European Heart Journal (1994) **15**, 1482–1485

Effect of beta-blockade on baroreflex sensitivity and cardiovascular autonomic function tests in patients with coronary artery disease

K. E. J. AIRAKSINEN, M. J. NIEMELÄ AND H. V. HUIKURI

From the Division of Cardiology, Department of Medicine, University of Oulu, Oulu, Finland

KEY WORDS: Autonomic nervous function, baroreflexes, beta-blockers, heart rate, diabetic neuropathy.

We wished to assess the effects of beta-blockade on baroreflex sensitivity and standard tests of integrity of autonomic nervous function in patients with coronary artery disease, and to determine whether the effects of lipophilic (metoprolol) and hydrophilic (atenolol) beta-blockers differ.

Beta-blocking drugs increase spontaneous heart rate variability in healthy subjects and in patients with coronary heart disease, but little is known about their effects on baroreflex sensitivity and heart-rate based tests of autonomic integrity.

In a randomly allocated double-blind crossover study with three 2-week treatment periods, metoprolol CR 200 mg once a day, or atenolol 100 mg once a day, or placebo once a day, were administered to 18 male patients with stable coronary artery disease. Baroreflex sensitivity was determined from the natural baroreflex challenge of Valsalva strain. Heart rate reactions to standard stimuli were measured.

No significant differences were found between the effects of atenolol and metoprolol. Beta-blockade did not significantly affect the baroreflex sensitivity, but it diminished the Valsalva ratio significantly ($P<0.001$). The difference between maximum and minimum heart rate during hyperventilation was also significantly lower during beta-blockade. The heart rate response to standing up and the ratio of maximum to minimum heart rate during deep breathing were not influenced by beta-blockade.

Discontinuation of beta-blockade seems to be unnecessary for reliable determination of baroreflex sensitivity in patients with coronary artery disease, when the natural pressure challenge of Valsalva strain is used. Both hydrophilic and lipophilic beta-blockers interfere with certain diagnostic tests of autonomic nervous function. These effects must be taken into account when using these tests in the diagnosis of autonomic dysfunction and neuropathy.

Introduction

Simple non-invasive tests of autonomic function based on measurements of reflex changes in heart rate response to standardized stimuli, such as the Valsalva manoeuvre, hyperventilation and standing, are used in the diagnosis of diabetic autonomic neuropathy and autonomic failure due to other causes[1]. Measurement of baroreflex sensitivity (BRS) offers important prognostic information after myocardial infarction [2,3]. Similarly, impaired BRS may identify subjects at an increased risk of developing essential hypertension[4].

Beta-blockers augment the spontaneous heart rate variability in healthy subjects[5] and in patients with coronary artery disease[6], but little is known about their effects on BRS measurement and standard diagnostic tests of autonomic dysfunction. This question has clinical importance, since beta-blocker treatment for coronary artery disease or hypertension frequently occurs in middle-aged diabetic patients with suspected autonomic dysfunction. Similarly, discontinuation of beta-blockers after myocardial infarction for BRS testing causes inconvenience and may even carry risks. The purpose of this study was to assess whether chronic beta-blocker therapy interferes with these cardiovascular tests. Secondly, our aim was to evaluate whether the effects of a lipophilic beta-blocker (metoprolol) differ from those of non-lipophilic beta-blocker (atenolol).

Submitted for publication on 11 April 1994.

Correspondence K. E. Juhani Airaksinen MD, Division of Cardiology, Department of Medicine, Oulu University Hospital, Kajaanintie 50, 90220 Oulu, Finland

Methods

PATIENTS

The study subjects consisted of 18 male patients, with a mean age of 54 years (range 41 to 73), with uncomplicated coronary artery disease referred to our institution for elective coronary angiography. All patients were in sinus rhythm and had no contraindications for beta-blockers.

STUDY PROTOCOL

The study design was double-blind, randomized, placebo-controlled, and three period crossover. Patients who were considered to be potential study candidates were asked to a screening visit. Before randomization, calcium antagonists and other cardioactive medications (except nitrates) were discontinued at the screening visit. Former beta-blocker therapy was stopped at the start of

0195-668X/94/111482+04 $08.00/0

the double-blind treatment periods. Patients, who were clinically stable, met all inclusion criteria and in whom no exclusion criteria applied, were randomized for double-blind treatment with either metoprolol CR 200 mg, atenolol 100 mg or placebo given once daily in the morning. Each treatment period lasted for 2 weeks, unseparated by wash-out periods. Thus, the randomized phase of the study lasted 6 weeks.

