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Effects of Valsartan Therapy on QT Interval Dispersion in Congestive Heart Failure

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Abstract: ***Aim:*** The aim of the research was to investigate the effects of Valsartan therapy on QT interval dispersion (QTd) in patients with Chronic Heart Failure (CHF). ***Material and Method:*** A sample of ambulatory patients, aged 22-79 years in NYHA class II to IV, with ventricular ejection fraction < 45 %, were followed prospectively. The patients were evaluated for hypertension, diabetes mellitus, smoking, alcohol abuse, concomitant medications, and QTd. Valsartan therapy was initiated in a dose of 80 mg once a day. Six months later, the patient were re-evaluated. Twelve lead electrocardiogram was recorded prior to and after 6 months Valsartan therapy. Data were analyzed according to the distribution at a significance level of 5% by using Statistica 6.0 software. ***Results:*** Eighty ambulatory patients were included in the study and they were divided into: group I, aged ≤ 65 years (n= 44), and group II, aged > 65 years (n = 36). At 6 months, there were identified on both groups that QTd significantly decreased comparing with baseline values (85 ms vs 112 ms; Wilcoxon Z = 7.77, n = 80, p < 0.0001). ***Conclusions:*** The results of the study showed that, in ambulatory patients with CHF, 6 months Valsartan therapy significantly decreases QTd. The decrease of the QTd was uniformly distributed between patients aged ≤ 65 years and those aged > 65 years. The reduction in QTd in patients with CHF using Valsartan could be responsible by the reduction in the risk of sudden cardiac death in the investigated group.

Keywords: Congestive heart failure; QT dispersion (QTd); Valsartan; Therapy.

Introduction

Heart failure is still a major public health problem. Seventy five percent of patients with congestive heart failure (CHF) eventually suffer sudden cardiac death [1]. It is difficult to find always the causes of these deaths and this is why are often presumed to be arrhythmic [2].

In cases of chronic congestive heart failure, QT interval dispersion is a strong predictor of death, being consider a marker of electrical myocardial instability [3]. It reflects variations in the repolarization in different regions of the myocardium. It has been demonstrated that heterogeneity of ventricular repolarization is associated with a higher vulnerability to arrhythmias and occurrence of sudden death [4]. Several clinical studies have suggested that, in the standard electrocardiogram (EKG), interlead variability of QT interval, defined as QT interval dispertion (QTd) reflects inhomogeneity in ventricular repolarization [5,6]. Increased QT dispertion proved that may predispose to arrhythmic events [7]. In a number of publications, increased QTd has been considered to be predictive for malignant arrhythmias and cardiovascular morbidity and mortality. Cardiologist, become increasingly interested in QTd in patients who have CHF, because QT interval dispertion could be a surrogate marker of prognostic significance, as well as a tool for monitoring the effectiveness of antiarrhythmic therapies [8].

There are studies that demonstrated that excessive angiotensin II induces myocardial damage through AT1-receptor –mediated pathways [9]. Using the AT1 receptor blockers (ARB's) can be suppressing angiotensin II cellular uptake and this could excert antiarrhythmic effects, and reduce mortality rates in patients with CHF. VALSARTAN, an angiotensin II receptor antagonist, acting on the AT_1 subtype has proven beneficial, in attenuating the incidence of morbidity and mortality

in patients with chronic heart failure [10]. In patients already taking other heart failure treatments, Valsartan leads to a reduction in morbidity and slows down the progression of disease associated with heart failure [11,12]. A number of studies presented during the ACC meeting support the intriguing hypothesis that ARB's may have direct antiarrhythmogenic effect [13]. In addition, reporting from the CHARM trial, Karl Swedberg, and colleagues demonstrated a borderline reduced incidence of new onset atrial fibrillation in patients receiving candesartan compared with placebo. To date no studies have investigated the relationship between CHF, QTd, Valsartan therapy and advanced age.

Because of the evidence that QTd is an important marker of cardiac death, both in elderly and in patients with CHF, a prospective study was undertook to determine: the effects of Valsartan therapy on QTd in patients with CHF (specifically in elderly patients, aged > 65 years), the benefits of this therapy in elderly patients compared with younger patients (aged ≤ 65 years).

