Original article

Sudden cardiac death risk factors in patients with heart failure treated with carvedilol

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Abstract

Background: Chronic heart failure (CHF) is associated with a high risk of sudden cardiac death (SCD). Most frequently SCD occurs in patients with NYHA class II and III.

Aim: To evaluate the influence of prolonged carvedilol therapy on SCD risk in CHF patients.

Methods: The study included 86 patients (81 men and 5 women) aged 56.8±9.19 (35-70) years with CHF in NYHA class II and III receiving an ACE inhibitor and diuretics but not beta-blockers. At baseline and after 12 months of carvedilol therapy the following risk factors for SCD were analysed: in angiography – occluded infarct-related artery; in echocardiography – left ventricular ejection fraction (LVEF) <30%, volume of the left ventricle (LVEDV) >140 ml; in ECG at rest – sinus heart rate (HRs) >75/min, sustained atrial fibrillation, increased QTc; in 24-hour ECG recording – complex arrhythmia, blunted heart rate variability (SDNN <100 ms) and abnormal turbulence parameters (TO and TS or one of them); in signal-averaged ECG – late ventricular potentials and prolonged fQRS >114 ms. The analysis of SCD risk factors in basic examination in patients who suddenly died was also performed.

Results: During one-year carvedilol therapy heart transplantation was performed in 2 patients; 5 patients died. At 12 months the following risk factors for SCD were significantly changed: HRs >75/min (50 vs. 16 patients, p=0.006), LVEF <30% (37 vs. 14 patients, p=0.01), SDNN <100 ms (19 vs. 9 patients, p=0.04). At 12 months the number of risk factors for SCD in each patient was significantly reduced (p=0.001). In patients who suddenly died we found a greater amount of SCD risk factors in basic examination (7 vs. 5) as compared to alive patients.

Conclusions: Prolonged beta-adrenergic blockade reduces risk of sudden cardiac death through significant LVEF increase, reduction of HR at rest and improvement of HRV.

Key words: sudden cardiac death, heart failure, carvedilol, risk factors, heart rate, heart rate variability, heart rate turbulence, ejection fraction, late potentials

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Introduction

Chronic heart failure (CHF) is a serious problem of public health in all European countries. The number of individuals with CHF in the general population of European countries is estimated to be as high as 6.5-10 million, which represents about 0.4-2% of all European citizens [1]. Heart failure is a disease with a very bad prognosis. According to available data 90% of patients with CHF die of cardiovascular causes [2]. Half of the patients die because of exacerbation of cardiac failure and the others die suddenly, most often due to arrhythmia. Most frequently sudden cardiac death (SCD) occurs in patients in functional NYHA class II or III [3]. In patients with CHF, the structural substrate that promotes the occurrence of arrhythmias is heart muscle fibrosis, which develops in cases of ischaemic cardiomyopathy (most often due to acute coronary episodes) and dilatation cardiomyopathy; both of these conditions lead to unfavourable left ventricular (LV) remodelling [4]. Activation of the sympathetic nervous system also plays an important role. Increased activation of the sympathetic system, apart from an unfavourable influence on LV remodelling and disturbances of its function, can also decrease the

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threshold of severe ventricular arrhythmias occurrence and therefore increase the risk of SCD [5].

The aim of the study was to evaluate the influence of chronic beta-adrenergic blockade with the use of carvedilol on the prevalence of SCD risk factors in patients with CHF.

Methods

The study included 86 patients (81 men) at the mean age of 56.8±9.19 (35-70) years with chronic symptomatic CHF of ischaemic aetiology (64 patients) or with idiopathic cardiomyopathy (22 patients) and LV ejection fraction (LVEF) <40% treated with angiotensin II converting enzyme inhibitor (ACE-I), diuretics and/or digoxin, but not receiving beta-blockers previously. Before the treatment 30 (35%) patients were diagnosed with class II and 56 (61%) patients with class III, according to NYHA. Selected clinical data of examined patients are presented in Table I. Before entering the study 14 (17%) patients underwent percutaneous transluminal coronary angioplasty (PTCA) and 7 (8%) patients had coronary artery bypass grafting (CABG). Three (3%) patients had an implanted pacemaker (dual chamber DDD) and one female patient underwent a cardioverter--defibrillator implantation. One of the study inclusion criteria was treatment with ACE-I, for at least three months prior to the study. Eighty-four patients received enalapril in a mean dose of 10.9 mg/24 h, and 2 patients, because of intolerance to ACE-I, received losartan. Forty-two patients were treated with loop diuretic furosemide in a mean dose of 39.1±19.2 mg/24 h, 61 patients with spironolactone in a mean dose of 46.3±22.7 mg/24 h, and 53 patients with simvastatin in a mean dose of 15.9±6.1 mg/24 h. Furthermore, 27 patients received acenocumarol and 66 patients – aspirin. The dosages of aforementioned medications did not change significantly during 12 months of the study treatment. The treatment of CHF was conducted according to conventional treatment standards valid during the observation period between 2001 and 2005 [6].

