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HIGHER DOSES OF LOSARTAN IMPROVE DIASTOLIC FUNCTION IN PATIENTS WITH DIASTOLIC HEART FAILURE DUE TO DECREASED COMPLIANCE

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Abstract

Diastolic heart failure due to decreased left ventricle (LV) compliance (diastolic heart failure DHF) contributes in substantial amount of all heart failure patients. Since no evidence based clearly established therapeutic regimens are available, we designed this study based on assumption that better control of renin-angiotensin-aldosteron system (RAAS) might be of benefit in this patients subset.

Methods: The study involved 120 patients (females: 46.7%;, mean age 67±8 years) with DHF NYHA II/III and EF > 50% randomized into 3 groups (n=40) in order to receive ramipril 10 *mg/day* (R), losartan 50 *mg/day* (LL) or losartan 100 *mg/day* (LH). Transmitral E-wave deceleration time (EDT), isovolumetric relaxation time (IVRT), duration of reversal in the pulmonary vein (RPV) and transmitral A-wave (RPV–A), left atrial volumes (LAV) and EF (LAEF) were obtained by transesophageal echocardiography (TEE) in 1, 30, 180 days and 1 year follow-up.

Results: Baseline characteristics were comparable between groups. In 30 days EDT, IVRT and RPV–A were better in R, compared with LL and LH (EDT: R 133±11 *ms** vs. LL 122±10 *ms* vs. LH 124±9 *ms*, *p < 0.05; IVRT R 52±6 *ms** vs LL 42±4 *ms* vs 45±3 *ms*, *p < 0, 05, RPV – A: 24±5 *ms** vs 32±3 *ms* vs 29±2 *ms*; *p < 0.05). In 180 days all parameters were better in LH and comparable between R and LL (EDT: R 132±12 *ms* vs LL 129±13 *ms* vs LH 138±9 *ms**, *p < 0.05; IVRT R 52±6 *ms* vs LL 48±4 *ms* vs LH 58±5 *ms**, *p < 0,05, RPV – A: R 22±4 *ms* vs LL 26±3 *ms* vs LH 18±3 *ms**; *p < 0.05, $LAV_{макс}$: R 76±18 *ml* vs LL 77±16 *ml* vs LH 68±15 *ml**; *p < 0.01, LAEF: R 35±16% vs LL 33±12% vs LH 41±12%*, *p < 0.01). Beneficial effects of LH maintained after 1 year follow-up and differences in all parameters indices were more pronounced between LH, on one hand, and LL and R, on the other.

Conclusion: Thus, higher doses of L favorably alter diastolic function parameters in DHF with decreased compliance probably through better RAAS control.

Keywords: diastolic heart failure, decreased compliance, ventricular stiffness, angiotensin receptor blockers.

Introduction

Diastolic heart failure (DHF) is defined as symptoms of heart failure in a patient with preserved left ventricular function [*Grossman W., 1991*]. DHF is characterized by a stiff left ventricle with decreased compliance and impaired relaxation, which leads to increased end-diastolic pressure. Signs and symptoms are similar to those of heart failure with systolic dysfunction.

It is difficult to distinguish between diastolic and systolic heart failures based on physical findings or symptoms. Doppler echocardiography has assumed the primary role in the noninvasive assessment of cardiac diastolic function and is used to confirm the diagnosis.

DHF accounts for more than 50% of all HF cases [*Senni M. et al., 1998*]. As many as 33%

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patients with obvious heart failure and normal ejection fraction (EF) may have DHF [Vasan R.S. et al., 1999]. The risk of DHF increases with age and accounts for 50% in patients over 70 years old [*Mosterd A. et al., 1999*]. Once DHF is developed, the prognosis is poor, and if caused by coronary artery disease (CAD) - comparable with that of HF due to systolic dysfunction [*Dauterman K.W. et al., 1998*].

