Acta Medica et Biologica
Vol. 51, No.2, 43-48, 2003

The Preventive Effect of β-blockers, Carvedilol and Metoprolol, on Mental Stress-induced Changes in Cardiovascular Functions by a Color Word Conflict Test

Yasuo WATANABE[1], Masayoshi OKADA[1], Tatsuru TSURUMAKI[1], Fumitake GEJYO[2] and Hiroshi HIGUCHI[1]

[1]Division of Pharmacology, Department of Molecular Genetics and Signal Transduction Research, Course for Molecular Cellular Medicine, [2]Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

Received March 5 2003 ; accepted April 3 2003

Summary. **Experimental mental stress by a computerized color word conflict test was developed. The effects of a single oral administration of two different β-blockers, carvedilol (a vasodilating β-/α_1-blocker, 20 mg) and metoprolol (a β_1-selective blocker, 20 mg), on a color word conflict test (mental stress)-induced increase in heart rate and systolic blood pressure were investigated in 108 healthy volunteers, 21-24 years of age, by double blind protocol. At rest carvedilol and metoprolol gradually reduced the heart rate, and slightly lowered systolic and diastolic blood pressure. The mental stress by the color word conflict test significantly increased the heart rate and systolic blood pressure by a respective 3.1±0.6 /min and 2.0±0.9 mmHg. Carvedilol completely inhibited the mental stress-induced increases in both systolic blood pressure and heart rate 3 h after administration, and metoprolol significantly blocked the increase in systolic blood pressure. These findings indicated that β-blockers effectively prevent mental stress-induced changes in cardiovascular functions.**

Key words—metoprolol, carvedilol, mental stress, color word conflict test, β-blocker, heart rate, blood pressure.

INTRODUCTION

Mental stress can often activate sympathetic nerve activity in ordinary life and increase blood pressure and heart rate. β-adrenergic blockers (β-blockers) are well known to reduce sympathetic nerve activity by inhibiting sympathetic β-adrenoceptor[1)]. They are widely used for the treatment of cardiovascular diseases which are associated, at least partially, with an enhanced sympathetic nerve activity, such as hypertension[2,3)], angina pectoris[4,5)], and tachyarrhythmia. Therefore, while mental stress-induced cardiovascular symptoms may be treated with β-blockers, to date there has been little study to investigate the effect of β-blockers.

For this purpose, we used two different β-blockers. Metoprolol, a second-generation β_1-selective adrenoceptor blocking agent without specific vasodilating properties, is useful for reducing both systolic and diastolic blood pressure and heart rate through the selective inhibition of cardiac β_1-adrenoceptor[1,6)]. It has been shown that metoprolol reduces resting blood pressure, resting heart rate, and also reduces increases in blood pressure and heart rate by sympathetic nerve stimuli during exercise in healthy volunteers[6-9)] and hypertensive patients. Because a few studies on metoprolol have reported that a direct intravenous administration or massive dose (100 mg) treatment of metoprolol could inhibit mental stress-induced change in cardiovascular functions[10,11)], our data with metoprolol provided a basis for the concept that a β-adrenoceptor blockade inhibits mental stress-induced change in cardiovascular functions.

Carvedilol is a different β-blocker with vasodilating properties that has a nonselective β-blockade[12)].

Correspondence: Hiroshi Higuchi, M.D., Ph.D., Division of Pharmacology, Department of Molecular Genetics and Signal Transduction Research, Course for Molecular Cellular Medicine, Niigata University Graduate School of Medical and Dental Sciences, Niigata 951-8510, Japan.

Abbreviations—ANOVA, analysis of variance; β-blocker, β-adrenergic blocker, α-blocker, α-adrenergic blocker

Carvedilol has also a weak α_1-blocking property for the treatment of mild to moderate hypertension[12-14]. It is being evaluated in clinical trials for application in chronic unstable angina and congestive heart failure[15-17]. The antihypertensive effect of carvedilol on resting and exercise blood pressure is obvious[14]. We therefore used carvedilol as another type of β-blocker in order to investigate the effect of a β-adrenoceptor blockade on mental stress-induced change in cardiovascular functions.

In this study the effects of two β-blockers, carvedilol and metoprolol, on increases in blood pressure and heart rate induced by a computerized color word conflict test were investigated in healthy volunteers.

