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Different Effects of Propranolol, Bisoprolol, Carvedilol and Doxazosin on Heart Rate, Blood Pressure, and Plasma Concentrations of Epinephrine and Norepinephrine

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Background: Despite of its beta-blocking effects, carvedilol has been shown not to decrease resting heart rate in healthy subjects. Therefore, we compared haemodynamic effects of carvedilol (an alpha- and beta-blocker), propranolol (a non-selective beta-blocker), bisoprolol (a $beta_1$-selective beta-blocker), doxazosin (an alpha-blocker) and placebo, at rest and during exercise. In addition, we measured plasma levels of epinephrine and norepinephrine.

Methods: Twelve healthy males received single oral doses of 80 mg propranolol, 5 mg bisoprolol, 50 mg carvedilol, 4 mg doxazosin and placebo according to a randomized, double-blind, crossover protocol. Three hours after drug intake, heart rate and blood pressure were measured at rest, after 10 min of exercise, and after 15 min of recovery. At the same times, plasma concentrations of epinephrine and norepinephrine were determined by HPLC.

Results: At rest, propranolol (–21 %, $p < 0.05$) and bisoprolol (–21 %, $p < 0.05$) decreased heart rate, doxazosin (+30 %, $p < 0.05$) increased heart rate, whereas carvedilol had no effect. During exercise, propranolol (–26 %, $p < 0.05$), bisoprolol (–19 %, $p < 0.05$) and carvedilol (–18 %, $p < 0.05$) decreased heart rate, whereas doxazosin (+6 %, $p < 0.05$) increased heart rate. During exercise, plasma levels of norepinephrine with doxazosin were higher than those with propranolol and bisoprolol ($p < 0.05$ in both cases).

Conclusions: These data show that "pure" beta-blockers decrease heart rate in healthy subjects even at rest. On the other hand, alpha-blockers increase heart rate, most likely caused by an increase of sympathetic tone as a physiological reaction to the blood pressure lowering effect of alpha-blockade. In carvedilol, which combines alpha- and beta-blockade in one molecule, these effects widely appear to compensate each other, thus resulting in a lack of effect on resting heart rate in healthy subjects. This low clinically effective beta-blockade of carvedilol at rest might explain the low incidence of side effects resulting from beta-blockade as well as the lack of effect of carvedilol on melatonin release. The slight differences between plasma levels of norepinephrine with doxazosin on the one hand and with propranolol and bisoprolol on the other hand give a weak support to the hypothesis that an increase of sympathetic tone caused by a decrease of blood pressure by alpha-blockade might weaken the net beta-blocking effects of carvedilol. *J Clin Basic Cardiol 2003; 6: 69–72.*

Key words: alpha-blockade, beta-blockade, sympathicus, sympathetic drive

Chronic administration of beta-blockers without intrinsic sympathomimetic activity (ISA) causes up-regulation of beta-receptor density [1]. In addition, beta-blockers have been shown to reduce nocturnal melatonin release [2] whereas carvedilol does not show this effect [3] and may fail to cause up-regulation of beta-receptor density [4]. Therefore, we hypothesized that the lack of these typical effects of beta-blockers in carvedilol, which is currently unexplained, might be caused by the following two mechanisms: Firstly, reflex activation of sympathetic tone in order to compensate a decrease of blood pressure caused by the alpha-blocking effects of the drug; secondly, inhibition of presynaptic alpha-receptors causing an increased release of catecholamines. Indeed, it was shown recently that single-dose administration of optically pure (R)-carvedilol may increase resting heart rate [5], and heart rates at rest increased with increasing doses of (R, S)-carvedilol, a behaviour contrary to what would be expected with a beta-blocker [6, 7].

