Mildronate improves carotid baroreceptor reflex function in patients with chronic heart failure

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Summary

Objectives: The aim of the study was to compare the efficacy of combined treatment of chronic heart failure (CHF) patients with mildronate and ACEI (lisinopril) and the treatment with ACEI (lisinopril) used alone. One of the objectives was to assess the influence of both therapies on the reactivity of the carotid baroreceptor reflex.

Design and Methods: The study was designed as a controlled, parallel-group, double-blind, randomised phase IV clinical trial. The study group comprised 57 patients (men and women; aged 30–80 years) with CHF (NYHA I–III) due to coronary heart disease (CHD). The first study group (ML20) received mildronate (M) 1000 mg and lisinopril (L) 20 mg daily; the second group (ML5) received M 1000 mg and L 5 mg, the third (control) group (L20) received L 20 mg daily. The treatment period lasted for 3 months.

Results: Improvement of the main symptoms of CHF, NYHA class, peripheral circulation and contractility of the myocardium in the ML5 and ML20 groups was reported in our previous papers.

In CHF patients receiving a prolonged treatment of cardioselective β-adrenergic blockers (metoprolol or bisoprolol), a three-month therapy of mildronate in combination with lisinopril has resulted in an increase of the amplitude of baroreflex bradycardic and hypotensive reactions. The effect was not found to be dependent upon the lisinopril dosage applied in this combination (within the range of the minimal-maximal dose). Besides, neither lisinopril by itself, nor the combination of mildronate with lisinopril were stated to be related with any changes in arterial pressure or the heart rate in CHF patients.

Conclusions: This study has revealed the advantage of the combined treatment with "lisinopril 20 mg/daily and mildronate 1000 mg/daily" and "lisinopril 5 mg/daily and mildronate 1000 mg/daily" over the treatment with "lisinopril 20 mg/daily" on the reactivity of the carotid baroreceptor reflex in CHF patients.

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Heart failure is a multifactorial disease with poor prognosis (about 50% mortality during the first 5 years of diagnosis) [1,2]. Despite the improvement in the therapeutic approaches, heart failure is one of the main causes of death in the developing countries.

From the previous studies we have learned that patients with heart failure have an increased sympathetic nerve activity, which seems to be important to maintain the cardiac output and blood pressure. The sympathetic nervous system activity progressively increases from mild to severe heart failure. Some investigators have attributed the increase in sympathetic nervous system activity to a cardiopulmonary and baroreflex dysfunction. Experimental studies have proved the changes in angiotensin II and noradrenaline levels to be related with the changed baroreflex control of the heart rate (HR) and the sympathetic nerve activity [3]. In chronic heart failure (CHF) patients, the decreased sensitivity of the baroreceptor reflex has been stated [4–7]. It follows that both cardiac and vascular components of the baroreflex in CHF patients are affected as well, as there are disturbances in both parts of autonomic nervous system, which manifest as an increased sympathetic and decreased parasympathetic activity. Moreover, several studies [8,9] substantiate the close relationship between these changes and the prognosis of CHF patients. A probable effect of any of ACE inhibitors on baroreflex function in CHF patients is only analysed in few publications [10–13]. CHF with its large human and economic toll is one of the main issues throughout

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the world. Ongoing studies are conducted in order to improve the management of patients with CHF. Alternative forms of therapy have attracted recent interest (angiotenin II receptor antagonists, renin, neutral endopeptidases, endotheline antagonists, selective Ca^{++} channel blockers, β-adrenoblockers, positive inotropes, including Ca^{++} sensitizers, etc.). In addition, a considerable attention has received an approach targeted to the improvement of cardiac autonomic nervous system function causing an increase of baroreflex function [14,15]. Mildronate, one of the cytoprotective agents, was demonstrated to improve myocardial contractile function and hemodynamic profile, to induce the regression of ischaemic cardiac remodelling during ishaemia and reperfusion. The efficacy of mildronate is shown to be similar to that of ACEI captopril [16–19]. Mildronate was found to improve symptoms of CHF, quality of life of the patients, exercise tolerance, systolic function and a decrease of peripheral arterial resistance [20–24]. Moreover, experimental studies have also substantiated mildronate as an agent possessing vasodilating and antispasmodic action [25,26].

Summarizing the results of our previous investigations, of primary importance are the facts that the addition of mildronate to the treatment with lisinopril facilitates the improvement in the left ventricular systolic function, the leading symptoms of CHF and the NYHA class. The combined treatment is associated with the improvement of the quality of life, exercise capacity and mechanisms of peripheral circulation [25,26].