All the study drugs were identical in appearance and taste. Metoprolol CR 200 mg was administered as two metoprolol CR tablets of 100 mg each. During the atenolol treatment period, patients received one active atenolol of 100 mg and one placebo tablet. To avoid withdrawal effects when crossing from active therapy to placebo, patients received one placebo and one 25 mg atenolol tablet daily during the first 4 days and thereafter two placebo tablets daily for the rest of the placebo period. Compliance was checked by tablet counts.

RANDOMIZATION

Patients were allocated to treatment according to a computer-generated randomization list. The six possible treatment orders were distributed at random among the patients in blocks of six.

ARTERIAL BLOOD PRESSURE

Arterial blood pressure was measured by the Finapres device which records finger arterial pressures on a beat-to-beat basis. The principle of operation of the device has been described earlier[7].

LABORATORY ASSESSMENT

A blood sample (5 ml) from a cubital vein was collected immediately before each testing for estimating the plasma concentration of the study drug. The samples were collected into heparinized tubes and centrifuged. The plasma was separated and stored at -20 °C until analysis.

TESTS OF AUTONOMIC FUNCTION

In the deep breathing test, the patients performed four cycles of maximal inspiration and expiration at the rate of 6 beats . min^{-1} in a supine position. The difference (max–min difference) and the ratio (max/min ratio) between the maximum and minimum heart rate during each breath were measured to evaluate the heart rate response to deep breathing.

The shortest RR interval at around the 15th beat and the longest at around the 30th beat after passive standing were measured to obtain heart rate response to standing[8].

The patients performed the Valsalva manoeuvre by blowing into a rubber tube connected to an aneroid manometer and maintaining a pressure of 40 mmHg for 15 s. A blow-off valve required the patient to blow continuously to maintain the pressure. The Valsalva ratio was calculated as the ratio of the longest RR interval after the strain to the shortest RR interval during the manoeuvre. The baroreflex slope was determined from a time window ranging from the beat when the systolic blood pressure exceeded the systolic blood pressure level at the end of the Valsalva strain to the next beat after the maximum systolic blood pressure overshoot[9]. Only regression lines with a correlation coefficient greater than 0·8 or that were significant ($P<0·05$) and with a blood pressure change ≥ 15 mmHg were accepted for analysis. The BRS was calculated as the mean value of two accepted tests with the best correlation coefficients of the regression lines.

DATA ACQUISITION

The RR intervals were collected from the surface electrocardiogram and fed to the analog-to-digital converter (DAP 1200, Microstar Laboratories, Inc., U.S.A.)) of an IBM PC/AT compatible microcomputer (MikroMikko 4TT, Nokia Oy, Finland). Non-invasive arterial pressure was collected on a beat to beat basis from the second finger of the left hand using the Finapres finger-cuff method. The principles underlying the operation of the Finapres and its reliability during the Valsalva manoeuvre have been described earlier[7]. Care was taken to ensure that the monitored finger was positioned on the same horizontal plane as the left ventricle by use of an adjustable support. Output from the Finapres was relayed via a serial interface to the microcomputer for data analysis.

DATA ANALYSIS

All data acquisition and analysis were accomplished with a menu driven software package (CAFTS, Medikro OY, Finland). A sampling frequency of 200 Hz was used for both ECG and blood pressure signals and the amplitude resolution was 12 bits. After completing the software QRS and pressure wave detection, the signals were plotted on the microcomputer screen for viewing with an option for editing.

STATISTICS

Analysis of variance for repeated measures followed by paired t-test was used to assess the significance of the changes in various parameters during treatment periods.

Results

PLASMA DRUG CONCENTRATIONS

The mean plasma concentration of atenolol was 1197 ± 550 nmol . l^{-1} during the atenolol period and the mean plasma concentration of metoprolol was 321 ± 200 nmol . l^{-1} during the metoprol period.

Table 1 Heart rate, blood pressure and cardiovascular tests during placebo, atenolol and metoprolol periods. Values are mean ± standard deviation

