Differential effects of carvedilol and atenolol on plasma noradrenaline during exercise in humans

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Aims Evidence of long-term beneficial effects of β–blockers on mortality and morbidity in patients with heart failure has been demonstrated in recent randomized trials. However, not all β–blockers are identical. Carvedilol, a nonselective β- and α-adrenergic blocker, can potentially blunt the release of noradrenaline by blocking presynaptic β_2-adrenergic receptors. To test this hypothesis, we have compared the effects of carvedilol and atenolol on plasma noradrenaline during exercise in healthy young volunteers.

Methods This study investigated the differential effects of 2 weeks pretreatment with carvedilol 25 mg day^{-1} and atenolol 50 mg day^{-1} on plasma noradrenaline at rest and during exercise on a treadmill in a double-blind randomized crossover study, involving 12 healthy male volunteers (mean age 21.6 ± 0.3 years).

Results Haemodynamic parameters at rest and during exercise were not significantly different in either carvedilol or atenolol pretreatment groups. However, carvedilol pretreatment significantly blunted the increase in plasma noradrenaline during exercise [393.8 ± 51.7 pg ml^{-1} (pretreatment) to 259.7 ± 21.2 pg ml^{-1} (post-treatment)], when compared with atenolol [340.4 ± 54.6 pg ml^{-1} (pretreatment) to 396.2 ± 32.0 pg ml^{-1} (post-treatment)]. The difference between carvedilol and atenolol (95% confidence interval) was -145.2, -351.0, $P < 0.05$.

Conclusions We have demonstrated that carvedilol but not atenolol significantly blunted the increase in plasma noradrenaline during exercise. These findings may suggest a sympathoinhibitory effect of carvedilol that may enhance its ability to attenuate the cardiotoxicity associated with adrenergic stimulation in patients with heart failure.

Keywords: β–adrenoceptor antagonist, chronic heart failure, noradrenaline

Introduction

Recent randomized trials have demonstrated that β–blockers have long-term beneficial effects on mortality and morbidity in patients with heart failure [1]. However, β–blockers differ substantially in their pharmacological properties in ways that may impact their relative efficacy and tolerability. Carvedilol, a third-generation β–blocking agent, is reported to have vasodilator activity and antioxidant properties [2, 3]. The basic pharmacology of carvedilol differs considerably from second-generation β–blocking agents [4, 5]. Significantly, carvedilol has 'atypical' effects on β–receptors in that it has a high affinity for agonist-binding receptors, a process mediated by an interaction with G protein that, in turn, leads to down-regulation of receptors. This property is more prominent for the human β_2- than for the β_1- adrenoceptor [6]. Finally, carvedilol may have a sympathoinhibitory effect attributable to blockade of peripheral presynaptic β_2-adrenoreceptors, which potentially may have additional beneficial effects [7].

In patients with heart failure, activation of the sympathetic nervous system is frequently excessive at rest, as evidenced by increased plasma levels of noradrenaline [8] and increased peroneal nerve activity [9]. Exercise triggers even more excessive activation, with plasma levels of noradrenaline markedly exceeding those noted in normal subjects at comparable workloads [10, 11].

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The present study was undertaken to compare the effects of atenolol, a selective β–blocker, and carvedilol on plasma noradrenaline during exercise in healthy volunteers.

Methods

Subjects

Twelve healthy male volunteers (mean age 21.6 ± 0.3 years) were studied. The absence of significant medical problems was verified by history and physical examination. Subjects did not take any medication for at least 2 weeks before and throughout the study. All subjects gave informed consent for this trial, which was approved by the local ethics committee.

Study design

The study was a double-blind randomized crossover comparison of 2 weeks treatment with carvedilol against atenolol, with a 2-week washout between both treatments. Exercise testing was performed before administration of carvedilol or atenolol and after 2 weeks washout period, and also after 2 weeks of administration of either drug. Thus, there were four assessment points. Measurements of interest included: (i) haemodynamic parameters of blood pressure at rest and heart rate at rest and during exercise; and (ii) plasma noradrenaline concentration at rest and during exercise.

Medication

Treatment consisted of either oral carvedilol or oral atenolol in a crossover design with a 2-week washout in between. Carvedilol was started at a dose of 12.5 mg daily for 3 days, followed by a dose of 25 mg daily. Similarly, atenolol was started at a dose of 25 mg daily for the first 3 days and then increased to a daily dose of 50 mg. These doses were selected in order to achieve comparable β-adrenoceptor blockade [12]. Compliance with medication was assessed by tablet counting.

Exercise testing

At each visit, following an overnight fast, the subjects were required to perform a treadmill exercise using the Bruce protocol [13] to stage 4 (total exercise time of 9 min, equivalent to 15 metabolic equivalents (METS). Blood pressure was measured using a semiautomatic sphygmomanometer at rest before the test. Twelve-lead electrocardiograph (ECG) was recorded using Max-1 (Sensor Medics Corporation, Yorba Linda, CA, USA) at rest, at the end of each stage of the Bruce protocol and at the recovery stage. Heart rate was determined from the ECG.

