Effects of nebivolol and atenolol on insulin sensitivity and haemodynamics in hypertensive patients

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Objectives **To compare the effects of nebivolol and atenolol in 25 ambulatory hypertensive patients with impaired glucose tolerance.**

Design **Clinic and ambulatory blood pressure, insulin sensitivity (euglycemic-hyperinsulinemic clamp), glucose tolerance (intravenous glucose tolerance test), systemic and regional haemodynamics were measured after 4 weeks of placebo and after each 16-week treatment period in a double-blind, crossover fashion.**

Results **Nebivolol and atenolol similarly reduced ($P < 0.001$) clinic and ambulatory blood pressure by approximately 15/10 mmHg, systolic and diastolic. Clinic and ambulatory heart rate was reduced to a greater extent ($P < 0.01$) by atenolol than nebivolol. Atenolol was associated with an approximately 20% reduction in insulin sensitivity (insulin-induced glucose disposal rate/mean insulin concentration ratio, $P < 0.01$) and an approximately 10% reduction in glucose disappearance rate (K-value, $P < 0.05$), whereas these variables were not significantly modified with nebivolol. Cardiac output was reduced similarly ($P < 0.05$) by both drugs at rest but forearm blood flow, forearm vascular resistance or total peripheral resistance were unaffected. A significant inverse correlation coefficient between cardiac output and insulin sensitivity was found at baseline, suggesting that a compensatory increase in systemic blood flow occurs in hypertensive patients with progressively more marked insulin resistance. This relationship was unaffected by nebivolol but was lost with atenolol.**

Conclusions **These results indicate that insulin sensitivity was not modified significantly by nebivolol, whereas it was reduced by atenolol, although blood pressure was decreased to the same extent by both drugs. Neither drug induced systemic or forearm vasodilatation but the inverse relationship between cardiac output and insulin sensitivity was preserved with nebivolol but not with atenolol.**
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Keywords: atenolol, nebivolol, beta-adrenergic blocking agents, insulin sensitivity, glucose intolerance, cardiac output, forearm blood flow

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Introduction

Insulin resistance may be a mechanism linking type 2 diabetes mellitus to hypertension [1]. Indeed, insulin sensitivity has been found to be decreased in patients with essential hypertension [2]. Therefore, reduction in insulin sensitivity induced by antihypertensive drugs may further increase the risk of type 2 diabetes mellitus in hypertensive subjects. Several widely used antihypertensive agents, such as diuretics and β-blockers, although effective in controlling hypertension, may diminish insulin sensitivity [3]. Although selective for β_1-adrenoreceptors, atenolol has been shown to have deleterious effects on both carbohydrate and lipid metabolism as well as on insulin sensitivity [4]. Nebivolol is a new cardioselective β-blocking agent [5] that has been shown to control blood pressure over 24 h with a single daily dose [6]. Nebivolol may have novel cardiovascular properties such as endothelium-dependent arterial and venous dilatation via the L-arginine-nitric oxide pathway [5,7,8]. These hemodynamic properties could favourably modify insulin sensitivity according to the hemodynamic theory of insulin resistance [9]. This study was thus designed to evaluate and compare the changes in insulin sensitivity after treatment with nebivolol and atenolol in patients with essential hypertension confirmed by ambulatory monitoring and with impaired glucose tolerance. In addition, the effects of nebivolol on clinic and ambulatory blood pressure, as well as on hemodynamic parameters at rest and during isometric and dynamic exercise, were compared with the cardioselective β-blocker, atenolol to gain additional insight into its antihypertensive effects during daily life activities.