MATERIALS AND METHODS

Volunteers

One hundred and eight healthy Japanese volunteers, 21-24 years of age (70 males and 38 females), participated in this study. Individuals who had a history of bronchial asthma, allergic disorders, or cardiovascular disease were excluded. All agreed with the purpose of this study and provided informed consent according to the protocol by the review board of Niigata University Medical School.

Drugs

Metoprolol tartrate (20 mg) was purchased from AstraZeneca Co. Ltd.. Carvedilol (20 mg) was purchased from Daiichiseiyaku Co. Ltd. A tablet of lactomine (Biofermin 6 mg, Takeda Pharmaceutical Co. Ltd.) was taken up as a placebo.

Protocol

The protocol of this double blind study is shown in Fig. 1. A computerized version of the Stroop's color word conflict test was taken as mental stress, which produced a more profound stimulation on sympathetic function than that with a Kleperin psychiatric arithmetic test[18]. The color word conflict test was performed 200 times for 4 min. To increase the effect of the color word conflict test as a stressor, the interval of each trial was shortened to 1.2 sec. Before and immediately after each set of mental stress, heart rates and systolic and diastolic blood pressure were measured. Blood pressure was measured by manometer and heart rate was calculated by counting pulses for 30 sec and doubling the value obtained. The first set of mental stress was performed before drugs were administrated at 1 : 30 pm. Thereafter, each drug or placebo was administrated orally under the double blind protocol. The second and third sets

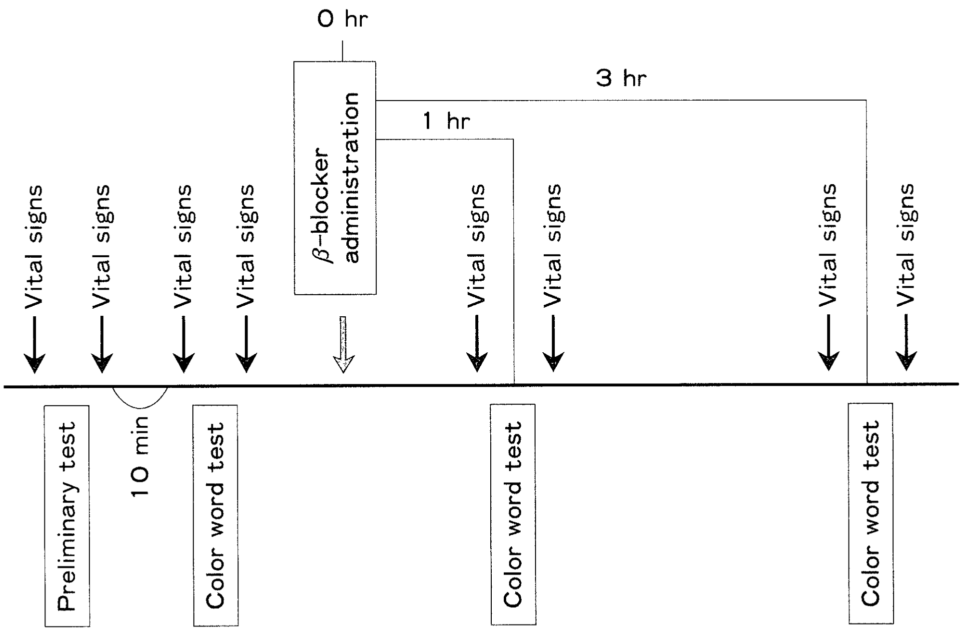

Fig. 1. Time course of experiment.
Vital signs (heart rate and blood pressure) were measured before and immediately after color word conflict tests. The effects of β-blockers, carvedilol and metoprolol, were investigated.