Sample collection and analysis

Blood samples for noradrenaline assessment were collected into a Vacutainer tube containing lithium heparin via an indwelling venous cannula at rest and at the end of stage 4 of the Bruce protocol. Blood samples were placed immediately in an ice-cold box and centrifuged at $1050\,g$ at 4°C for 5 min. Plasma was separated and stored at −70°C until the analysis. Plasma concentration of noradrenaline was assayed using a gas chromatograph mass spectrometer as previously described (14). The intra- and inter-assay coefficients of variation for this assay were 4.76% and 4.76%, respectively. The lower limit of detection was 100 pg ml^{-1}.

Statistical evaluation

Data was analysed using the SPSS program (SPSS Inc, 2335 Wacker Drive, Chicago, IL, USA). All values were presented as mean ± s.e.m. The statistical significance of the differences was evaluated using two-tailed Student's t-test for paired and unpaired values; $P < 0.05$ was considered statistically significant.

Results

Both carvedilol and atenolol decreased heart rate and blood pressure equally at rest. The increase in heart rate

Table 1 Haemodynamic effects in both carvedilol and atenolol.

	Carvedilol (n = 12)		Atenolol (n = 12)	
	Pretreatment	Post-treatment	Pretreatment	Post-treatment
Heart rate at rest (bpm)	73.6 ± 2.2	66.8 ± 3.0	77.3 ± 3.1	62.5 ± 1.7
Heart rate at peak exercise (bpm)	137.6 ± 5.31	17.5 ± 5.5★	136.1 ± 5.21	19.3 ± 4.1★
Systolic pressure at rest (mmHg)	126.8 ± 3.01	19.4 ± 2.4★	125.4 ± 2.61	16.3 ± 2.5★
Diastolic pressure at rest (mmHg)	72.0 ± 2.5	69.8 ± 2.5	72.8 ± 2.7	67.5 ± 2.4

Results are expressed as mean ± s.e.m. ★$P < 0.05$ pretreatment *vs* post-treatment. Haemodynamic parameters did not differ between atenolol and carvedilol pretreatment groups. bpm, Beats per minute.
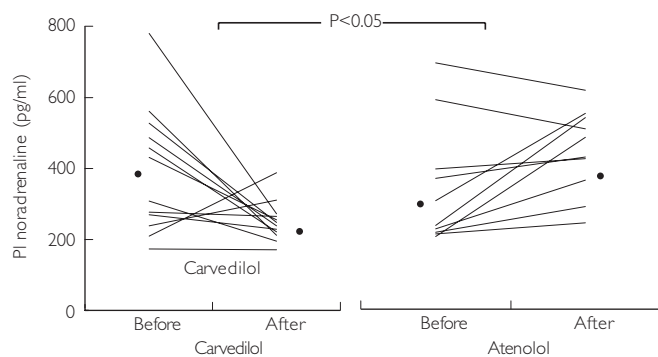
Figure 1 Effect of carvedilol or atenolol on plasma noradrenaline at peak exercise. Results are individual pairs of plasma noradrenaline levels obtained from each patient at peak exercise (Stage 4 Bruce exercise protocol, equivalent to 15 METS) prior to and after treatment with carvedilol (left panel) and atenolol (right panel). ★Mean plasma noradrenaline level. $P < 0.05$, 95% confidence interval for the difference carvedilol *vs* atenolol was −145.2, −351.0.

during exercise was also equally blunted by carvedilol and atenolol (Table 1). Plasma noradrenaline concentration at rest also did not significantly differ after 2 weeks of treatment in both groups, from 229.4 ± 12.5 pg ml^{-1} (pretreatment) to 212.7 ± 14.7 pg ml^{-1} (post-treatment) in the carvedilol pretreatment group, and from 211.9 ± 7.9 pg ml^{-1} (pretreatment) to 194.2 ± 13.5 pg ml^{-1} (post-treatment) in the atenolol pretreatment group. However, carvedilol significantly ($P < 0.05$) blunted the increase in plasma noradrenaline at peak exercise from 393.8 ± 51.7 pg ml^{-1} (pretreatment) to 259.7 ± 21.2 pg ml^{-1} (post-treatment), when compared with atenolol, from 340.4 ± 54.6 pg ml^{-1} (pretreatment) to 396.2 ± 32.0 pg ml^{-1} (post-treatment). The difference between carvedilol and atenolol was 248.1 pg ml^{-1} (95% CI −145.2, −351.0, $P < 0.05$, Figure 1).

Discussion

This study has two main findings. Firstly, we showed that both carvedilol and atenolol had similar blunting effects on heart rate and blood pressure at rest and during exercise. Secondly, this study showed that despite similar effects on haemodynamic responses, carvedilol but not atenolol blunted the increase in plasma noradrenaline during exercise.