The aim of this study was to compare the effect of the combination of ACEI (lisinopril) with mildronate and ACEI (lisinopril) used alone on the bradycardic and hypotensive reactions of the carotid baroreflex, and, thus, to judge the effect of mildronate on the reactivity of the baroreceptor reflex.

Design and methods

The study was designed as a controlled, parallel-group, double-blind, randomised phase IV clinical trial (120 patients). The study sub-group for the evaluation of reactivity of the carotid baroreflex comprised 57 patients (men and women; aged 30–80 years) with CHF (NYHA I–III) due to coronary heart disease (CHD). Written informed consent was obtained from all the patients before enrolment. The study was performed in accordance with the principles outlined in the Declaration of Helsinki and approved by the Ethics Committee of the Latvian Institute of Cardiology. Patients were randomly selected into three groups receiving different treatment during a 3-month period. Patients of the first study group (ML20) received mildronate (M) 1000 mg and lisinopril (L) 20 mg daily; the second study group (ML5) received M 1000 mg and L 5 mg daily; patients of the third (control) group (L20) received L 20 mg daily. All the patients received cardioselective beta adrenoblockers (metoprolol or bisoprolol) and diuretics.

The baroreflex assessment was started with the measurement of systolic and diastolic arterial blood pressure using the Korotkoff's method after a 15-minute period of adaptation. Bradycardic and hypotensive responses evoked by carotid zone activation were evaluated applying the Eckberg's neck chamber method [27,28] by 60 mmHg suction for 5 seconds. Measurements were repeated seven times within a minute's interval. Usually, the values show only slight inter-individual differences for the mentioned parameters, although they can be affected moderately by the breathing cycle. Therefore, to obtain more precise readings, the study person was asked to restrain breathing for 5 seconds during the recording period. A continuous non-invasive monitoring of arterial blood pressure and the HR was performed throughout the test using Physiograph UT-8505 elaborated at Tartu University. Seven measurements of bradycardic and hypotensive response to carotid baroreceptor activation served as the basis for the calculation of the mean values of these parameters. Carotid baroreflex activity was detected before and after the three-month therapy course.

Results

Comparing the amplitude of the bradycardic response before (B) and after (A) the treatment, the ML20 group showed an increase from 2.5 ± 0.58 to 4.61 ± 0.67 beats/min ($p = 0.004$), i.e., by 84%, but the ML5 group – from 2.89 ± 0.65 to 4.61 ± 0.77 beats/min ($p = 0.001$), i.e., by 59%. Additional treatment with lisinopril (L20) only was not related with statistically significant changes in the bradycardic response (2.56 ± 0.53 vs. 2.12 ± 0.39 beats/min). Bradycardic reactions to carotid baroreceptor reflex activation in the compared groups are presented in Figure 1.

A hypotensive reaction increased from 2.39 ± 0.6 to 6.56 ± 0.9 mmHg ($p = 0.0004$), i.e., by 174% in the ML20 group, but in the ML5 group the increase was from 2.05 ± 0.44 to 6.17 ± 0.85 mmHg ($p = 0.0002$), i.e., by 200%. Whereas, the additional treatment with lisinopril (L20) only evoked an increase in the hypotensive reaction realized by the carotid baroreflex from 1.89 ± 0.62 to

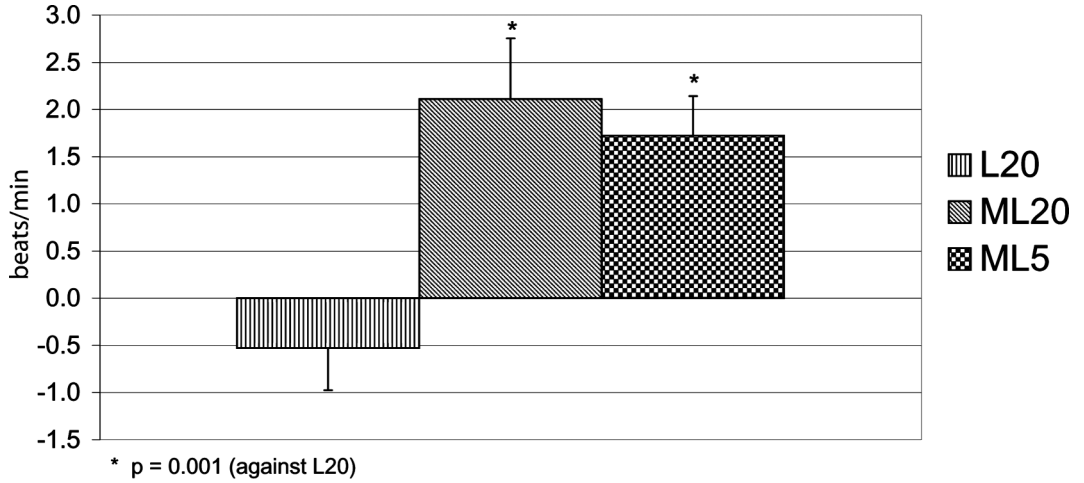

Figure 1. Changes in bradycardic reactions after the treatment (Y-axis, mean heart rate decrease, beats/min ± standard error).