Despite DHF prevalence in cohort and unfavorable prognosis, no evidence-based clearly established therapeutic regimens are available.

Based on current knowledge, pharmacologic treatment of diastolic heart failure should focus on normalizing blood pressure, promoting regression of left ventricular hypertrophy, avoiding tachycardia, treating symptoms of congestion, and maintaining normal atrial contraction when possible.

Diuretic therapy is the mainstay of treatment for preventing pulmonary congestion, while beta-blockers appear to be useful in preventing tachycardia and thereby prolonging left ventricular diastolic filling time [*Shibata M.C. et al., 2002*].

Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-receptor blockers (ARB) may be beneficial in patients with diastolic dysfunction, especially those with hypertension [*Friedrich S.P. et al., 1994*]. However, the evidence from adequately powered randomized controlled trials is not available yet [*Warner J.G. Jr. et al., 1999*].

The outcomes of ongoing clinical trials may provide important information to move forward from intuitive treatment to evidence-based therapy that is to decreased morbidity and mortality and improved quality of life.

For DHF management it is useful to know what type of dysfunction resulted in HF symptoms [*Hatle L., 2007*]. Whether abnormal relaxation or decreased compliance is predominant cause of DHF? Such assessment is helpful in choice of therapy. In DHF with predominant abnormal relaxation heart rate reduction is essential or at least beneficial, but cannot be of value in case of decreased compliance.

Diastolic heart failure due to decreased left ventricle (LV) compliance (DHF) contributes in substantial amount of all heart failure patients. Since evidence-based and clearly established therapeutic regimens are unavailable, we designed this study based on the assumption that better control of RAAS, which is a major contributor to myocardial stiffness, might be of benefit in this patients subset.

Material and methods

The study involved 120 patients (46.7%: female) with mean age 67±8 years with DHF NYHA II/III mainly due to decreased compliance and in sinus rhythm.

Patients were randomized into three equal groups (n = 40) in order to receive ramipril titrated to 10 mg/day (R), losartan 50 mg/day (LL), or losartan, titrated to 100 mg/day (LH).

Main causes of DHF were arterial hypertension (AH), diabetes mellitus (DM), and CAD. There were no significant differences in DHF causes distribution in groups (Table 1).

Table 1.

Distribution of patients in groups by DHF cause.

Causes of DHF	Distribution of patients in groups by DHF cause		
	R	LL	LH
AH	14	17	15
DM	15	14	16
CAD	23	21	24
Aging (>70 yrs)	3	2	2

Patients with multicause DHF referred in all corresponding cells.

Increased left ventricular stiffness was determined by shortened mitral deceleration time (MDT) ≤ 150 *ms* [*Zile M.R., Brutsaert D.L., 2002*], abbreviated A-waves, shorter isovolumetric relaxation time (IVRT) ≤ 55 *ms* [*Zile M.R. et al., 2004*], difference duration of reversed pulmonary vein atrial systole flow (AR) and duration of A-wave flow (A) > 30 *ms*, increased left atrial maximum volume (LAV), and decreased LA total emptying ejection fraction (LAEF).

Measurements were obtained by transthoracic EchoCG (TTE) and transesophageal EchoCG (TEE).

MDT, IVRT, and AR–A were measured by pulsed wave Doppler as mean values of three subsequent cardiac cycles.

To obtain more precise measurements, AR–A, LAV, and LAEF were measured by TEE.

LAVs were measured with the biplane area-length method. Off-line rest images of maximum (LAV_{max}) and minimum volumes (LAV_{min}) were measured at the end of LV systole just before opening of the mitral valve and at the end of LV diastole respectively [*Dernelis J. et al., 2000*]. LAVs were calculated as follows:

$$LAVs = \frac{Area4\text{-}chamber.X\ Area2\text{-}chamber.\ X.\ 0.85}{Shortest\ length}$$

[*Dernelis J. et al., 2000*], and LAEF was estimated as follows:

$$LAEF = 100\ x\ \frac{(LAV_{max} - LAV_{min})}{LAV_{max}}$$

Serum NT-pro-BNP levels were measured by Roche diagnostics as a quantitative assay. Values were compared with control levels corresponding to age and gender. Blood sample was taken in recumbent position after 10 minutes rest [*Jensen K.T. et al., 1997*].