The objective of the present study was to investigate our hypotheses mentioned above. If they were true, one would expect: Firstly, that propranolol, a non-selective beta-adrenergic antagonist, and bisoprolol, a selective antagonist of $beta_1$-receptors, would decrease heart rate even at rest; doxazosin, an $alpha_1$-antagonist, would increase heart rate at rest; and carvedilol, a non-selective beta-blocker with additional blocking effects on $alpha_1$-adrenoceptors, would lie in between with little or no effect on heart rate at rest, thus indicating a lack of clinically effective beta-blockade at rest in healthy subjects which might explain why carvedilol does not influence nocturnal melatonin production and may fail to cause up-regulation of beta-receptor density. Secondly, plasma concentrations of catecholamines would be higher with doxazosin and carvedilol than with propranolol, bisoprolol and placebo.

In order to further investigate this issue, we performed a randomized, double-blind, placebo-controlled, crossover study in twelve healthy males who received single oral doses of 80 mg propranolol, 5 mg bisoprolol, 50 mg carvedilol, 4 mg doxazosin and placebo in order to determine the effects of these drugs on heart rate and blood pressure both at rest and during exercise, as well as their influence on plasma concentrations of epinephrine and norepinephrine.

All beta-blockers investigated in the present study are currently used as racemates, ie, as racemic mixtures of their (R)- and (S)-enantiomers both in scientific investigations and in clinical practice, although it is clear that only the (S)-enantiomers exert beta-blockade in clinical practice whereas the (R)-enantiomers do not contribute to this effect but may cause adverse effects [8, 9]. In the present study, we also used the currently available racemic mixtures of (R, S)-propranolol, (R, S)-bisoprolol and (R, S)-carvedilol. There-

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fore, whenever propranolol, bisoprolol and carvedilol are mentioned without their (R)-/(S)-prefixes in the present manuscript, the racemic (R, S)-mixtures were used.

Methods

Twelve healthy males received single oral doses of 80 mg propranolol, 5 mg bisoprolol, 50 mg carvedilol, 4 mg doxazosin and placebo at intervals between 3 and 7 days according to a randomized, double-blind, placebo-controlled, crossover protocol. Prior to inclusion in the study subjects signed informed consent and underwent a short clinical examination, ECG, and determination of routine laboratory parameters to ensure current health representing inclusion criteria. In particular, subjects with obstructive pulmonary disease, diabetes mellitus, peripheral occlusive disease, AV-block, bradycardia (resting heart rate < 50/min) or hypotension (blood pressure < 110/70 mmHg) were excluded from the study. The study was approved by the Ethics Committee of the Faculty of Medicine of the Karl Franzens University, Graz, Austria.

On each day of investigation, subjects entered the laboratory in the morning following an overnight fast. The blinded study medications were swallowed together with about 50 ml of water. Three hours later, exercise was performed over 10 min on a bicycle ergometer with 80 % of mean individual work load. Heart rate and blood pressure were measured at rest immediately before the onset of exercise, during the last minute of exercise, and at rest after 15 min of recovery. Heart rate was derived from continuous ECG monitoring, and blood pressure was measured by the cuff method.

Blood samples (5 ml) from an indwelling venous catheter were collected in chilled sodium ethylenediaminetetraacetic acid (EDTA) tubes containing 2 mg sodium metabisulfite to prevent oxidation of the catecholamines. Plasma was immediately separated in a refrigerated centrifuge and stored frozen at –70 °C until analysis. To 1 ml of rethawed plasma, 1.5 ml of 0.4 mmol/l perchloric acid containing 0.5 mmol/l EDTA and 0.5 mmol/l sodium metabisulfite were added to precipitate proteins. After centrifugation at 2000 g for 10 minutes, the supernatants were further extracted by use of the alumina absorption method. Plasma concentrations of epinephrine and norepinephrine were determined by reversed-phase HPLC using a LiChrospher 100 RP_{18} 5 µm column (Merck, Darmstadt, Germany) and electrochemical detection was performed according to a method described previously [10].