Materials and methods

Study design

This double-blind, randomized, crossover trial included a 4-week single-blind placebo run-in phase (baseline)

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and two 16-week double-blind treatment (nebivolol 2.5–5 mg/day or atenolol 50–100 mg/day) phases separated by a 4-week single-blind placebo washout period. Patients were randomly allocated to one of the two treatment sequence groups, nebivolol–atenolol or atenolol–nebivolol. During active treatment periods, patients were seen biweekly for the first month and monthly thereafter. The dose of each drug was titrated after 4 or 8 weeks according to antihypertensive response as assessed by clinic sitting diastolic blood pressure < 90 mmHg. Clinic and ambulatory blood pressures as well as metabolic and hemodynamic assessments were made over the final 2 weeks of each treatment phase, including baseline, allowing 2–4 days between each procedure. All the procedures followed were in accordance with our institutional guidelines.

Patients

Patients aged 40–65 years with essential hypertension associated with elevated body mass index (25–35 kg/m^2) and impaired glucose tolerance were candidates for enrollment. Impaired glucose tolerance was based on accepted criteria at the time of the study and was characterized by fasting plasma glucose value < 7.8 mmol/l, and a 2 h value > 7.8 mmol/l after a standard oral glucose tolerance test (75 g) prior to the placebo run-in period. Patients with clinic sitting diastolic blood pressure between 95 and 114 mmHg and a mean daytime ambulatory diastolic blood pressure of ≥ 90 mmHg at baseline were randomized to active treatments. Exclusion criteria included diabetes mellitus, secondary hypertension and significant organic diseases. All subjects gave their written consent, and study was approved by the local ethics committee.

Blood pressure determinations

Clinic blood pressure was measured with a standard calibrated mercury sphygmomanometer after a 10 min rest period. Phase I and phase V Korotkoff sounds were used to determine systolic and diastolic blood pressure. Clinic blood pressure defined as the mean of three consecutive readings was measured 23–25 h after drug intake (trough level). Twenty-four hour ambulatory blood pressure was measured at 15 min intervals from 0600 h to 2159 h (daytime) and at 30 min intervals from 2200 h to 0559 h (night-time) using a calibrated portable device (SpaceLabs ICR 90207, Montréal, Canada).

Metabolic assessments

Glucose and insulin homeostasis was assessed from an intravenous glucose tolerance test (IVGTT) and a euglycemic-hyperinsulinemic clamp in patients fasted for 12 h. The IVGTT comprised the injection of a 20 g/m^2 body surface area with a 50% dextrose solution (Abbott, Montréal, Canada) over 3 min. Plasma glucose and insulin levels were measured [10,11] 15 and 1 min prior to the injection and 1, 2, 4, 6, 10, 15, 20, 30, 40, 50, 60, 75, 90, 105 and 120 min after the bolus. The glucose disappearance rate (K) was calculated as previously described [12] as an index of glucose tolerance. Peak insulin response was defined as the mean of 2, 4 and 6 min values. Insulin sensitivity was assessed by the euglycemic–hyperinsulinemic clamp technique of DeFronzo *et al.* [13] and values were collected during the final 60 min of the test and lasted for 2 h. The rate of glucose infusion needed to maintain euglycemia for a given concentration of insulin was taken as the insulin-induced glucose disposal rate (M). The ratio of M over mean insulin concentration (M/I) was calculated as an index of insulin sensitivity.