Statistical comparison was made among all groups by Excel 2007. All tests were two-sided and the result with $p < 0.05$ was considered statistically significant.

Measurements were performed after titration in 1, 30, 180 days follow-up.

Results

Baseline characteristics did not differ significantly between groups (Table 2).

In 30 days better indices of EDT, IVRT and RPV-A were observed in R, compared with LL and LH (Figure 1). Other parameters were comparable in groups.

In 180 days, we observed more favorable changes in all parameters of LH, whereas parameters between R and LL did not reach statistical significance (Figures 2, 3).

Beneficial changes in LH group maintained

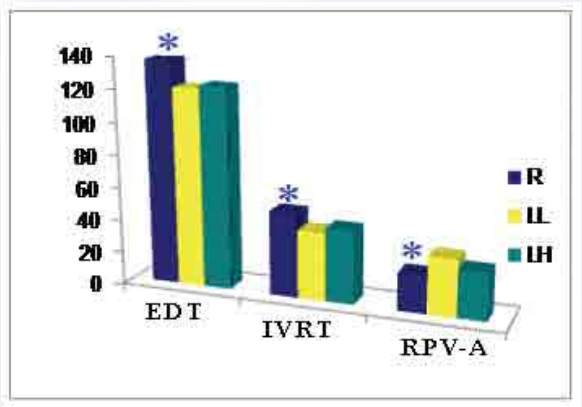

Figure 1. *Comparison of EDT, IVRT, and RVP–A in groups. 30-day follow-up, * p < 0.05.*

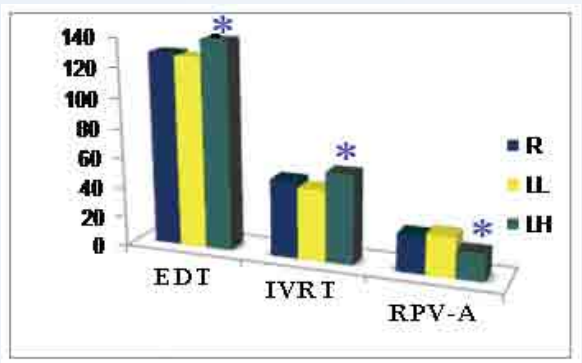

Figure 2. *Comparison of EDT, IVRT, and RVP – A in groups. 180 day follow up, * p < 0.05.*

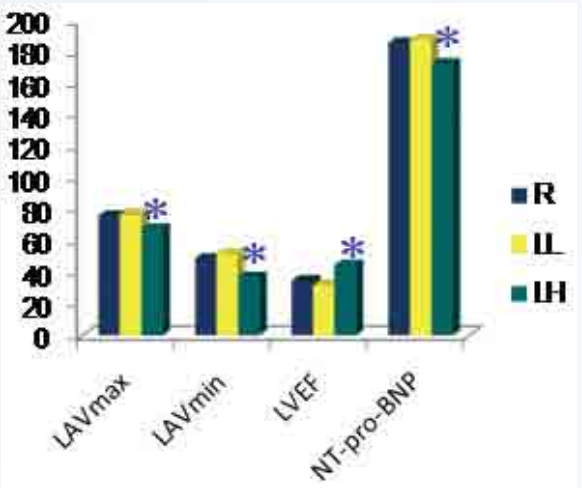

Figure 3. *Comparison of LAVmax, LAVmin, LAEF after 1 year follow up, * p < 0.01*

Table 2.