Table 1: Heart rate (beats/min) and systolic and diastolic blood pressure (mmHg) at rest, after 10 min of exercise, and after 15 min of recovery

	Placebo	80 mg Propranolol	5 mg Bisoprolol	50 mg Carvedilol	4 mg Doxazosin
Heart rate (rest) ($p < 0.001$)	70 ± 8	55 ± 10 –21 % $p < 0.05$	55 ± 10 –21 % $p < 0.05$	62 ± 6 –11 % n. s.	91 ± 14 +30 % $p < 0.05$
Systolic BP (rest) (n.s.)	120 ± 10	110 ± 11 –8 % n.s.	112 ± 8 –7 % n.s.	108 ± 9 –10 % n.s.	114 ± 11 –5 % n.s.
Diastolic BP (rest) (n.s.)	72 ± 4	70 ± 5 –3 % n.s.	70 ± 6 –3 % n.s.	67 ± 5 –7 % n.s.	70 ± 4 –3 % n.s.
Heart rate (exercise) ($p < 0.001$)	171 ± 22	127 ± 12 –26 % $p < 0.05$	138 ± 16 –19 % $p < 0.05$	140 ± 14 –18 % $p < 0.05$	181 ± 13 +6 % $p < 0.05$
Systolic BP (exercise) ($p = 0.028$)	188 ± 13	167 ± 12 –11 % $p < 0.05$	169 ± 20 –10 % $p < 0.05$	167 ± 21 –11 % $p < 0.05$	165 ± 26 –12 % $p < 0.05$
Diastolic BP (exercise) (n.s.)	68 ± 5	66 ± 6 –3 % n.s.	68 ± 7 ± 0 % n.s.	65 ± 6 –4 % n.s.	60 ± 8 –12 % n.s.
Heart rate (recovery) ($p < 0.001$)	80 ± 10	69 ± 10 –14 % $p < 0.05$	70 ± 11 –12 % $p < 0.05$	76 ± 10 –5 % n.s.	93 ± 12 +16 % $p < 0.05$
Systolic BP (recovery) ($p = 0.002$)	118 ± 7	111 ± 9 –6 % n.s.	111 ± 7 –6 % $p < 0.05$	105 ± 4 –11 % $p < 0.05$	108 ± 8 –8 % $p < 0.05$
Diastolic BP (recovery) (n.s.)	68 ± 4	65 ± 6 –4 % n.s.	66 ± 7 –3 % n.s.	64 ± 7 –6 % n.s.	61 ± 7 –10 % n.s.

Means ± 1 SD; n = 12; % differences from placebo; significances of differences within groups were calculated by Repeated Measures ANOVA (Friedman's Repeated Measures ANOVA on Ranks when applicable) and *post-hoc* analyses from placebo by Student-Newman-Keuls test

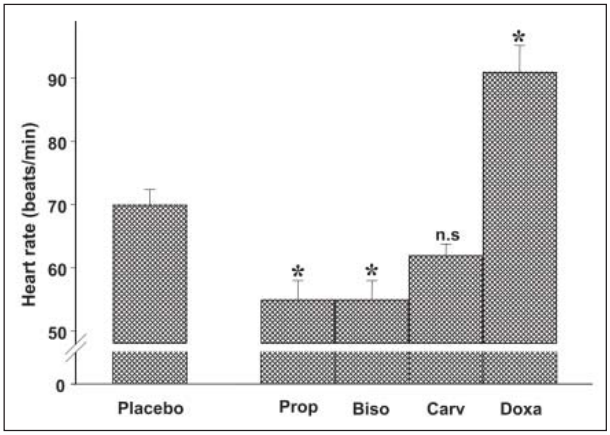

Figure 1. Effects of 80 mg propranolol (Prop), 5 mg bisoprolol (Biso), 50 mg carvedilol (Carv) and 4 mg doxazosin (Doxa) on heart rate at rest. * $p < 0.05$; n.s. = not significant (compared to placebo); n = 12

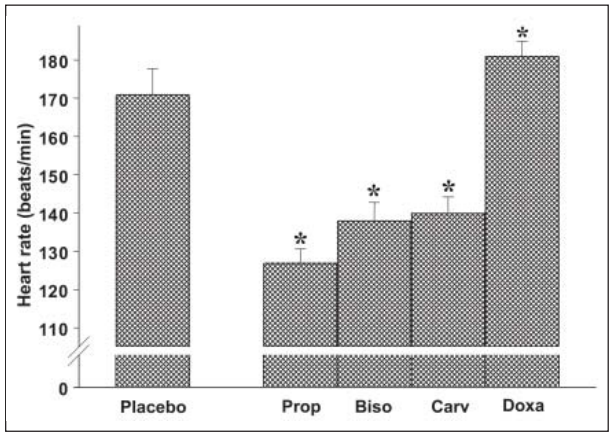

Figure 2. Effects of 80 mg propranolol (Prop), 5 mg bisoprolol (Biso), 50 mg carvedilol (Carv) and 4 mg doxazosin (Doxa) on heart rate during exercise. * $p < 0.05$ (compared to placebo); n = 12