Hemodynamic assessments

Forearm blood flow, blood pressure and heart rate were measured during supine rest and during 2 min of isometric handgrip exercise at 30% of maximal voluntary contraction. The subjects then moved over to the ergocycle where cardiac output was assessed at rest and during 30 min of submaximal exercise at 50% peak aerobic capacity. During the double-blind phases, the subjects then exercised up to peak oxygen uptake. During the placebo run-in phase, peak oxygen uptake was measured 1 week prior to hemodynamic assessment to allow determination of the workload required to elicit 50% of peak aerobic capacity. Peak oxygen uptake was measured (Energy Expenditure Unit 2900, Sensormedics, Anaheim, California, USA) during an increased work test with the legs on an ergometer cycle (829E, Monark Varberg, Sweden) with 2 min steps of progressively increasing work load up to maximal predicted heart rate and respiratory exchange ratio above 1.10 [14]. Heart rate was measured with a tachograph triggered by the R-wave of the electrocardiogram recorded in lead III (7P4, Grass Instruments, Massachusetts, USA). Blood pressure was measured in duplicate with a standard mercury sphygmomanometer. Mean arterial pressure was calculated as diastolic plus one-third pulse pressure. As previously described in detail [15], forearm blood flow (ml/100 ml per min) was measured with venous occlusion plethysmography (Hokanson EC-4, Issaquah, Washington, USA) using mercury-in-silastic strain gauges [16]. Blood flow variability (standard deviation) calculated on two sequential averages was 5%. Forearm vascular resistance (mmHg/ml per 100 ml per min) was calculated by dividing mean arterial pressure by forearm blood flow (mean of four to six individual flows). Cardiac output was measured in duplicate using a computer-based version (Energy Expenditure Unit 2900, Sensormedics) of the CO_2 rebreathing technique of Collier [17]. For measurements to be valid, the CO_2 equilibrium had to start within 15 s of rebreathing and maximal PCO_2 variation could not exceed 1 mmHg for at least a 5 s period. Stroke volume was calculated by dividing cardiac output by heart rate. Total peripheral resistance (mmHg/l

per min) was obtained by dividing mean arterial pressure by cardiac output.

Statistical analysis

The sample size was determined based on insulin sensitivity index at 16 weeks in comparison with placebo. Power calculation and sample size assessments were performed based on a between-treatment comparison of the change from baseline for each treatment group. Preliminary estimates indicated a between-treatment difference of 0.18 mg/kg per min per pmol/l (SD 0.3). Using an alpha of 0.05 (two-tailed) and the *t*-test model with equality of the standard deviations, it was estimated that 25 patients per treatment group would result in a power of approximately 85%. In order to provide a balanced randomization and appropriate block size, 28 patients were targeted for enrollment. Due to the crossover design, carry-over effects were first tested using an analysis of covariance with baseline values as covariates but none was found to be significant at $P < 0.10$. When no significant carry-over effect was found, the comparison between the three treatment phases was performed using an analysis of variance on repeated values in order to establish not only a difference (or a lack of difference) between the two active treatments, but also between each of the active treatments and the placebo phase. When a significant *F*-value was found ($P < 0.05$), a means comparison was used as the post-hoc contrast test to establish the statistical significance of the difference between each phase of the protocol. $P < 0.05$ was considered statistically significant. All results are presented as means $\pm$ SD.

Results

From the 28 patients with confirmed essential hypertension (by ambulatory monitoring) and impaired glucose tolerance who entered the placebo run-in period, 27 (18 women, nine men) aged 45–64 years (mean 54 ± 8 years) were randomized into the double-blind active treatment phase of the study. From these, two patients dropped out and 25 patients (height 162 ± 8 cm; weight 80.8 ± 13.2 kg; body mass index 30.4 ± 3.3 kg/m^2) completed the trial. The mean doses used were 4.5 ± 1.0 mg of nebivolol (20/27 patients at 5 mg) and 94.0 ± 16.6 mg of atenolol (24/27 patients at 100 mg). A total of 13 patients were allocated in the sequence receiving atenolol and then nebivolol, while 12 patients were first treated with nebivolol and then received atenolol. There was no difference in both treatment sequence groups in terms of demographics as well as baseline clinic and ambulatory blood pressures.

Blood pressure

Both treatments induced significant ($P < 0.001$) and similar clinic sitting systolic and diastolic blood pressure decrements at the end of the active treatment (Table 1). With regard to clinical heart rate, nebivolol and atenolol induced significant ($P < 0.001$) and similar reductions of approximately 10 beats/min. Blood pressure measured by ambulatory monitoring revealed that nebivolol and atenolol induced significant decrements during each period of the 24 h interval (Table 1 and Fig. 1). Although similar reductions in clinic blood pressure were found with nebivolol and atenolol, atenolol was associated with additional small (approximately 3 mmHg) but significantly greater mean 24 h and daytime diastolic blood pressure reductions compared to nebivolol. Ambulatory heart rate was significantly reduced by both active treatments during the entire 24 h interval but greater reductions were found with atenolol than nebivolol (Table 1).

