatory candidates for cardiac transplantation, which are representative of 90–95% of listed patients worldwide [30]. This is the first report to describe the effects of a combination therapy of amiodarone and the beta-blocker carvedilol in these severely ill patients. The only other studies on beta-blocker/amiodarone interactions were done by a French group dealing with arrhythmia patients suffering from refractory ventricular tachycardia. Although small and a decade old, this report showed that the combination of amiodarone and beta-blockers was well tolerated and effective at suppressing arrhythmias, where either agent alone was ineffective [31].

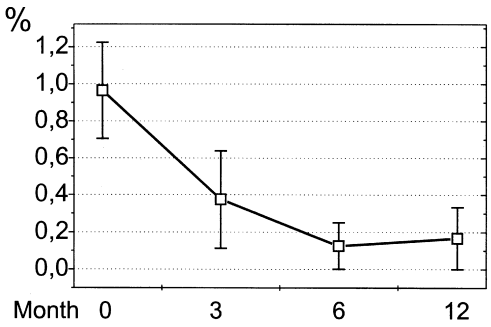


Fig. 2. Ventricular ectopy in conventional holter studies expressed as % VES/24 h, month 0 vs. other months: $P < 0.01$.

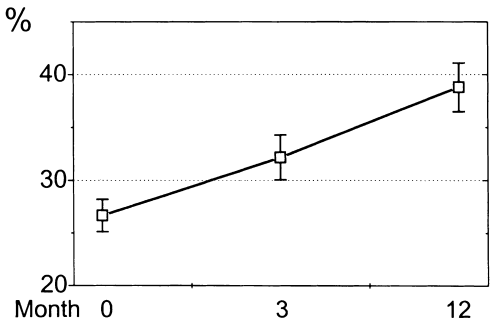


Fig. 3. Time course of left ventricular ejection fraction in 47 CHF patients under carvedilol/amiodarone treatment for at least 1 year. Month 0 vs. months 3 and 12: $P < 0.0001$. Results at month 0 were obtained by angio or echo, results of months 3 and 12 were obtained by radionuclidventriculography.

In our study, 109 out of 124 patients tolerated a long-term therapy with both agents. Patients under a combination therapy with carvedilol and amiodarone had a significant reduced heart rate (Fig. 1), an effective suppression of ventricular ectopies (Fig. 2), an increase in LV ejection fraction (Fig. 3) and were greatly improved in their NYHA stage (Fig. 4). Especially heart rate reduction reflects the alleviation of neurohumoral activation and is most likely induced by the combined negative chronotropic action of both drugs. In this context it is of interest that amiodarone exerts beta-blocking effects [32] besides its class III anti-arrhythmic action. This effect may be due to an interference with the intracellular signaling pathway rather than with the beta receptor itself [33]. In conclusion, a combination of blockade and down-regulation of β-receptors may achieve the most potent anti-adrenergic action. Actions of several anti-arrhythmic drugs may be fully or partially reversed during beta-adrenergic sympathetic stimulation [34]. From a theoretical point of view, a beta-blocking agent without intrinsic sympathomimetic activity is an ideal adjunct to a class III anti-arrhythmic agent. According to our findings the EMIAT study showed greatest impact on prolonged survival, when heart

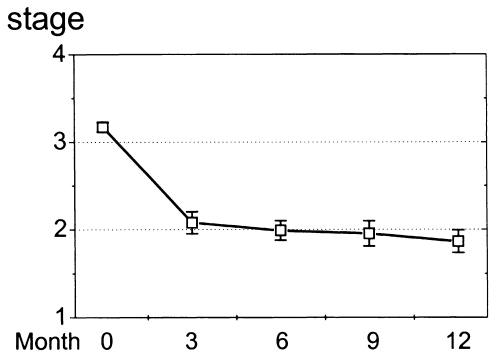
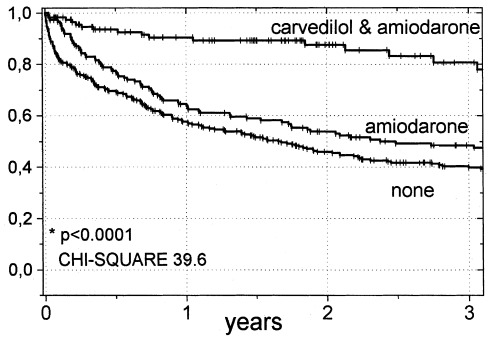


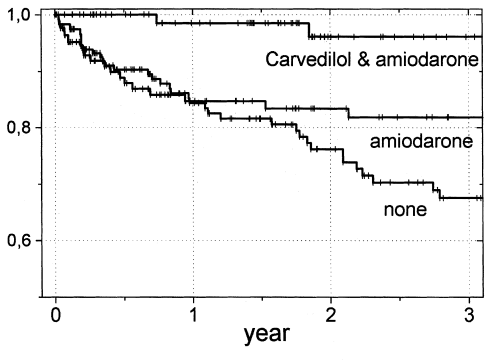
Fig. 4. NYHA class (stage) of 47 CHF patients under combined carvedilol/amiodarone therapy, $P < 0.01$ follow-up month vs. entry.