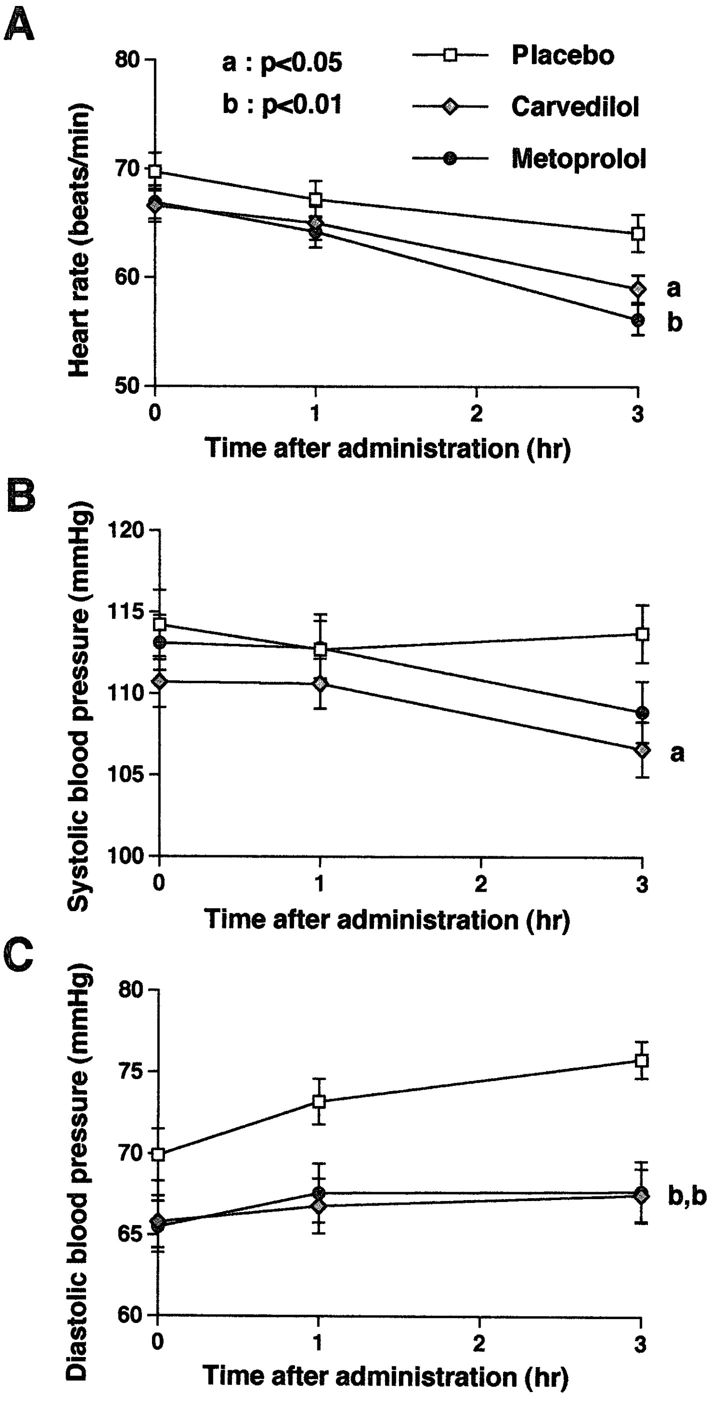

Fig. 2. Effect of β-blockers on resting heart rate and blood pressure.
Heart rates and systolic and diastolic blood pressure of healthy volunteers at rest were measured before, and 1 and 3 h after the oral administration of β-blockers. (**A**) Effects of β-blockers on heart rate (**B**) Effects on sytolic blood pressure (SBP) (**C**) Effects on diastolic blood pressure (DBP). Each value indicates mean and S.E.M. of placebo group (□, n=36), carvedilol group (◈, n=36), and metoprolol group (●, n=36). Student's *t*-test was performed 3 h after oral administration and the data of carvedilol and metoprolol groups were compared with the values of the placebo group, a; $p<0.05$, b; $p<0.01$.

of mental stress were performed 1 and 3 h after drug administration, respectively. No volunteers experienced any trouble or illress under this study protocol.

Data analysis

Data are means±standard error. Student's *t*-test and ANOVA followed by a post-hoc analysis using Fisher's test were employed to investigate the effect of the β-blockers on the resting cardiac functions and mental stress-induced changes in cardiovascular functions. A value of $p<0.05$ was considered significantly.

RESULTS

Effect of oral administration of β-blockers on resting heart rate and blood pressure

Fig. 2 shows the effect of β-blockers on resting heart rate and resting blood pressure. During the experimental period, the heart rate of subjects decreased gradually in the placebo group, probably due to the circadian rhythm of heart rate (Fig. 2A). The oral administration of low doses (20 mg) of carvedilol and metoprolol reduced heart rates more than that of the placebo group 3 h after oral administration. The decrease in heart rate by β-blockers was modest but significant. The difference was not significant 1 h after oral administration.