Metabolic parameters

Results of the euglycemic-hyperinsulinemic clamp and IVGTT are presented in Table 1. Nebivolol did not significantly modify *M*-value, mean insulin concentration or *M*/*I* index compared to placebo. In contrast, atenolol significantly decreased the glucose disposal rate and the *M*/*I* ratio compared to placebo. During the IVGTT, a significant reduction in glucose disappearance rate (*K*-value) and a significant increase in the glucose area under the curve were found during atenolol compared to placebo. Nebivolol did not significantly affect these parameters (Table 1). The peak insulin response and the insulin area under the curve were not significantly different with either treatment compared to placebo.

Hemodynamics

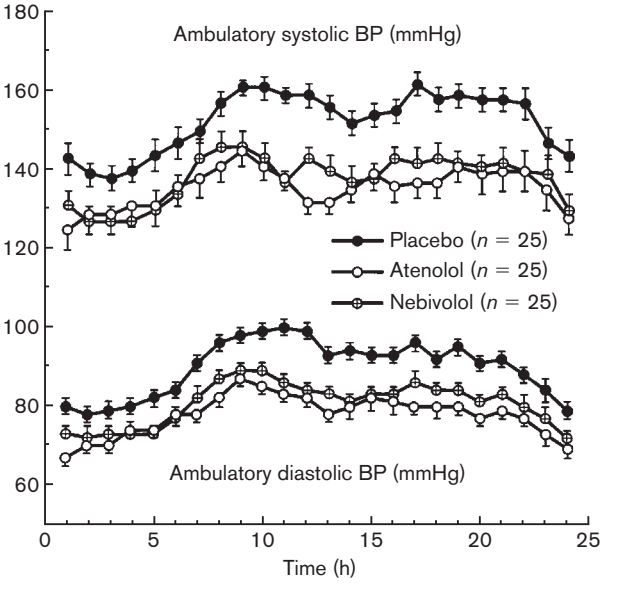
Compared to placebo, peak oxygen uptake (22.0 ± 5.7, 20.6 ± 4.1 and 19.7 ± 5.0 ml/kg per min) and peak workload (115 ± 36, 109 ± 37 and 105 ± 45 W) were not significantly modified by nebivolol or atenolol, respectively. The results for regional and systemic hemodynamics are shown in Table 2. During supine rest, mean arterial pressure was significantly reduced by nebivolol and atenolol compared to placebo. During isometric exercise, mean arterial pressure was similar with all three treatments. Forearm blood flow and resistance were not different with placebo, nebivolol or atenolol at rest or during isometric exercise. Both treatments were similar in terms of hemodynamics. Indeed, total peripheral resistance was unaffected by either drug. However, atenolol exerted a greater bradycardia at rest and submaximal exercise leading to differences between the two β-blockers in mean arterial blood pressure at submaximal exercise and stroke volume at rest (Table 2). During exercise at peak oxygen uptake, compared to placebo, both nebivolol and atenolol reduced heart rate (from 153 ± 13 to 121 ± 21 and 127 ± 17 beats/min, respectively) and systolic and diastolic blood pressure (from $212 \pm 20/99 \pm 8$ to $190 \pm 20/94 \pm 10$ and $190 \pm 21/92 \pm 11$

Table 1 **Effects of 16 weeks of double-blind treatment with nebivolol or atenolol compared to placebo on clinic and ambulatory blood pressures as well as on glucose and insulin homeostasis parameters**