	Placebo	Atenolol	Metoprolol
Heart rate (beats . min^{-1})	66·8 ± 8·7	51·0 ± 5·9***	53·7 ± 7·1***
Blood pressure, supine (mmHg)			
systolic	134 ± 18	124 ± 16**	123 ± 16**
diastolic	77 ± 12	65 ± 11**	68 ± 14**
Blood pressure, standing (mmHg)			
systolic	142 ± 17	127 ± 16**	129 ± 16**
diastolic	89 ± 11	73 ± 13**	76 ± 11**
Valsalva ratio	1·68 ± 0·36	1·34 ± 0·24***	1·37 ± 0·26***
Heart rate response to standing	1·04 ± 0·06	1·03 ± 0·08	1·02 ± 0·06
Heart rate variation during deep breathing			
Max–min heart rate difference (beats . min^{-1})	15·1 ± 6·4	11·1 ± 6·0*	10·2 ± 5·2**
Max/min heart rate ratio	1·26 ± 0·12	1·25 ± 0·15	1·22 ± 0·12
Baroreflex sensitivity (ms . mmHg^{-1})	10·6 ± 4·4	9·7 ± 4·2	10·4 ± 5·3

**P<0·01.
***P<0·001.

CARDIOVASCULAR TEST

No significant differences were found between the effects of metoprolol and atenolol. BRS was not significantly altered by beta-blockers (Table 1). On the other hand, the Valsalva ratio was significantly (P<0·001) blunted by both beta-blockers. Similarly, the deep breathing difference in heart rate was diminished during both beta-blocker periods. Deep breathing ratio in heart rate, and heart rate response to standing were not affected by beta-blockade. Resting heart rate was significantly (P<0·001) lower during atenolol and metoprolol treatment than during the placebo period. The average systolic and diastolic blood pressures were significantly (P<0·01) lower during beta-blockade both in the supine and standing position.

Discussion

Autonomic dysfunction has been described in a broad variety of diseases, including diabetes mellitus and this dysfunction may carry an increased risk of mortality[10]. A battery of cardiovascular tests assessing mainly the heart rate responses to standard stimuli is still the cornerstone of the diagnosis of autonomic failure due to diabetes or other causes[1]. One common problem complicating the testing is the fact that beta-blocker therapy for coronary artery disease or hypertension is common, particularly in middle-aged diabetic patients. Discontinuation of therapy causes inconvenience and may carry some extra risks for the patient.

In view of frequent use of beta-blockers, our findings, which show that these drugs significantly modify certain standard cardiovascular tests, are clinically important. The heart rate responses to Valsalva manoeuvre and deep breathing (max–min heart rate difference) were significantly blunted by beta-blockade. On the other hand, the heart rate response to standing and the response to hyperventilation, expressed as the ratio of maximum and minimum heart rates, which normalizes the change for heart rate, were not significantly affected. It has been speculated that the ability of a beta-blocker to penetrate the blood-brain barrier is crucial for the autonomic effects of a drug. In the present study, we did not, however, find any difference between the effects of a lipophilic and a non-lipophilic beta-blocker.

Interest in determination of BRS in clinical practice is growing fast, together with the accumulation of evidence on its prognostic value[2–4]. The development of reliable non-invasive blood pressure monitoring systems, coupled with on-line methods of analysis, has largely solved the technical problems of BRS determination. Earlier studies have shown that the overshoot blood pressure reaction after Valsalva strain is a natural challenge for baroreflexes which can be used for the determination of BRS[9,11–14]. A good linear correlation between the BRS indices derived from the Valsalva strain and the standard phenylephrine test has been found both in healthy and hypertensive subjects and in patients with coronary artery disease[9,11 14]. In this study, we showed that the BRS determined from the Valsalva test remained unchanged during beta-blocker treatment, suggesting that the discontinuation of beta-blocker therapy is not necessary for reliable determination of BRS in the patients with coronary artery disease.

Previous studies have shown that beta-blocker therapy has a beneficial effect on spontaneous heart rate variability in healthy subjects and in patients with coronary artery disease[5,6]. Beta-blockers significantly increase high frequency power spectra and the time domain indices of heart period variability, suggesting enhanced vagal tone[15]. In the light of these earlier studies, the present findings on blunting of certain cardiovascular responses which measure the integrity of vagal cardiac control, seem confusing. It must, however, be emphasized that these measures reflect different aspects of vagal cardiac control. Measures of spontaneous respiratory heart rate variation reflect prevailing vagal tone, while the heart rate responses reflect the maximal strength of vagal responses to specific stimuli. It is possible that when the basal vagal tone of an

individual is enhanced by a drug, the maximal capacity of vagal control is not increased to the same degree, leading to attenuation of vagal responses compared to the increased baseline vagal activity. Secondly, change in average heart rate by itself may result in changes of both time and frequency domain measures of heart rate variability and also affect tests of autonomic integrity[16,17]. In this respect, it was noteworthy that when the heart rate response to deep breathing was normalized for heart rate by expressing the response as the ratio of maximum and minimum heart rates instead of their difference, the response remained unchanged during beta-blockade.