As shown in Fig. 2B, systolic blood pressure in the placebo group was constant during the experimental period. Carvedilol caused a slight but significant reduction of systolic blood pressure 3 hr after oral administration (Fig. 2B). In contrast, the diastolic pressure in the placebo group was increased gradually and significantly during the experimental period, probably due to circadian rhythm (Fig. 2C). Treatment with 20 mg carvedilol and 20 mg metoprolol abolished the gradual increase in diastolic blood pressure (Fig. 2C).

Color word conflict test-induced increases in blood pressure and heart rate

Changes in blood pressure and heart rate by mental stress were investigated, as shown in Fig. 3A and 3B. The color word conflict test increased heart rate and systolic pressure slightly but significantly in the placebo group (by 3.1±0.6 /min and 2.0±0.9 mmHg, respectively) 3 h after administration. The color word conflict test-induced changes in cardiovascular functions was the same before and 1 h and 3 h after oral administration of placebo, suggesting absence of acclimation to the test under the present conditions (data not shown). This mental stress did not affect diastolic blood pressure.

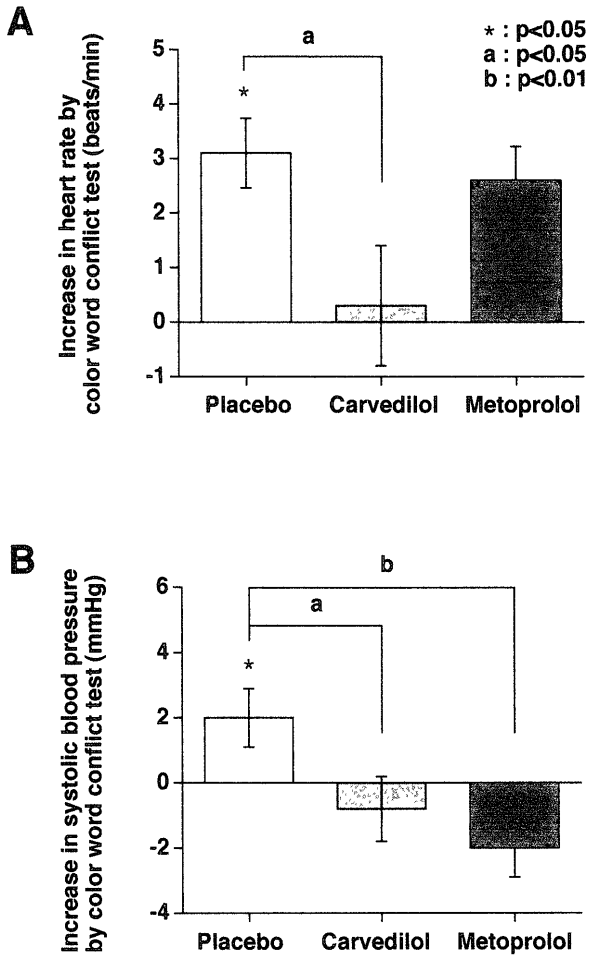

Fig. 3. Effect of β-blockers on color word conflict test-induced increases in heart rate and systolic blood pressure.
(**A**) Effects of β-blockers on a color word conflict test-induced increase in heart rate were measured 3 h after oral administration. Each value indicates changes (mean+S.E.M.) induced by a color word conflict test on the placebo, carvedilol, and metoprolol groups ($n=36$). (**B**) Effects of β-blockers on a color word conflict test-induced increase in systolic blood pressure were measured 3 h after oral administration. Student's *t*-test was performed and the data immediately after the color word conflict test were compared with the values before the test; *; $p<0.05$. ANOVA analysis was performed and the data of carvedilol and metoprolol groups were compared with each value of the placebo group, a; $p<0.05$, b; $p<0.01$.

Effect of oral administration of β-blockers on mental stress-induced change in heart rate and systolic blood pressure

Carvedilol (20 mg) inhibited mental stress-induced increase in heart rate 3 h after oral administration (Fig. 3A), but not 1 h after (data not shown). Metoprolol (20 mg) did not protect the change under the present experimental conditions. The mental stress-induced increase in systolic blood pressure was significantly inhibited by treatment with carvedilol and metoprolol 3 h after oral administration (Fig. 3B). Thus, the low doses of different β-blockers, both carvedilol and metoprolol, significantly inhibited the mental stress-induced changes in cardiovascular functions by a color word conflict test.