Table I. Selected clinical data of examined patients at baseline

Parameter		Number of patients
Hypertension grade III WHO		59 (68%)
Hypercholesterolaemia		53 (62%)
Diabetes mellitus type 2		15 (17%)
Previous myocardial infarction (MI)	Q-wave MI	45 (52%)
	non-Q-wave MI	11 (13%)
Heart rate	sinus rythm	73 (85%)
	atrial fibrilaltion	13 (15%)
Coronary angiography n=70	normal vessels	14 (20%)
	one vessel disease	11 (20%)
	two vessel disease	15 (27%)
	multi-vessel disease	30 (53%)

The following SCD risk factors were analysed in all patients at baseline and after 12 months of treatment with carvedilol:

- in coronary angiography – presence of chronic occlusion of infarct-related artery [7],
- in echocardiography – low LVEF (<30%) and increased volume of the LV (LVEDV) >140 ml [7, 8],
- in ECG at rest heart rate (HR) >75 min [9], presence of persistent atrial fibrillation [10], and the occurrence of prolonged QT interval (QTc >440 ms). The QTc interval was measured manually, according to standard definitions and current guidelines [11]
- in 24 h ECG Holter monitoring – presence of severe ventricular arrhythmias [the occurrence of >10 premature ventricular contractions (PVC) per hour and/or >10 couples of PVCs per 24 hours and/or the occurrence of >2 ventricular tachycardia (VT) episodes per 24 hours] [12]. The definition of sudden death and VT was based on the criteria included in the executive summary of the ESC guidelines for the management of patients with ventricular arrhythmias and prevention of SCD [13].

In patients with sinus rhythm, heart rate variability (HRV) was evaluated. The risk factor was established as SDNN <100 ms [7]. Heart rate turbulence parameters of sinus rhythm were also established and as the risk factor abnormal values of both TO and TS or of one of them were used [9].

On the basis of the averaged high amplification ECG, the presence of late ventricular potentials and prolongation of fQRS >114 ms were analysed [14].

In all patients, after initial examinations, carvedilol was added to the previous medical regimen. Dosing of carvedilol was titrated individually to reach the maximum well tolerated dose. The treatment was started with the dose of 3.125 mg twice a day for two weeks. Then it was increased every two weeks (similarly to all randomised studies with the use of beta-blockers) [15]. If the previous dose was well tolerated, it was increased to 6.25 mg, 12.5 mg and eventually 25 mg twice a day (and in patients with a weight of more than 75 kg – 50 mg twice a day). The maximum tolerated carvedilol dose was estimated between the 4th and the 12th week, on average after 7.95±2.58 weeks of treatment. The average dose of carvedilol in the third month of treatment was 23.0±13.5 mg/d and did not significantly change after 12 months of treatment. In each patient the risk factors present at baseline and at 12 months of treatment were added together. Furthermore, the number of SCD risk factors present in the initial examination of patients who died was also analysed. Patients who were taking medications known to have an impact on the QT interval were excluded from the study.

Statistical analysis

The results are presented as mean ± SD or numbers and percentages. The evaluation of the differences between the

studied parameters in the analysed groups was carried out using Student's t-test for continuous variables. If the analysed variable did not follow a normal distribution, the Mann-Whitney test was used. The calculations of all statistical tests and corresponding p values were done with the statistical package STATISTICA. Significance level for all tests was established as 0.05.

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Results

In two patients, during the annual treatment and after a prolonged observation lasting on average 36±8 months, elective heart transplantation was performed.

Five patients died. Three patients experienced sudden death outside of the hospital, during the first year, between the 3rd and the 12th month of the study. During a prolonged follow-up another 2 patients died with predominant symptoms of worsening CHF.

An analysis of the SCD risk factors was performed in 79 living patients and, separately, in 3 patients who died suddenly. The frequency of SCD risk factors' occurrence in examined patients before beta-blocker administration and at 12 months of treatment is presented in Table II and III.

