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BAROREFLEX GAIN IN ESSENTIAL HYPERTENSION: THE EFFECT OF COMBINED TRANDOLAPRIL AND DILTHIAZEM THERAPY

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A b s t r a c t

The aim of the study was to compare the gain of baroreflex due to a combined therapy with dilthiazem and trandolapril, including the vasomotor response, in patients with essential hypertension. We examined 18 patients with mild essential hypertension. Baroreflex sensitivity and baroreflex gain were determined according to the methods developed in our laboratory. It is concluded that, in patients with essential hypertension, the gain of the whole baroreflex due to a combined therapy with dilthiazem and trandolapril corresponded to that in healthy subjects.

K e y w o r d s

Baroreflex sensitivity, Essential hypertension, Therapy

INTRODUCTION

A reduction in baroreflex gain may play some role in the long-term development of hypertension. The assessment of baroreflex gain is usually based on open and closed-loop models. In patients with essential hypertension, one part of the baroreflex gain, i.e., baroreflex heart rate sensitivity (BRS, ms/mmHg), increased due to the combined therapy with dilthiazem and trandolapril in comparison with the placebo therapy *(1, 2, 3, 4).* The aim of the study was to compare the baroreflex gain, including the vasomotor response which has not been studied up to the present.

MATERIALS AND METHODS

We examined 18 male patients (group EH TD) with mild essential hypertension (48±5 years old; body weight, 88±9 kg) after 3 months of the combined therapy with trandolapril (2 mg in a single morning dose) and dilthiazem (retard, 90 mg, twice a day,) with mean BRS 8.2±3.4 ms/mmHg. We compared them with 10 normotensives (group C-HBRS) with high BRS>10 ms/mmHg and with 10 normotensives (group C-LBRS) with low BRS<5 ms/mmHg. Both normotensive control groups were selected from a population of 100 healthy adults. A further control group of 10 untreated patients (EH) with essential hypertension, with mean BRS 4.7±1.8 ms/mmHg, was included in the study.

The blood pressure component of the baroreflex was examined by the following procedure *(6).* The subjects were studied in the supine position. An inflatable cuff (width, 12 cm) was placed over each thigh of all subjects. After the subject had been recumbent for at least 20 min, the thigh cuffs were abruptly inflated to 180 mmHg or to a level 20 mmHg above the patient's systolic pressure. Five

minutes later, a rapid decrease in cuff pressure to 60 mmHg elicited a decrease in systolic and diastolic blood pressure. The pressure of 60 mmHg in the occluding cuffs was chosen in order to prevent an increased venous return from the legs and stimulation of low pressure receptors. Blood pressure in the digital arteries was recorded continuously with a Finapres BP Monitor 2300 (Ohmeda, Engelwood, USA) *(5).* After a decrease in blood pressure of approximately 10-20 mmHg, the pressure returned to its original level (*Fig.1*). The curve of systolic and diastolic blood pressure return is S-shaped, with a linear central part. The slope of the systolic blood pressure return (SLOPE-SBP) and the slope of the diastolic blood pressure return (SLOPE-DBP) were calculated by means of linear regression and were expressed in mmHg/s. The magnitude of SLOPE-SBP and that of SLOPE-DBP corresponded with the gain in the blood pressure component of the baroreflex.

The statistical significance of differences between EH P and EH TD groups was determined by the Wilcoxon test for paired data; that between EH P and C groups by the Wilcoxon unpaired test. Further analysis was performed by analysis of variance. The results were expressed as mean SD.

The study was approved by the Ethics Committee of the Teaching Hospital of Masaryk University.

RESULTS

The combined therapy with trandolapril and dilthiazem, administered to EH TD group for 3 months, significantly decreased systolic and diastolic blood pressure and heart rate and significantly increased BRS. The analysis of the blood pressure component of the baroreflex revealed that, in groups EH TD and EH, the gain in the whole baroreflex (mean SBP, 166±12 mmHg; DPB, 102±8 mmHg) corresponded with that in the healthy subjects with high BRS (*Table 1*).

The respective values for SLOPE-SBP and SLOPE-DBP in the four groups were: EH TD, 0.93±1.33 and 0.55±0.65; C-LBRS, 0.48±0.18 and 0.30±0.14; C-HBRS, 1.29±0.62 and 1.18±0.58; EH, 1.04±0.64 and 0.48±0.18. The SLOPE-SBP and SLOPE-DBP values in group C-LBRS were significantly different from those in the other groups (ANOVA, $P<0.05$).