Material and Method

It was a prospective study performed from November 2004 through May 2007 at University Diagnostic Centre from Cluj-Napoca, Romania. The study included 80 ambulatory patients (55 men and 25 women), aged 22-79 years (mean 62 years). All patients had symptoms and objective evidence of chronic heart failure, including a left ventricular ejection fraction of < 0.45 and pulmonary venous congestion or oedema. All patients were hypertensive with essential hypertension. The patients who have experienced a recent myocardial infarction (within 6 months) and patients with secondary hypertension and patients on ACEI treatment were excluded.

A 12 lead ECG and transthoracic echocardiogram were made to each patient according to the recommendations of the American Society of Echocardiography [14].

The treatment with VALSARTAN began with a dose of 80 mg once a day and was titrated up to 160 mg twice a day. The morbidity, defined as acute MI, new supraventricular arrhythmias (such as new atrial fibrillation), worsening New York Heart Association (NYHA) functional class was recorded after beginning of the treatment.

In order to investigate the effects of VALSARTAN in elderly patients, the patients were divided according to age in 2 groups, group I consisted of 44 patients aged ≤ 65 years (n=44 patients – 34 men and 10 women) and group II aged > 65 years (n=36 patients – 21 men and 15 women).

Each patient underwent a 12 lead ECG before VALSARTAN treatment and 6 months after the initiation of therapy. The 12 lead ECG was recorded at a paper speed of 25 mm/s. QTd was evaluated in as many of 12 leads as possible (a minimum of 9 leads). Each measurement was the mean value of 3 consecutive QT intervals. The QTd was defined as the difference between the maximum and minimum QT intervals. The QT intervals were measured from the onset of the QRS to the end of the T wave. The end of T wave has been defined as the intersection of an extrapolated line of the downward slope to the isoelectric line, at the return of the T wave to the isoelectric line, and the nadir between the T and U waves when U wave was present. When the end of T wave could not be identified, the lead was not included.

Data were summarized and analyzed according with distribution at a significance level of 5% by using STATISTICA 6.0 software.

Results

Eighty ambulatory patients, 25 women (31.25 %, CI 95% [21.27- 42.48]) and 55 men (68.75 %, CI 95 % [57.52-78.73]) aged 22-79 years (mean 62 years, CI 95% [59.50 – 64.57]), in NYHA class II to IV, with ventricular ejection fraction < 45 %, were included into the study and followed up prospectively. The patients were divided into 2 groups: group I, aged < 65 years (n = 44, 34 men); and group II, aged ≥ 65 years (n = 36, 21 men)

On enrolment in the study, most patients were mild to moderate symptomatic (see Figure 1): 30% of the patients were in NYHA functional class II; 56.25 % patients were in NYHA functional class III; and 13.75% patients were in NYHA functional class IV.

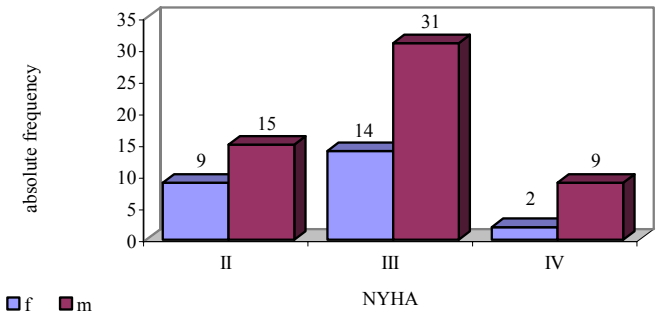

Figure 1. Patients' distribution by NYHA functional class

The investigated patients were divided into two classes by age: class I (age < 65 years) and class II (age ≥ 65 years). Forty-six patients were included in class I (11 women and 35 men) and thirty-four patients were included in class II (14 women and 20 men). The NYHA functional class by age class affiliation is represented by Figure 2.

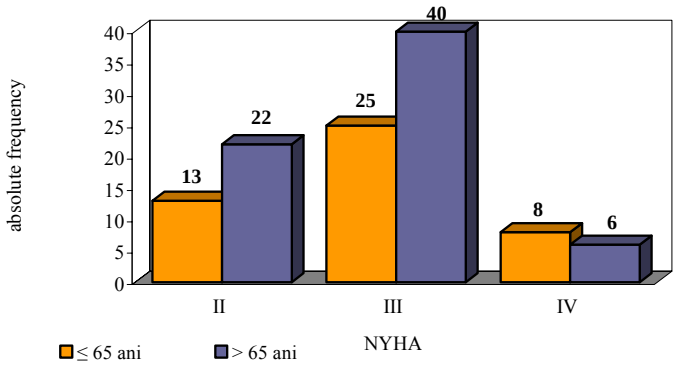

Figure 2. NYHA functional class according to the patient's age class

The aetiology of CHF, expressed as absolute, relative frequency and associated confidence interval is represented in Table 1**.**