DISCUSSION

It has been shown that metoprolol reduces resting systolic and diastolic blood pressure and resting heart rate[9] as well as suppressing the increases in blood pressure and heart rate triggered by sympathetic nerve stimuli during exercise[6,9]. In addition, we have shown that the low doses (20 mg) of metoprolol and carvedilol slightly inhibit the resting blood pressure and heart rate.

More interestingly, in spite of their minimum suppression of resting cardiovascular functions, both β-blockers remarkably inhibited mental stress-induced changes in heart rate and systolic blood by a computerized color word conflict test, at a lower concentration than those at rest or durirg exercise (Fig. 3 and ref. 9,14). These findings suggested that a mental stress-induced change in cardiovascular functions is greatly dependent on the activation of β-adrenoceptors.

It is well known that sympathetic nerve stimuli such as mental stress and exercise release catecholamines from both sympathetic nerve terminals and the medulla of the adrenal gland, i.e., in sympathetic nerve terminals norepinephrine is released, and in the adrenal gland, both epinephrine and norepinephrine are released[11,19]. Several studies have demonstrated that during mental stress the increase in the plasma epinephrine level is higher than that of norepinephrine level[11,19]. In contrast, during exercise the increase in the plasma norepinephrine level is higher than that of epinephrine[19]. Since the β_1-blocker, metoprolol, reduced the plasma epinephrine level during mental stress[11], the inhibition by metoprolol of a mental stress-induced change in systolic blood might result from the same inhibitory mechanism of metoprolol on the plasma epinephrine level.

It is supposed that during mental stress, epinephrine-induced and β_2 adrenoceptor-mediated peripheral vascular dilatation plays a key role in the maintenance of peripheral circulation and decrease in peripheral blood vessel resistance. Non-selective β-blockers could block this peripheral vascular dilatation through the β_2-adrenoceptor, but a β_1-selective blocker, metoprolol, could neither inhibit the peripheral vascular dilatation nor increase peripheral blood vessel resistance. Thus the β_1-selective blocker, metoprolol, was shown to be a useful drug to prevent a mental stress-induced inappropriate cardiovascular response.

Noteworthily, carvedilol, a different type of β-blocker with non-selective β-blocking and α_1-blocking action, showed effective inhibition against mental stress induced in both systolic blood pressure and heart rate than did metoprolol (Fig. 3A and 3B). Although calvedilol might block β_2-adrenoceptor-mediated peripheral vascular dilatation to reduce peripheral blood circulation, carvedilol has a more beneficial α_1-blocking action and an antioxidative action. Especially, its α_1-selective blocking action could maintain peripheral circulation, due to the blockade of α_1-adrenoceptor-mediated contraction in the peripheral vascular smooth muscle and prevention of an increase in peripheral blood vessel resistance. This effect might overcome the blockade of the β_2-adrenoceptor in vascular smooth muscle so as to maintain the peripheral blood circulation. In fact, carvedilol (20 mg, p.o.) seemed to be more effective for prevention of mental stress-induced changes in cardiovascular functions than metoprolol. Thus, the preventive effect of carvedilol on mental stress-induced changes in cardiovascular functions suggests that carvedilol is also a useful drug for managing mental stress.

Mild mental stress such as from computer-based events is very common at present. The present study indicated the preventive effect of carvedilol and metoprolol on mental stress (computerized color word conflict test)-induced increases in blood pressure and heart rate. This study was performed in a total of 108 healthy volunteers, indicating that mental stress-induced changes in cardiovascular functions by the present procedure are physiologically relevant and important. Further study requires to elucidate the preventive mechanism of the β-blocking agents on stress from mental work.