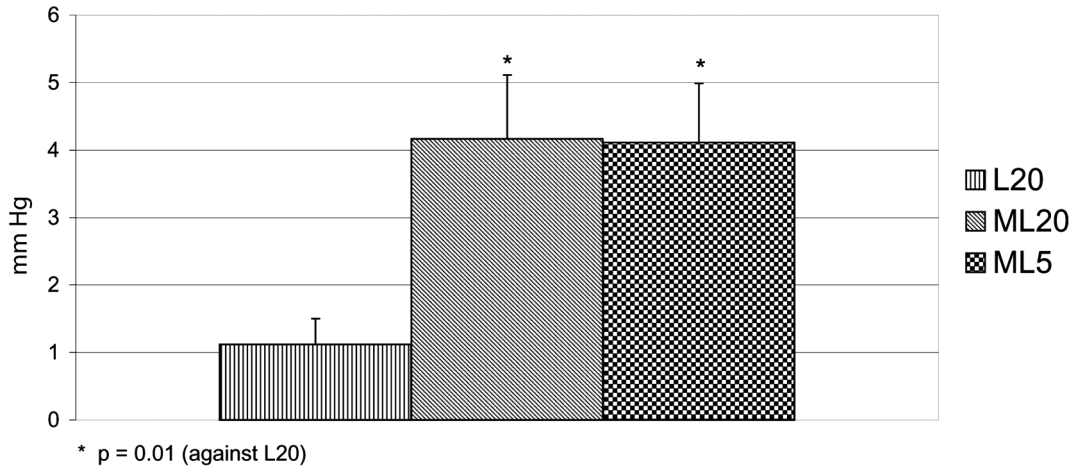

Figure 2. Changes in hypotensive reactions to carotid baroreceptor activation after the treatment (Y-axis, mean pressure decrease, mmHg ± standard error).

3.12 ± 0.64 mmHg ($p = 0.01$), i.e., by 65% (Figure 2).

Thus, in both study groups that received the combined treatment (ML20 and ML5), irrespectively of the dose of lisinopril, the increase in bradycardic and hypotensive responses was approximately the same. Although in the L20 group that received only lisinopril, the hypotensive response was less pronounced than in the ML20 and ML5 groups, where it was statistically significant ($p = 0.01$). Of note, there were no statistically significant changes of systemic arterial blood pressure and HR values after the treatment found in comparison with those before the treatment in any of the study groups.

Discussion

The activation of neurohumoral mechanisms is believed to play an important role in the development of pathophysiological mechanisms of CHF. Moreover, an interrelation is known to exist between renin-angiotensin-aldosterone and sympathetic systems [29–33]. An augmented sympathetic activation increases the level of plasma angiotensin II, which, in turn, facilitates sympathetic activation [34]. At the onset of CHF, sympathetic-adrenergic activation compensates the attenuated myocardial function stabilizing blood pressure by vasocontrictor mechanisms and providing vitally important perfusion of target organs [35]. Sympathetic activation, in the long run, was proved to exhibit a negative effect not only on cardiovascular system but it was found to correlate with a bad prognosis in patients with CHF [36,37].

The CONSENSUS and SOLVD studies have ascertained a favourable effect of ACE inhibitor enalapril on the mortality of patients with CHF. In general, ACE inhibitors are supposed to possess such a positive effect. In patients with CHF, the treatment with ACE inhibitors (benazepril 10 mg/daily; lisinopril 20 mg/daily) was shown

to increase plasma renin activity and to decrease plasma angiotensin II, aldosterone and noradrenaline levels [38,39]. The decrease of the noradrenaline level was observed in CHF patients receiving captopril, enalapril [13] and lisinopril [38]. A continuous treatment with benazepril (10 mg/daily for 2 months) revealed no essential changes in plasma noradrenaline levels, but microneurographically a relevant decrease was stated in the level of *n. peroneus* sympathetic efferent impulses [39]. As to baroreflex sensitivity, it was found to be diminished in patients with CHF [6,40–42]. It follows that both baroreflex cardiac and vascular components are altered in patients with CHF. The latter is clearly revealed applying a microneurographical method for recording alterations in sympathetic efferent activity, at least in the skeletal muscles. As *n. vagus* is responsible for modulating the baroreflex heart rate response [43,44], it could be concluded that there are disturbances in both parts of autonomic nervous system activity in patients with CHF. An increased sympathetic and decreased parasympathetic activation was stated. These changes were found to correlate with the prognosis of patients with CHF.