Baseline characteristics of groups

Parameters		R	LL	LH
EDT	(ms)	120 ± 12	125 ± 11	123 ± 13
IVRT	(ms)	48 ±4	47 ± 6	45 ± 7
RVP – A	(ms)	33± 3	34 ± 3	35 ± 4
LAV_{max}	(ml)	80 ± 18	85 ± 20	82 ± 23
LAV_{min}	(ml)	57 ± 19	59 ± 21	56 ± 18
LAEF	(%)	28 ± 10	30 ± 14	32 ± 10
NT-pro-BNP	(pg/ml)	205 ± 32	208 ± 34	211 ± 38

after 1-year follow-up and differences in all parameters were more pronounced between LH, on one hand, and LL and R, on the other.

There were no statistically significant differences in parameters of LL and R after 1-year follow-up.

Although most pronounced changes were observed in LH compared with both R and LL, all groups showed significantly better indices compared with the baseline (Table 3).

Drug regimen of L 100 mg/day was well tolerated with side effects comparable to L 50 mg/day (5 pts vs. 4 pts, p = NS).

Discussion

This study was conducted to determine whether higher doses of L are more favorable to effect on diastolic function parameters in patients with DHF due to decreased compliance.

Our findings show that effects of L on LV compliance/stiffness are dose dependent.

RAAS plays a major role in LV hypertrophy and myocardial fibrosis formation [*Yusuf S. et al., 2003*]. The beneficial effects of bradikinin on ventricular remodeling and compliance also have been shown [*Cleland J.G. et al., 1999*]. The latter may be of value in better diastolic indices in patients on R rather than on L in 30-day follow-up in our study.

Since both drugs influence tissue RAAS, we expected to find effects similar to those found in groups on R 10 *mg/day* and L 50 *mg/day*. Both therapeutic regimens equally altered diastolic parameters in terms of reducing LV stiffness compared with the baseline without significant differences between them.

Higher dose of L showed better effectiveness probably through better control of myocardial and circulating angiotensin II, which resulted in reversed structural and functional remodeling [*Warner J.G. Jr. et al., 1999*].

Significant reduction in NT-pro-BNP levels observed in LH group indicates the better course

Table 3.

Baseline and comparison of 1-year follow-up parameters in groups.

Parameters		R		LL		LH	
		Bl	1 yr	Bl	1 yr	Bl	1 yr
EDT	(ms)	135 ± 12	140 ± 18*	133 ± 11	143 ± 17*	136 ± 13	152 ± 18**
IVRT	(ms)	52 ± 4	58 ± 6*	54 ± 6	59 ± 8*	54 ± 7	65 ± 9**
RVP – A	(ms)	35 ± 3	29 ± 3*	33 ± 4	28 ± 3*	34 ± 5	20 ± 4**
LAVmax	(ml)	80 ± 18	76 ± 13*	85 ± 20	77 ± 18*	82 ± 23	68 ± 19**
LAVmin	(ml)	57 ± 19	49 ± 16*	59 ± 21	52 ± 19*	56 ± 18	37 ± 14**
LAEF	(%)	28 ± 10	35 ± 15*	30 ± 14	32 ± 15*	32 ± 10	45 ± 16**
NT-pro-BNP	(pg/ml)	205 ± 32	186 ± 25*	208 ± 34	188 ± 29*	211 ± 38	175 ± 23**

*p < 0.05; **p < 0.01

of DHF, since this hormone is over-released in response to ventricular dysfunction [*Maisel A.S. et al., 2003*] and is a strong predictor of mortality [*de Lemos J.A. et al., 2001*].

We studied effectiveness of both medications separately in patients with DHF in order to reveal differences between ACEI and ARB. Our study was not designed to compare effectiveness of their combination. Recently we have shown that this combination is of benefit in patients with systolic LV dysfunction due to myocardial infarction [*Adamian K.G. et al., 1998; Adamian K.G. et al., 2000*].

Effects of ACEI and ARB combination in patients with DHF due to increased LV stiffness remains to be elucidated.

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