In conclusion, our study suggests that reliable determination of BRS using Valsalva strain as the blood pressure stimulus is possible during chronic beta-blocker therapy. On the other hand, both hydrophilic and lipophilic beta-blockers interfere with certain heart-rate based cardiovascular tests, namely the Valsalva ratio and the deep breathing difference in heart rate, used in the assessment of the integrity of autonomic nervous function. This interference must be remembered when interpreting the test results and the deep breathing test should be analysed as the ratio of maximal and minimal heart rates instead of their difference.

Astra Hässle Ab, Mölndal, Sweden, provided the metoprolol and atenolol used in this study. This study was supported by grants from the Finnish Foundation for Cardiovascular Research, Helsinki, Finland, the Medical Council of the Academy of Finland, Helsinki, Finland and Paavo Nurmi Foundation, Helsinki, Finland.

References

[1] Ewing DJ, Clarke BF Diagnosis and management of diabetic autonomic neuropathy. Br Med J 1982; 285: 916–8.

[2] La Rovere MT, Specchia G, Mortara A, Schwartz PJ. Baroreflex sensitivity, clinical correlates, and cardiovascular mortality among patients with a first myocardial infarction. Circulation 1988; 78: 816–24.

[3] Farrell TG, Odemuyiwa O, Bashir Y *et al.* Prognostic value of baroreflex sensitivity testing after myocardial infarction Br Heart J 1992; 67: 129–37.

[4] Parmer RJ, Cervenka JH, Stone RA. Baroreflex sensitivity and heredity in essential hypertension. Circulation 1992; 85: 497–503.

[5] Cook JR, Bigger JT, Kleiger RE, Fleiss JL, Steinman RC, Rolnitzky LM. Effect of atenolol and diltiazem on heart period variability in normal persons. J Am Coll Cardiol 1991; 17: 480–4.

[6] Niemelä MJ, Airaksinen KEJ, Huikuri HV. Effect of beta-blockade on heart rate variability in patients with coronary artery disease. J Am Coll Cardiol 1994; 23: 1370–7.

[7] Imholz BPM, van Montfrans GA, Settels JJ, van der Hoeven GMA, Karemaker JM, Wieling W. Continuous non-invasive blood pressure monitoring: reliability of Finapres device during the Valsalva manoeuvre. Cardiovasc Res 1988; 22: 390–7.

[8] Airaksinen KEJ, Koistinen MJ, Ikäheimo MJ, Takkunen JT. Effect of Type 2 diabetes and coronary artery disease on parasympathetic cardiovascular reflexes. Diabetes Care 1990; 13: 83–6.

[9] Airaksinen KEJ, Hartikainen JEK, Niemelä MJ, Huikuri HV, Mussalo HM, Tahvanainen KUO. Valsalva manoeuvre in the assessment of baroreflex sensitivity in patients with coronary artery disease. Eur Heart J 1993; 14: 1519–23.

[10] Ewing DJ, Canpbeel IW, Clarke BF. Mortality in diabetic autonomic neuropathy. Lancet 1976; 1: 601–3.

[11] Smith SA, Stallard TJ, Salih MM, Littler WA. Can sinaortic baroreceptor heart rate reflex sensitivity be determined from phase IV of the Valsalva manoeuvre? Cardiovasc Res 1987; 21: 422–7

[12] Pickering TG, Sleight P. Quantitative index of baroreflex activity in normal and hypertensive subjects using Valsalva's manoeuvre. Br Heart J 1969; 31: 392.

[13] Palmero HA, Caeiro TF, Iosa DJ, Bas J. Baroreceptor reflex sensitivity derived from phase 4 of the Valsalva's maneuver. Hypertension 1981; 3 (Suppl II): 134–7.

[14] Trimarco B, Volpe M, Ricciardelli B *et al.* Valsalva maneuver in the assessment of baroreflex responsiveness in borderline hypertensives. Cardiology 1983; 70: 6–14.

[15] Akselrod A, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981; 213: 220–3.

[16] Ziegler D, Laux G, Dannehl K *et al.* Assessment of cardiovascular autonomic function: Age-related normal ranges and reproducibility of spectral analysis, vector analysis, and standard tests of heart rate variation and blood pressure. Diabetic Med 1992; 9: 166–75.

[17] Van Hoogenhuyze D, Weinstein N, Martin GJ *et al.* Reproducibility and relation to mean heart rate of heart rate variability in normal subjects and in patients with congestive heart failure secondary to coronary artery disease. Am J Cardiol 1991; 68: 1668–76.