The increase of the baroreflex bradycardic reaction amplitude (applying the Eckberg's neck chamber method) was observed in captopril (25 mg/daily) treated CHF patients [12]. These authors concluded that the captopril treatment had increased the parasympathetic tone. The similar conclusion was made concerning the effect of captopril (50 mg/daily, 17 days) and enalapril (8–10 mg/daily, 17 days) adding it to routine therapy (digitalis + diuretics) [45]. This positive effect was found only in CHF patients having improvement in hemodynamics. The effect of benazepril (10 mg/daily, 2 months) together with the routine therapy (digitalis + diuretics) as well as the effect of activation and deactivation of the baroreflex (with phenylephrin and sodium nitroprusside) was analysed evaluating HR and the changes of *n. peroneus* sympathetic eferentation microneurographically [39]. Bradycardic and sympathetic eferentation, as well as calculated baroreflex sensitivity were found to increase during the baroreflex activation. In the same time, a tachycardic reaction and sympathetic efferent activity as well as calculated baroreflex sensitivity were not substantially altered during the baroreflex deactivation. The authors of the above analysed study concluded that improvement of baroreflex sympathetic and parasympathetic components was the result of the treatment.

Analysing the effect of lisinopril (titrating to 20 mg/daily, 4 months) in CHF patients receiving neither ACE inhibitors, nor β-adrenoblockers during the last month, it was stated that baroreflex sensitivity did not change and the level of plasma noradrenaline decreased significantly [38]. Similar effect was found in HCF patients receiving ATI receptor antagonist valsartan (titrated to 160 mg/daily, 4 months) [38].

In these studies on the effect of ACE inhibitors on baroreflex, practically all ACE inhibitor subgroups (captopril, enalapril, benazepril and non-metabolising lisinopril) were used in medication.

Cardioselective β-adrenoblocker metoprolol (100 mg/daily, 4 weeks) was found to increase baroreflex sensitivity in CHF patients [46]. In addition, the effect of β-adrenoblocker with sympathomimetic activity celiprolol (200 mg/daily, 4 weeks) was studied and the results showed any changes similar to those evoked by metoprolol.

The authors stated that metoprolol evoked an increase in parasympathetic effect along with an increase in baroreflex sensitivity but celiprolol did not possess such an effect.

As to our results, the lack of the bradycardic reaction in the L20 group can probably be explained by the altered sympatho-vagal balance due to the effect of basic therapy (metoprolol or bisoprolol + diuretics). This is a barrier to manifest the bradycardic reaction although the hypotensive reaction occurs as a result of baroreflex activation. The above discussed literature sources support this suggestion.

No data have been found in literature concerning the effect of mildronate on the baroreflex function. But our results have shown that the effect of the combination of mildronate + lisinopril on the baroreflex function is more pronounced than that of lisinopril alone. Moreover, the effect does not depend on the dose of lisinopril in the ML5 and ML20 groups. This suggests a direct influence of mildronate on baroreflex function. Hypothetically, this could be connected with the influence of mildronate on the release of nitric oxide (NO) [47].

A significant role of NO on the baroreflex control of HR is proved by the results of experimental animal studies [48,49] and clinical investigations [50,51].

The inhibitory effect N-monomethyl-l-arginine 3 mg/kg/h on endogenous NO generation and baroreflex function was studied in CHF patients and healthy subjects analysing HR variability [52].

The increase in baroreflex sensitivity (tested by the phenylephrin infusion) and variability of HR was found to depend on the synthesis of endogenous NO.

Conclusions

1. In CHF patients treated with the combination of mildronate and lisinopril for 3 months, an increase in the amplitude of the bradycardic and hypotensive reaction to carotid baroreceptor activation was revealed. This effect did not depend on the dose of lisinopril in the combination (in the range of the minimal–maximal dose).
2. Neither lisinopril, nor the combination of mildronate+lisinopril evoked any alterations in arterial blood pressure and the heart rate in CHF patients during a three-month treatment.
3. Interpreting the increase of the amplitude of the baroreflex bradycardic reaction as an enhancement of vagal outflow and an increase of the amplitude of hypotensive reaction as an integral hemodynamic effect, it could be concluded that the addition of the combination of mildronate+lisinopril to the treatment of CHF increased the reactivity of the carotid baroreceptor reflex.

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