Patient numbers				
None	283	164	122	88
Amiodarone	154	86	66	56
Carv + Amio	109	72	42	28

Fig. 5. Probability of death under different treatment schedules according to the intention to treat principle (carvedilol and amiodarone, $n = 123$, including 14 patients not tolerating carvedilol, $P < 0.0001$ vs. amiodarone alone, $n = 154$ or none, $n = 283$).

rate lowering with amiodarone was effective in primarily tachycardic patients and when additional beta-blockers were given [22]. On the other hand, when amiodarone was given to patients with a low basal heart rate, EMIAT data [22] suggested a small increase in all-cause mortality. One can speculate that the negative amiodarone effect in patients with a low basal heart rate, which neutralizes its beneficial effect in tachycardic patients, is caused by bradyarrhythmic death. Bradycardic death might have been prevented by back-up stimulation illustrated by the fact that a significant rate of bradycardic disturbances was noted and seven patients (6%) became completely pacemaker-dependent (defined as the need for reprograming of the already implanted dual-chamber pacemaker to DDD mode at a higher basal rate, 65 i.p.m. instead of 40 i.p.m./hysteresis 30 due to documented arrhythmias and bradycardic symptoms). Data of patients becoming pacemaker-dependent or not were compared and were not significantly different (data not shown), therefore the development of pacemaker dependency under amiodarone and carvedilol seems to be unpredictable for an individual patient and prophylactic pacemaker implantation seems to be justified and indicated when co-therapy with both agents was instituted. As to the characteristics of the bradycardias most are sinus bradycardia as was described by Tonet [35], who treated patients with amiodarone and celiprolol. A significant negative chronotropic influence of concomitant digitalis therapy seems unlikely since we use low doses of digitoxin (mean dose 0.06 mg/patient/day) and serum digitoxin levels are within the therapeutic ranges. Another beneficial effect of both agents may be the stability of sinus rhythm, as this is another important goal in heart failure therapy [36]. Compared to controls either with amiodarone only or without any agent prognosis was better and the need for heart transplantation was lower with this therapeutic regimen even when analyzed according to the intention to treat principle (Fig. 5). Also sudden death rate was lower in the combined vs. the other treatment groups (Fig. 6). Residual sudden death in patients under the combined use of beta-blockers and amiodarone may be a result from ineffective suppression of intrinsic disturbances or pro-arrhythmic effects. This pro-arrhythmia may also be augmented by bradycardia and long–short cycles [37] and may be further diminished by pacing at a higher basal rate. Six percent of the patients experienced symptomatic bradycardias under VVI back-up stimulation at a low basal rate (40 i.p.m.). It is suggestive that pacemakers prevented sudden death in these six patients presenting with VVI 40 stimulation. Whether rate-responsive pacing was of benefit in CHF with chronotropic incompetence is currently under study [38] and results of long-term pacemaker holter monitoring gave prognostic informations in CHF patients [39].



Patient numbers				
None	283	164	122	88
Amiodarone	154	86	66	56
Carv + Amio	109	72	42	28

Fig. 6. Probability of sudden death in candidates for heart transplantation according to the intention to treat principle under different treatment schedules (carvedilol and amiodarone, $n = 109$, $P < 0.01$ vs. amiodarone alone, $n = 154$ or none, $n = 283$).

5.1. Study limitations

Results provided in this report are stemming from an unblinded pilot study to evaluate hemodynamic and electrophysiological changes under combined amiodarone and carvedilol therapy. The sample size is relatively small and therefore, may have inadequate power to detect significant differences in clinical outcome. Data from the control group without amiodarone or carvedilol were collected at different time points. This study therefore, is limited since patients were not randomized either to no treatment to both

drugs or to either agent alone. This comparison should now be done on the basis of our results in a larger randomized study. Until these data are available, the exact role of either agent in combination or alone remains uncertain. Furthermore, our results may be biased in some way due to a lower captopril equivalent dose in the group without amiodarone and or beta-blockers. However, the value of this parameter is questionable because it includes also losartan which was given to 30% of patients under combined amiodarone/carvedilol. Another weak point is that ejection fraction at baseline was calculated either from LV angiograms, when this study was done within 3 months prior submission (in 53% of patients) or from baseline echocardiography. However, results of fractional shortening determined by echo gave comparable results (Table 2).

6. Conclusions

Combination therapy with amiodarone and carvedilol was well tolerated and seems to be effective in severe heart failure in terms of improved symptoms, reduced heart rate and increased ejection fraction. Prophylactic pacemaker implantation should be considered due to a significant rate of bradycardic events.

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