DISCUSSION

The mechanism resulting in BRS normalisation after a combined therapy with trandolapril (angiotensin converting enzyme inhibitor) and dilthiazem (Ca antagonist) in not yet understood. The baroreflex gain depends on involvement of two of its components: baroreceptor sensitivity including amplification of the neuronal net and the effectivity of the effector branches of the reflex, modulating cardiac output and peripheral resistance.

A low baroreflex gain was found in patients with heart failure in whom reduced muscle sympathetic nerve activity (MSNA) modulation by the baroreflex was found *(7).* This finding can be explained by low sensitivity of baroreceptors. Aldosterone, the concentration of which is increased in heart failure, stimulates Na/K-ATPase of receptors. This results in hyperpolarisation of receptor cells and a decreased frequency of the efferent train of spikes *(8).* The deactivation of baroreceptors and their stimulation by vasoactive drug-induced changes in blood pressure can influence MSNA that, in essential hypertension, remains unchanged,

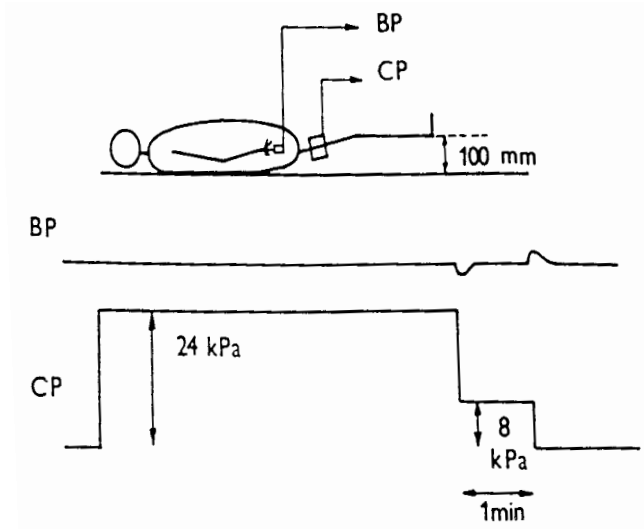

Fig. 1

Schematic presentation showing the experimental procedure, schematic blood pressure (BP) curve and cuff pressure (CP) before, during and after the 5-minute occlusion (24 kPa).

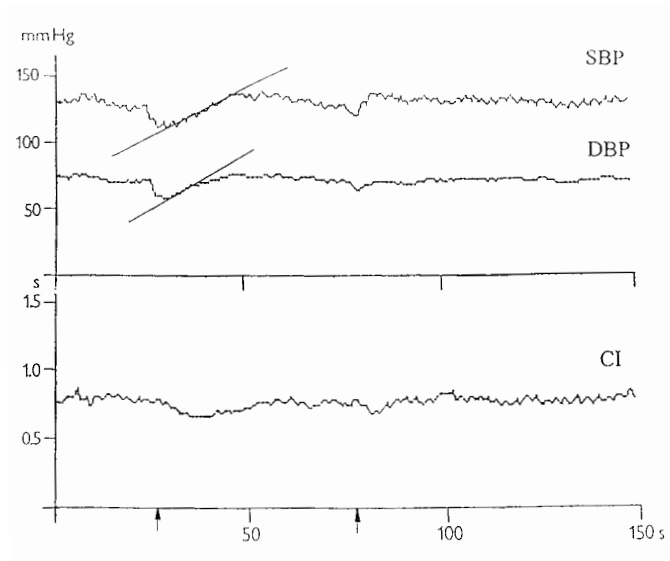

Fig. 2

A record of systolic (SBP) and diastolic (DBP) blood pressure and cardiac interval (CI) in a healthy subject. The left arrow indicates the moment of cuff pressure decrease from 180 to 60 mmHg, the right arrow shows a decrease from 60 to 0 mmHg. The slope of SBP return and that of DBP return are indicated by solid lines.

Table 1

Systolic and diastolic blood pressure (SBP, DBP, mmHg, meanSD), BRS (ms/mmHg), Slope-SBP and Slope-DBP (mmHg/s) in the groups of subjects studied.