Table 1. The Chronic Heart Failure aetiology on investigated sample

CHF aetiology	≤ 65 years			> 65 years			Total f_a
	f_a	f_r	IC_{fr} 95%	f_a	f_r	IC_{fr} 95%	
Dilatative cardiomyopathy	4	8.70	[2.22-21.69]	0	0.00	n.a.	4
Congenital cardiomyopathy	1	2.17	[0.05-10.82]	0	0.00	n.a.	1
Hypertensive cardiomyopathy	6	13.04	[4.39-26.04]	13	38.24	[20.67-55.80]	19
Ischemic heart disease	26	56.52	[41.35-71.69]	17	50.00	[32.44 -67.56]	43
Ischemic and hypertensive cardiopaty	2	4.35	[0.05-15.17]	0	0.00	n.a.	2
Valvulopathy	7	15.22	[6.57-28.21]	4	11.76	[3.03-26.38]	11
Total	46	100		34	100		80

f_a =absolute frequency; f_r = relative frequency; IC_{fr} 95% = confidence interval of 95% associated to f_r; n.a. = not applicable

After 6 months of treatment, most of the patients were in NYHA functional class II, as it could be seen in Figure 3**.**

56.25% of CHF were ischemic heart disease. All 80 patients were in sinus rhythm and were receiving additional CHF therapy including diuretics, digitalis, nitrates, and amiodarone. The distribution of medication is represented in Table 2.

All patients had a history of essential hypertension. Patient medical history also included: diabetes mellitus (31.25%), hypercholesterolemia (33.75%), smoking (62.5%), and admitted to alcohol abuse (> 2 drinks/day) (16.25 %).

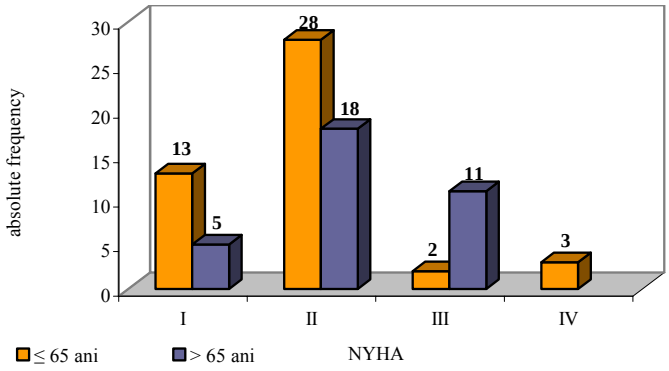

Figure 3. NYHA functional class by age after 6 month of Valsartan treatment

Table 2. The concomitant medication distribution

Concomitant treatment	≤ 65 years	> 65 years	Total
Diuretic, amiodarone	0	1	1
Amiodarone	3	3	6
Digoxin	5	0	5
Diuretic	7	14	21
Nitrate	28	13	41
Nitrate, digoxin, diuretic	2	2	4
Nitrate, digoxin	1	0	1
Nitrate, diuretic	0	1	1
Total	46	34	80

During the follow-up period, eight deaths occurred, most of which were cardiovascular in origin (4 sudden deaths, 3 progressive heart failure and 1 leukaemia).

At 6 months, there were identified on both groups that QT interval dispersion significantly decreased comparing with baseline values (values on both groups: 85 ms vs 112 ms; Wilcoxon Z = 7.77, n = 80, $p < 0.0001$) (see Table 3).

Table 3. Descriptive statistics parameters on baseline and 6 months according to group age

Parameter	**QT_d (msec)**		**QT_d (msec)**	
	Baseline	**6 month**	**baseline**	**6 months**
≤ 65 years (n = 46)			> 65 years (n = 34)	
Mean [95%IC]	111 [97-125]	84 [70-89]	113 [96-129]	86 [69-102]
Standard error	7.13	7.13	8.17	8.17
Kurtosis	-0.11	-0.11	-1.12	-1.12
Skewness	0.74	0.74	0.21	0.21
Minimum	48	21	49	22
Maximum	240	213	202	175

An elevated QT interval dispersion value at baseline has been associated with increase in morbidity ($p < 0.05$). After 6 months of Valsartan therapy, both groups had significantly reduced QTd compared with baseline values. The QTd reduction was the same for both groups (see Table 4 and Figure 4).