Treatment with carvedilol significantly reduced sinus heart rate, increased LVEF and improved SDNN.

Before the treatment sustained and non-sustained ventricular tachycardia occurred in 31 (42%) patients, couples of PVCs were present in 40 (50%) patients and single PVCs occurred in 76 (88%) patients. After 12 months of treatment the prevalence of both complex ventricular arrhythmias and single PVCs did not change significantly.

The mean dose of carvedilol in patients in whom a decrease of HR was not obtained was, after the dose adjustment (3rd month of treatment), 22.07±13.2 mg/24 h, and in patients with decreased HR, 26.07±9.9 mg/24 h, and at 12 months 26.46±15.2 vs. 26.56±9.8 mg/24 h respectively. In both analysed periods the differences were not statistically significant.

The mean value of SDNN did not increase significantly; however, there was an increase in the number of patients in whom the parameter increased to >100 ms in the course of the treatment.

In each patient the number of risk factors present at baseline and at 12 months was calculated. In the initial examination the mean number of SCD risk factors in one patient was 5 and it significantly decreased to 4 after 12 months of beta-blockade (p=0.001) (Figure 1).

The prevalence of SCD risk factors was also analysed at baseline in patients who died suddenly. In all these three patients, HR was >75/min (99.5±24.6), higher than in surviving patients (85.9±17.2) (NS), similarly to LFEF <30% (25.3±2.6 vs. 28.96 ± 6.09) (NS) and end-diastolic volume LVEDV >140 ml (215.5±45 vs. 187.96±62.14) (NS). In 3 patients previous myocardial infarction (MI) was found, in another 3 patients abnormal turbulence parameters were noted, in 2 patients prolonged QTc interval was observed, in 2 patients late ventricular potentials were present, in 3 patients severe ventricular arrhythmias were diagnosed and in one patient HRV <100 ms was detected. The mean number of risk factors at baseline in the group of patients who died was 7 and was higher than in those who survived.

Table II. The frequency of sudden cardiac death risk factors' occurrence in examined patients before beta-blocker administration and after 12 months of treatment

Parameter	Examination (number of patients)		p
	before beta-blocker administration	after 12 months of treatment	
Presence of AF	13 (17%)	12 (15%)	NS
Resting HR >75/min	50 (64%)	16 (21%)	0.006
Prolonged QTc >440 ms	30 (39%)	31 (41%)	NS
Presence of LP	42 (53%)	31 (42%)	NS
Prolonged fQRS >114 ms	42 (60%)	36 (50%)	NS
LVEF <30%	37 (47%)	14 (18%)	0,01
LVEDV >140 ml	58 (74%)	56 (72%)	NS
Ventricular arrhythmias	31 (42%)	26 (38%)	NS
SDNN <100 ms	19 (39%)	9 (17%)	0.046
Pathological HRT	38 (76%)	31 (55%)	NS
Previous Q-wave MI	42 (55%%)	43 (56%)	NS

Abbreviations: AF – atrial fibrillation, HR – heart rate, LP – late potentials, fQRS – filtered QRS duration, LVEF – left ventricular ejection fraction, LVEDV – left ventricular end-diastolic volume, SDNN – standard deviation of all NN intervals, HRT – heart rate turbulence, MI – myocardial infarction

Table III. Selected sudden cardiac death risk factors and their changes after the administration of beta-blockade

Parameter	Examination		p
	before beta-blocker administration	after 12 months of treatment	
HR [l/min]	86.39±17.54	68.90±11.71	0.001
QTc	433.56±43.70	436.68±40.00	NS
fQRS [ms]	128.27±33.56	123.40±30.03	NS
LVEF [%]	28.96±6.09	36.83±8.68	0.001
SDNN	115.8±32.5	125.22±32.81	NS
LVEDV [ml]	187.96±62.14	170.87±59.62	0.006