	EH TD	EH	C	C-LBRS	C-HBRS
BRS (ms/mmHg)	9.0±5.5	4.7±1.8	7.8±3.8	4.5±4.0 +	16.70±4.6
Slope-SBP (mmHg/s)	0.93±1.33	1.04±0.64	0.95±0.72	0.30±0.14*	1.29±0.62
Slope-DBP (mmHg/s)	1.31±0.97	0.92±0.68	0.98±0.65	0.48±0.18*	1.18±0.58

SBP, systolic blood pressure; DBP, diastolic blood pressure; BRS, baroreflex sensitivity; EH TD, treated hypertonics; EH, untreated hypertonics; C, control group; C-LBRS, controls with low BRS; C-HBRS, controls with high BRS; *, significant differences ($P<0.05$) of C-LBRS *vs.* other groups; +, significant differences ($P<0.05$) of C-LBRS *vs* EH TD and C-HBRS.

as compared to normotension; this is at variance with a reduction in heart rate alteration *(9, 10).*

It is possible that the sympathetic overactivity shown by increased MSNA in subjects with essential hypertension *(9, 11)* inhibits the baroreflex-mediated vagal response. Angiotensin II activates the sympathetic nervous system both centrally and peripherally *(12).* This influence is not reversed by enalapril, given in a single morning dose, probably because of an insufficient trough-to-peak ratio. The trough-to-peak ratio of trandolapril is higher. Verapamil, another Ca-antagonist, increases the threshold in sinoatrial pacemaker cells *(9)*. The increased variation in inter-beat intervals at the constant variation of the slope of diastolic prepotential is probably the consequence of administration of verapamil; the same influence may be exerted also by dilthiazem.

It is concluded that, in patients with essential hypertension receiving a combined therapy of trandolapril and dilthiazem for 3 months (EH TD), the whole baroreflex gain is similar to that in healthy subjects with high BRS.

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BAROREFLEX U ESENCIÁLNÍ HYPERTENZE: ÚČINEK KOMBINOVANÉ TERAPIE TRANDOLAPRILEM A DILTHIAZEMEM

S o u h r n

Cílem studie bylo srovnání celkového výkonu baroreflexu u nemocných s esenciální hypertenzí léčených kombinací dilthiazemu a trandolaprilu. Vyšetřili jsme 18 nemocných s mírnou esenciální hypertenzí. Baroreflexní sensitivita a celkový výkon baroreflexu byly stanoveny metodami vyvinutými v naší laboratoři. Dospěli jsme k závěru, že celkový výkon baroreflexu u nemocných s esenciální hypertenzí léčených kombinací dilthiazemu a trandolaprilu odpovídá normotonikům.

A c k n o w l e d g e m e n t s

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REFERENCES

1. *Robbe HWJ, Mulder LJM, Ruddel H, Langewiz WA, Mulder G*. Assessment of baroreceptor reflex sensitivity by means of spectral analysis. Hypertension 1987;10:538–43.
2. *Siegelová J, Fišer B, Dušek J, AL-Kubati M*: Baroreflex-Senstivitaetsmessung bei Patienten mit essentieler Hypertonie: Einfluss von Enalapril. Nieren und Hochdruckkrankheiten 1995;24:20–22.
3. *Siegelová J, Fišer B, Dušek J*. Baroreflex heart rate sensitivity in essential hypertension: the effect of Isoptin SR 240 therapy. In: Varrů V, de Chantel R, eds. 22nd Congress of International Society of Internal. Medicine, Bologna: International Proceeding Div. Monduzzi Editore, 1994:99–102.
4. *Al-Kubati M, Fišer B, Siegelová J*. Baroreflex sensitivity during psychological stress. Physiol Res 1997;46:27–33.
5. *Peňáz J*. Photoelectric measurement of blood pressure, volume and flow in the finger. In: Digest of the 10th Int. Conf. Med. Biol. Engineering, Dresden, 1973:104.
6. *Savin E, Siegelová J, Fišer B, Bonnin P.* Intra- and extracranial artery blood velocity during a sudden blood pressure decrease in humans. Eur J Appl Physiol 1997;76:289–93.
7. *Grassi G, Seravalle G, Gattaneo BM et al*. Sympathetic activation and loss of reflex sympathetic control in mild congestive heart failure. Circulation 1995;92:3206–211.
8. *Wang SJ, McClain JM, Zucker H.* Aldosterone reduced baroreceptor discharge in the dog. Hypertension 1992;19:270–77.
9. *Mancia G.* The sympathetic nervous system in hypertension. J Hypertens 1997;15:1553–65.
10. *Grassi G, Gattaneo BM, Seravalle G, Lanfranchi A, Mancia G.* Baroreflex control of sympathetic nerve activity in essential and secondary hypertension. Hypertension 1998;31:68–72.
11. *Folkow B*. The Fourth Volhard Lecture: cardiovascular structural adaptation: its role in the initiation and maintenance of primary hypertension. Clin Sci Mol Med 1978;4:3s–22s.
12. *Zimmerman BG*. Adrenergic facilitation by angiotensin: does it serve a physiological function? Clin Sci 1981;60:343–48.