Table 4. QTd baseline and 6 months: comparison between groups

	$m_{\leq 65\ ani}$	$m_{> 65\ ani}$	t-Student	df	p	$n_{\leq 65\ ani}$	$n_{> 65\ ani}$
QTd – baseline	111.4130	112.7647	-0.12436	78	0.901351	46	34
QTd - 6 months	84.4130	85.7647	-0.12436	78	0.901351	46	34

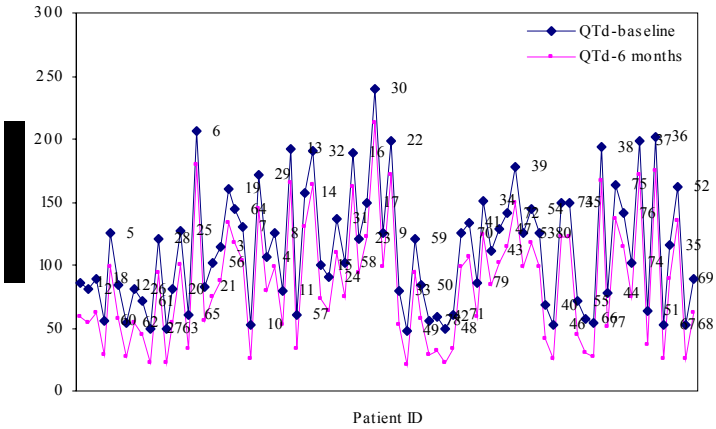

Figure 4. QTd values after 6 months of Valsartan treatment

Discussion

Despite new therapeutic advances in the treatment of patients who have CHF, morbidity and mortality rates remain high, and most of them suffer sudden deaths. Patients with CHF are known as high-risk group for sudden death, resultant to severe arrhythmias; sudden death is common in this patient category and is associated with increased QTd.

QT interval dispersion was first described by Day and co-authors, and since then the QT interval dispersion was considered a significant prognostic marker especially in ischemic heart disease [15]

QT interval is generally defined as total duration of cardiovascular electrical activity, including depolarization and repolarization time. QTd, calculated as the difference between the largest and the smallest of the total QT values on 12 lead ECG, is believed to reflect regional variations in ventricular repolarization and to be predictive for the risk of ventricular arrhythmias. QTd is an independent predictor of a high rate of malignant arrhythmias and cardiovascular morbidity and mortality .The results presented here demonstrated, that QTd reduction can be achieved in CHF patients when targeting RAS by ARB therapy.

The aim of the research was to investigate the effects of Valsartan therapy on QTd in patients with CHF and specifically whether elderly patients with CHF (aged > 65 years) would receive any additional observable benefit from Valsartan therapy in comparison with younger patients with CHF (aged ≤ 65 years).

After 6 months of Valsartan treatment our patients had a significant improvement in their clinical status, considering the NYHA functional class.

After 6 months of Valsartan therapy, our patients had a significant reduction on QTd.

This findings reveals that, in reducing QTd, the effects of VALSARTAN are uniformly distributed between groups of patients aged <65 years and aged > 65 years.

To date, no studies have investigated the relationship between CHF, QTd, Valsartan therapy and advanced age. The data from this study reveals that in reducing QTd, the effects of VALSARTAN are uniformely distributed between groups of patients aged ≤ 65 years and aged > 65 years.

In patients with CHF, the QTd prognostic usefulness is controversial. There are studies which showed that in patients with CHF and increased QTd value there was an increase incidence of ventricular arrhythmias and sudden death but this result could not be reproduced in larger series [16].

This therapy may prevent sudden cardiac death by altering ventricular remodelling effect that could generate arrhythmias.

Conclusions

The obtained results showed that targeting the Renin Angiotensin System by AT1 receptor blockade lead to the reduction of QTd in patients with CHF. A 6 months Valsartan therapy leads to a significant decrease in QT interval dispersion values in ambulatory patients with CHF. This effect was uniformly distributed between patients aged ≤ 65 years and those aged > 65 years.

Reduction in QT dispersion in patients with heart failure using Valsartan could explain the reduction in the risk of sudden cardiac death with angiotensin receptor therapy, in the investigated group of patients.

More studies involving a larger sample of patients are needed in order to define the implication of these findings in clinical practice.

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