Abbreviations: see Table I

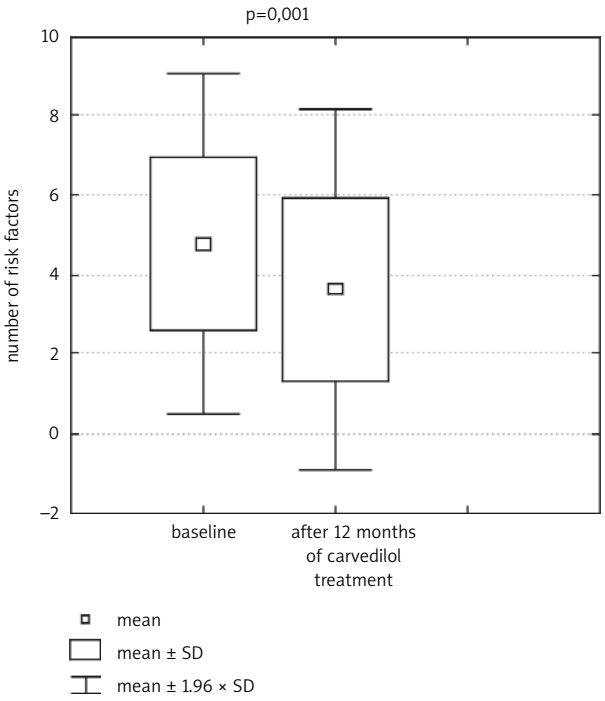

Figure 1. Comparison of the total risk of sudden cardiac death depending on the number of SCD risk factors in patients before the beta-blockade and after 12 months of treatment

Discussion

For the past 20 years it has been documented that the cause of death in patients suffering from CHF can be either the worsening of CHF with accompanying complications of target organs, or SCD due to arrhythmia despite relatively stable clinical condition [2]. The total mortality risk in patients with CHF increases along with the deterioration of LV function, whereas the ratio of SCD to non-sudden deaths is inversely proportional to the advancement of CHF [3].

Heart failure is characterised by a decreased threshold for ventricular fibrillation (VF), which means an increased risk of arrhythmias. Experimental and clinical studies proved that high concentration of catecholamines and strong activation of the sympathetic system, present in CHF, can be the cause of severe ventricular arrhythmias and SCD [16]. In patients with CHF activation of the sympathetic system leads to extensive neurohormonal activation (the increase of epinephrine, norepinephrine, angiotensin II and endothelin-1 concentrations) as well as to the increase of inflammatory cytokines levels (TNF-α, interleukin), resulting in unfavourable heart remodelling. Heart failure is also characterised by decreased threshold for VF, which leads to increased risk of arrhythmias. The reasons for the low threshold for VF are strong activation of the sympathetic system, high concentration of epinephrine, ischaemia and decreased vagal activation [17].

In our study in half of the patients complex ventricular arrhythmias were observed at baseline, and their frequency did not change in the course of the treatment with carvedilol. Our observations are consistent with the study of Metra et al. [15], in which changes in the frequency or intensity of ventricular arrhythmias in 24 hour ECG monitoring in patients with CHF treated with carvedilol or metoprolol were not detected.

In our study the analysed group of patients was the most endangered by the risk of SCD. In 3 patients who died, 24 hour ECG monitoring revealed complex ventricular arrhythmias at baseline.

The analysis of the prevalence of selected risk factors showed that parameters that were significantly modified with time included resting HR (which was decreased) and LVEF (which increased). Furthermore, a significant decrease in the number of patients with pathological baseline values of 24-hr HRV parameters was observed. Our study showed that the resting HR decreased significantly after beta-adrenergic blockage administration. According to available reports, tachycardia resulting from extensive sympathetic activation is a risk factor of SCD in the mechanism of VT and VF, especially in patients after MI [18]. According to Kannel et al., the risk for cardiovascular death increases along with the increase of resting HR [19]. Increase in HR exceeding 10 beats per minute is associated with 14% increase in cardiovascular mortality and 20% increase in total mortality. This emphasises the significance of resting HR in SCD risk.

In some patients chronic treatment with carvedilol had a positive influence on 24-hr HRV, which is recognised as the basic parameter of the sympathetic--parasympathetic balance. Heart rhythm variability reflects the functional condition of the heart's autonomic nervous system and results from its influence on the sinus node. Available data confirm that decreased HRV in patients with CHF is associated with increased mortality [20].

Our analysis revealed that SDNN was improved after 12 months of treatment with carvedilol, but these changes were not statistically significant. These observations confirm the findings from the study of Sanderson et al. [21], in which there was no statistically significant improvement in the baseline SDNN values after the use of carvedilol. Our study showed that chronic treatment with carvedilol significantly decreased the number of patients with SDNN <100 ms.

According to available studies, the improvement of LV function, characterised by an increase in LVEF and a decrease in end-diastolic volume, is an important factor influencing patients' survival [2, 3]. In the examined group both these parameters were significantly improved in the course of the treatment with carvedilol.