Results are given as arithmetic means ± 1 SD unless otherwise indicated. Significances of differences within groups were calculated using Repeated Measures ANOVA (Friedman's Repeated Measures ANOVA on Ranks when applicable) and Student-Newman-Keuls test for *post-hoc* testing. A p-value < 0.05 was considered statistically significant.

Results

Haemodynamic data

Results are shown in detail in Table 1. Shortly, heart rate at rest with placebo was 70 ± 8 beats/min. Propranolol (–21 %, $p < 0.05$) and bisoprolol (–21 %, $p < 0.05$) decreased heart rate, doxazosin (+30 %, $p < 0.05$) increased heart rate whereas carvedilol had no significant effect (–11 %, n. s.) (Figure 1). During exercise, heart rate with placebo was 171 ± 22 beats/min, and propranolol (–26 %, $p < 0.05$), bisoprolol (–19 %, $p < 0.05$) and carvedilol (–18 %, $p < 0.05$) decreased heart rate, whereas doxazosin (+6 %, $p < 0.05$) increased heart rate (Figure 2). Systolic blood pressure during exercise (placebo 188 ± 13 mmHg) was decreased by all drugs to a similar extent (–10 to –12 %, $p < 0.05$ in all cases), whereas the effects of all drugs on systolic blood pressure at rest as well as on diastolic blood pressure failed to reach statistical significance in this single-dose study in healthy subjects.

Plasma concentrations of catecholamines (Table 2)

Plasma levels of both epinephrine and norepinephrine were higher during exercise than at rest and after 15 min of recovery ($p < 0.05$ in all groups). In addition, ANOVA revealed differences between plasma levels of norepinephrine ($p = 0.03$) and the increase of plasma levels of norepinephrine during exercise ($p = 0.006$) between the five drugs, and both plasma levels of norepinephrine as well as their increase during exercise with doxazosin were higher than those observed with both propranolol and bisoprolol ($p < 0.05$ in all cases). However, there were no further significant differences of plasma concentrations of either epinephrine or norepinephrine between any of the investigated substances.

Discussion

These data show that "pure" beta-blockers such as propranolol and bisoprolol decrease heart rate in healthy subjects even at rest. On the other hand, the alpha-blocker doxazosin increases heart rate, most likely caused by an increase in sympathetic tone as a physiological reaction to the blood pressure lowering effect of alpha-blockade. In carvedilol, which combines alpha- and beta-blockade in one molecule, these effects widely appear to compensate each other, thus resulting in a lack of effect on resting heart rate, particularly in healthy subjects which usually have a low sympathetic tone at rest (Figure 1). Furthermore, "pure" beta-blockers such as propranolol and bisoprolol exert inverse agonist sympathetic activity, whereas carvedilol does not show this effect [11–14]. During exercise, propranolol and bisoprolol decrease heart rate to a greater extent than at rest, and doxazosin still significantly increases heart rate but to a lower extent than at rest. Therefore, it does not appear unexpected that carvedilol effectively decreases heart rate during exercise, ie, when sympathetic tone is high, as shown in the present study, and the same appears to be true in patients with heart failure. Thus, the relatively low clinically effective net beta-blockade of carvedilol at rest might explain the low incidence of side effects resulting from beta-blockade in patients treated with carvedilol, as well as the lack of effect of carvedilol on nocturnal melatonin release.