REFERENCES

1) Åblad B, Carlsson E, EK L: Pharmacological studies of two new cardioselective adrenergic beta-receptor antagonists. *Life Sci* **12:** 107-119, 1973.
2) Bengtsson C: Comparison between metoprolol and propranolol as antihypertensive agents. A double-blind cross-over study. *Acta Med Scand* **199:** 71-74, 1976.
3) Hansson B-G, Dymling J-F, Hedeland H, Hulthén U: Long term treatment of moderate hypertension with the $beta_1$-receptor blocking agent metoprolol. *Eur J Clin Pharmacol* **11:** 239-245, 1977.
4) Keyriläinen O, Uusitalo A: Effect of metoprolol in angina pectoris. A subacute study with exercise tests and a long-term tolerability study. *Acta Med Scand* **199:** 491-497, 1976.
5) Ekelund L-G, Olsson AG, Orö L, Rössner S: Effects of the cardioselective beta-adrenergic receptor blocking agent metoprolol in angina pectoris. Subacute study with exercise tests. *Br Heart J* **38:** 155-161, 1976.
6) Johnsson G: Influence of metoprolol and propranolol on hemodynamic effects induced by adrenaline and physical work. *Acta Pharmacol Toxicol* **36 (Suppl V):** 59-68, 1975.
7) Johnsson G, Nyberg G, Sölvell L: Influence of metoprolol and propranolol on hemodynamic effects induced by physical work and isoprenaline. *Acta Pharmacol Toxicol* **36 (Suppl V):** 69-75, 1975
8) Lundborg P, Steen B: Plasma levels and effect on heart rate and blood pressure of metoprolol after acute oral administration in 12 geriatric patients. *Acta Med Scand* **200:** 397-402, 1976.
9) Williams FM, Singh BN, Ambler PK, Dorrington R: The effects of propranolol, practolol and metoprolol on exercise-induced tachycardia in relation to plasma levels in man. *Clin Exp Pharmacol Physiol* **3:** 473-482, 1976.
10) Nyberg G, Graham RM, Stokes GS: The effect of mental arithmetic in normotensive and hypertensive subjects, and its modification by β-adrenergic receptor blockade. *Br J Clin Parmacol* **4:** 469-474, 1977.
11) Freyschuss U, Hjemdahl P, Juhlin-Dannfelt A, Linde B: Cardiovascular and sympathoadrenal responses to mental stress: influence of β-blockade. *Am J Physiol* **255:** H1443-H1451, 1988.
12) Yue T-L, Cheng H-Y, Lysko PG, Mckenna PJ, Feuerstein R, Gu J-L, Lysko KA, Davis LL, Feuerstein G: Carvedilol, a new vasodilator and beta adrenoceptor antagonist, is an antioxidant and free radical scavenger. *J Pharmacol Exp Ther* **263:** 92-98, 1992.
13) Ruffolo Jr RR, Gellai M, Hieble JP, Willette RN, Nichols AJ: The pharmacology of carvedilol. *Eur J Clin Pharmacol* **38:** S82-S88, 1990.
14) Franz I-W, Agrawal B, Wiewel D, Ketelhut R: Comparison of the antihypertensive effects of carvedilol and metoprolol on resting and exercise blood pressure. *Clin Invest* **70:** S53-S57, 1992.
15) Kukin ML, Kalman J, Charney RH, Levy DK, Buchholz-Varley C, Ocampo ON, Eng C: Prospective, randomized comparison of effect of long-term treatment with metoprolol or carvedilol on symptoms, exercise, ejection fraction, and oxidative stress in heart failure. *Circulation* **99:** 2645-2651, 1999.
16) Watanabe K, Ohta Y, Nakazawa M, Higuchi H, Hasegawa G, Naito M, Fuse K, Ito M, Hirono S, Tanabe N, Hanawa H, Kato K, Kodama M, Aizawa Y: Low dose carvedilol inhibits progression of heart failure in rats with dilated cardiomyopathy. *Br J Pharmacol* **130:** 1489-1495, 2000.
17) Maack C, Elter T, Nickenig G, LaRosee K, Crivaro M, Stäblein A, Wuttke H, Böhm M: Prospective crossover comparison of carvedilol and metoprolol in patients with chronic heart failure. *J Am Coll Cardiol* **38:** 939-946, 2001.
18) Halliwill JR, Lawler LA, Eickhoff TJ, Dietz NM, Nauss LA, Joyner MJ: Forearm sympathetic withdrawal and vasodilatation during mental stress in humans. *J Physiol* **504:** 211-220, 1997.
19) Paran E, Neumann L, Cristal N: Effects of mental and physical stress on plasma catecholamine levels before and after β-adrenoceptor blocker treatment. *Eur J Clin Pharmacol* **43:** 11-15, 1992.