These observations show that chronic treatment with carvedilol decreases the number of SCD risk factors in

patients suffering from CHF NYHA class II or III due to the decrease of HR, increase in LVEF and SDNN improvement.

Risk factors of SCD are multiple. Our study shows that only some of them were significantly changed. The advantages of the treatment of CHF with beta-blockers are not only the result of the blockage of the sympathetic system but also of the decrease of RAA system's activity. In our study the beta-adrenergic blockage was obtained with the use of carvedilol, a non-selective beta-blocker, which, apart from its anti-adrenergic activity, also results in vasodilatory and antioxidative effects as well as inhibits proliferation and migration of the smooth muscle cells.

The results of our study show that mortality in patients with CHF treated with carvedilol can be reduced because this treatment is associated with a decrease of mortality risk from both worsening CHF and SCD causes [22].

It should be emphasised that in our study a comparative analysis of the changes of risk factors in groups of patients treated with carvedilol and carvedilol-naive (the lack of a control group resulted from ethical reasons) was not performed. Despite the simplified method of evaluation, it has been shown that beta-adrenergic blockage significantly decreases the burden of SCD risk factors.

Conclusions

Chronic beta-adrenergic blockage decreases the risk of SCD by a significant increase of LVEF, decrease of resting HR and improvement of HRV.

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Czynniki ryzyka nagłej śmierci sercowej u chorych z niewydolnością serca przewlekle leczonych karwedilolem

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Streszczenie

Wstęp: Niewydolność serca należy do chorób o bardzo złym rokowaniu. Połowa chorych z przewlekłą, objawową niewydolnością serca (CHF) umiera na skutek pogorszenia wydolności układu krążenia, a druga połowa umiera nagle, najczęściej z powodu arytmii. Szczególnie często zgony nagłe występują u chorych z wydolnością czynnościową klasy II i III wg NYHA.

Cel: Ocena wpływu przewlekłego leczenia karwedilolem na ryzyko nagłej śmierci sercowej (SCD) u chorych z niewydolnością serca.

Metodyka: Badaniami objęto 86 chorych (81 mężczyzn i 5 kobiet) w wieku 56,8±9,19 roku (35–70 lat) z CHF klasy II i III wg NYHA, otrzymujących przez co najmniej 3 mies. ACE-I i diuretyki, wcześniej nieleczonych beta-blokerami. U wszystkich chorych wyjściowo, a następnie po 12 mies. leczenia karwedilolem analizowano czynniki ryzyka SCD: frakcję wyrzutową lewej komory (LVEF <30%) i objętość późnorozkurczową lewej komory (LVEDV >140 ml) w badaniu echokardiograficznym, spoczynkową częstotliwość rytmu serca (HRs >75/min), obecność utrwalonego migotania przedsionków (AF) i odstęp QTc >440 ms w EKG, występowanie złożonych zaburzeń rytmu, obecność SDNN <100 ms oraz nieprawidłowych wartości parametrów turbulencji (TO i TS lub jednego z nich) w 24-godzinnym monitorowaniu EKG. Obecność późnych potencjałów komorowych oraz wydłużenie czasu trwania fQRS >114 ms oceniano na podstawie zapisów uśrednionego, filtrowanego EKG o wysokim wzmocnieniu. Przeprowadzono także analizę obecności czynników ryzyka SCD w badaniu wyjściowym u chorych, którzy zmarli nagle.

Wyniki: Po 12-miesięcznym leczeniu istotnym zmianom uległy 3 spośród 11 analizowanych parametrów: HRs >75/min (64 *vs* 21% chorych, p=0,006), LVEF <30% (47 *vs* 18% chorych, p=0,01), SDNN <100 ms (39 *vs* 17% chorych, p=0,04). Pod wpływem zastosowanego leczenia stwierdzono znamienne zmniejszenie liczby czynników ryzyka przypadających na jednego chorego (p=0,001). U chorych zmarłych w badaniu wyjściowym stwierdzono większą liczbę czynników ryzyka (7 *vs* 5) w stosunku do osób żyjących.

Wnioski: Przewlekła blokada beta-adrenergiczna zmniejsza liczbę czynników zagrożenia SCD poprzez istotne zwiększenie LVEF, obniżenie HRs oraz poprawę zmienności rytmu.

Słowa kluczowe: nagła śmierć sercowa, niewydolność serca, karwedilol, czynniki ryzyka, częstotliwość rytmu serca, zmienność dobowa rytmu, turbulencja rytmu zatokowego, frakcja wyrzutowa lewej komory, późne potencjały komorowe

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