Plasma noradrenaline levels are commonly elevated during exercise [15]. This level is much higher in congestive heart failure. The mechanisms responsible for this maladaptive process remain to be precisely defined. An impairment of baroreflex sensory mechanism may play an important role underlying the sympatho-excitation [16–18]. A recent report suggests that a rapidly responsive and sensitive arterial baroreflex, and activation of a car-

diac sympatho-excitatory reflex related to increased cardiopulmonary filling pressures, could be responsible [19]. The high levels of noradrenaline may lead to systemic vasoconstriction with a further consequent excessive reduction in tissue perfusion (20). Impaired skeletal muscle perfusion during exercise appears to be involved in reduced exercise capacity in patients with chronic heart failure [21],

Previous studies have compared the effects of carvedilol and atenolol on haemodynamic parameters in patients of mild to moderate essential hypertension. Like our study, there were no consistently significant differences between the effects of carvedilol and atenolol on either heart rate or blood pressure during treatment [22, 23].

The key finding of our present study was that carvedilol statistically significantly lowered plasma noradrenaline levels at peak exercise in our subjects. In contrast, atenolol tended to increase the concentration of plasma noradrenaline at peak exercise. These findings suggest that carvedilol may possess a sympathoinhibitory effect, although it should be noted that responses of plasma noradrenaline to exercise are a net effect of a number of processes. Radioisotope noradrenaline kinetic studies would have been useful to differentiate an effect on noradrenaline spillover and clearance. Nevertheless, our results support the findings of two previous studies demonstrating a sympathoinhibitory effect of carvedilol. Gilbert *et al.* [7] investigated the differential effects of carvedilol and metoprolol on coronary sinus and central venous noradrenaline levels in patients with heart failure at rest. They reported there were no significant differences in haemodynamic effects between the carvedilol and metoprolol active-treatment groups. However, they found carvedilol selectively lowered coronary sinus noradrenaline levels, an index of cardiac adrenergic activity, whereas metoprolol did not lower coronary sinus noradrenaline levels and actually increased central venous noradrenaline levels. In addition, they showed that metoprolol was associated with an increase in cardiac β-receptor density, whereas carvedilol did not change cardiac β-receptor expression. More recently, Azevedo *et al.* [24] reported that carvedilol, when compared with metoprolol, decreased both resting total body and cardiac noradrenaline spillover. Importantly, microneurographic measures of sympathetic nerve traffic to skeletal muscle did not change in either group. These findings suggest that carvedilol caused a sympathoinhibitory effect by blocking peripheral β-adrenergic receptors. It should be noted that both these studies were conducted on heart failure patients at rest. Our study would suggest such an effect of carvedilol during exercise.

There are some potential advantages of carvedilol over selective β$_1$-blockers. β$_1$-selective blocking agents may re-

couple uncoupled cardiac β_2-adrenergic receptors [25] through a crossregulatory effect, further predisposing β-adrenergic signal transduction pathways to withdrawal phenomena. Because selective β_1-blockers such as metoprolol have been shown to increase systemic noradrenaline levels through effects on noradrenaline clearance [26], they may increase cardiac noradrenaline spillover in chronic heart failure in the short term [27]. Thus, there is obvious potential for drug-related increases in adrenergic activity to produce adverse events in the failing heart. On the other hand, because carvedilol lowers cardiac adrenergic activity, blocks β_1-, β_2-, and α_1-adrenergic receptors at high doses, and does not upregulate or downregulate β_1-receptors, its antiadrenergic properties greatly exceed those of metoprolol. This sympathoinhibitory effect of carvedilol as shown in this study could also result in a decrease in the release of other potentially harmful neurotransmitters such as neuropeptide Y (NPY) which coexist with noradrenaline in perivascular sympathetic fibres [28]. NPY has been reported to have a direct vasoconstrictor effect on blood vessels and may potentiate the noradrenaline-evoked response [28]. This sympathoinhibitory effect may enhance the ability of carvedilol to attenuate the cardiotoxicity associated with adrenergic stimulation in patients with heart failure.

Several randomized controlled trials have compared metoprolol and carvedilol in heart failure and the results have been inconsistent. In general, no significant differences have been found, although carvedilol may lower blood pressure and peripheral resistance more than metoprolol due to its α-adrenergic blocking properties [29–31]. It should be noted that the recent BEST trial [32] with bucindolol, which is a nonselective β-blocker, failed to reduce heart failure mortality. The reasons for this have not been defined, although bucindolol, unlike carvedilol, does display intrinsic sympathomimetic activity which may be harmful in heart failure [33]. Whether the pharmacological differences between carvedilol and a selective β_1-blocker will be translated into differences in survival is not known, but is being evaluated in the ongoing Carvedilol or Metoprolol European Trial (COMET) [34].

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