The determination of plasma levels of epinephrine and norepinephrine did not yield pronounced differences between the investigated drugs. An increase of plasma concentrations of both epinephrine and norepinephrine during exercise was what one would have predicted merely from physiological knowledge. The only significant differences between the drugs were those observed with norepinephrine during exercise: In this particular point, our study revealed differences between plasma levels of norepinephrine ($p = 0.03$) and the increase of plasma levels of norepinephrine during exercise ($p = 0.006$) between the five drugs, and plasma levels of norepinephrine as well as their increase during exercise with doxazosin were higher than those observed with both propranolol and bisoprolol ($p < 0.05$ in all cases). However, we observed no significant differences with plasma concentrations of norepinephrine between carvedilol and any of the other substances. Therefore, these slight differences between plasma levels of norepinephrine with doxazosin on the one hand and with propranolol and bisoprolol on the other hand merely give a weak support to the hypothesis that an increase of sympathetic tone caused by a decrease of blood pressure by alpha-blockade might weaken the net beta-blocking effects of carvedilol.

In conclusion, our data show that propranolol and bisoprolol may decrease heart rate even at rest. Although our data do not prove this behaviour, the increase of heart rate resulting from alpha-blockade appears to be caused by an increase in sympathetic tone as a compensatory reaction to a decrease of blood pressure caused by alpha-blockade. In carvedilol, which inhibits both alpha- and beta-adrenoceptors, these effects widely appear to compensate each other, thus resulting in a lack of effect on resting heart rate in healthy subjects which usually have a low sympathetic tone

Table 2: Plasma concentrations (ng/ml) of epinephrine and norepinephrine at rest, after 10 min of exercise, and after 15 min of recovery

	Placebo	80 mg Propranolol	5 mg Bisoprolol	50 mg Carvedilol	4 mg Doxazosin
Epinephrine (rest) (n.s.)	175 ± 40	196 ± 58 +12 % n.s.	163 ± 23 –7 % n.s.	175 ± 34 ± 0 % n.s.	171 ± 26 –2 % n.s.
Norepinephrine (rest) (n.s.)	441 ± 143	504 ± 190 +14 % n.s.	529 ± 172 +20 % n.s.	458 ± 92 +4 % n.s.	446 ± 141 +1 % n.s.
Epinephrine (exercise) (n.s.)	263 ± 86	242 ± 73 –8 % n.s.	225 ± 81 –14 % n.s.	242 ± 70 –8 % n.s.	283 ± 78 +8 % n.s.
Norepinephrine (exercise) ($p = 0.03$)	875 ± 242	800 ± 292 –9 % n.s.	804 ± 295 –8 % n.s.	983 ± 314 +12 % n.s.	1113 ± 188 +27 % n.s.
Epinephrine (recovery) (n.s.)	171 ± 26	208 ± 97 +22 % n.s.	192 ± 42 +12 % n.s.	171 ± 33 ± 0 % n.s.	196 ± 45 +15 % n.s.
Norepinephrine (recovery) (n.s.)	533 ± 121	667 ± 377 +25 % n.s.	679 ± 319 +27 % n.s.	513 ± 130 –4 % n.s.	588 ± 227 +10 % n.s.

Means ± 1 SD; n = 12; % differences from placebo; significances of differences within groups were calculated by Repeated Measures ANOVA (Friedman's Repeated Measures ANOVA on Ranks when applicable) and *post-hoc* analyses from placebo by Student-Newman-Keuls test

at rest. On the other hand, it does not appear unexpected that carvedilol significantly decreases heart rate when sympathetic tone is high, ie, during exercise as well as in patients with heart failure. Furthermore, the low clinically effective beta-blockade of carvedilol at rest might explain the low incidence of side effects resulting from beta-blockade as well as the lack of effect of carvedilol on nocturnal melatonin release. The slight differences between plasma levels of norepinephrine with doxazosin on the one hand and with propranolol and bisoprolol on the other hand only weakly support our hypothesis that an increase of sympathetic tone caused by a decrease of blood pressure by alpha-blockade might weaken the net beta-blocking effects of carvedilol. In this context, further studies appear warranted which should investigate sympathetic drive in a more detailed fashion, eg, by measuring cardiac norepinephrine spillover and/or muscle sympathetic nerve activity.

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