Variable	Placebo	Nebivolol	Atenolol
Clinic values (seated)			
SBP/DBP (mmHg)	160 ± 11/101 ± 4	148 ± 21***/92 ± 8***	147 ± 20***/91 ± 5***
Heart rate (beats/min)	78 ± 2	67 ± 7***	66 ± 11***†
Ambulatory monitoring			
24 h means			
SBP/DBP (mmHg)	152 ± 11/90 ± 5	138 ± 16***/81 ± 8***	136 ± 19***/78 ± 9***†
Heart rate (beats/min)	75 ± 9	66 ± 7***	61 ± 7*††
Daytime			
SBP/DBP (mmHg	158 ± 10/94 ± 6	142 ± 16***/84 ± 8***	138 ± 17***/81 ± 9***††
Heart rate (beats/min)	79 ± 9	70 ± 7***	63 ± 8***†††
Night-time			
SBP/DBP (mmHg)	144 ± 14/82 ± 7	131 ± 20***/75 ± 9***	131 ± 23***/73 ± 12***
Heart rate (beats/min)	67 ± 9	60 ± 7***	57 ± 7***†
CLAMP			
Glucose disposal rate (*M*) (mg/kg per min)	4.62 ± 2.04	4.30 ± 2.17	3.89 ± 1.68*
Mean insulin concentration (*I*) (pmol/l)	672 ± 150	723 ± 168	722 ± 157
Insulin sensitivity index (*M*/*I*)	0.74 ± 0.40	0.65 ± 0.39	0.58 ± 0.33**
IVGTT			
Glucose disappearance rate (*K*) (min^{-1})	1.12 ± 0.34	1.16 ± 0.41	1.00 ± 0.31*††
Peak insulin response (pmol/l)	322 ± 231	347 ± 266	350 ± 287
Insulin AUC (nmol/l.min) 0–120 min	38 ± 19	42 ± 27	46 ± 28
Glucose AUC (mmol/l.min) 0–120 min	1258 ± 177	1244 ± 229	1323 ± 190*††

Data are means ± SD. SBP/DBP, systolic/diastolic blood pressure; AUC, area under the curve; IVGTT, intravenous glucose tolerance test.
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ versus placebo; † $P < 0.05$, †† $P < 0.01$, ††† $P < 0.001$ versus nebivolol.

Fig. 1



Hourly ambulatory systolic (upper curves) and diastolic (lower curves) blood pressure (BP) values during placebo (filled circles), atenolol (open circles) and nebivolol (cross-filled circles) over 24 h.

mmHg) significantly (all $P < 0.05$) and to the same extent.

Relationship between insulin sensitivity and hemodynamics

Significant inverse relationships were found between resting cardiac output and M/I ratio at baseline and with nebivolol but not with atenolol (Fig. 2). Significant correlation coefficients were also found between resting cardiac output and glucose disposal rate (M) at baseline ($r = -0.41$, $P < 0.05$) and with nebivolol ($r = -0.51$, $P = 0.01$) but not with atenolol ($r = 0.31$, $P = 0.14$). Forearm blood flow at rest did not correlate significantly with M or M/I.

Discussion

The main finding of the present study is that nebivolol did not negatively alter insulin sensitivity, as seen either from the M-value or the M/I ratio, whereas atenolol significantly reduced both indices for clinically similar blood pressure control. In addition, the inverse relationship between cardiac output and insulin sensitivity found at baseline was preserved with nebivolol but was lost with atenolol. Both drugs reduced blood pressure during submaximal and at peak dynamic exercise but not during isometric exercise. Atenolol exerted a somewhat greater reduction in blood pressure than nebivolol during submaximal dynamic exercise which was related to a more pronounced bradycardia during this level of exercise. The metabolic advantages of nebivolol over atenolol must therefore be weighed against a small additional antihypertensive effect of atenolol during submaximal dynamic exercise.

Our results, showing an approximately 20% reduction in insulin sensitivity with atenolol, are in agreement with the previously reported detrimental effects of this drug on insulin sensitivity [18]. Several authors have shown that conventional cardioselective β-blockers such as metoprolol or non-cardioselective β-blockers such as

Table 2 Effects of 16 weeks of treatment with nebivolol or atenolol compared to placebo on regional hemodynamics at rest and during isometric hand grip exercise as well as on systemic hemodynamics at rest and during submaximal dynamic cycle exercise

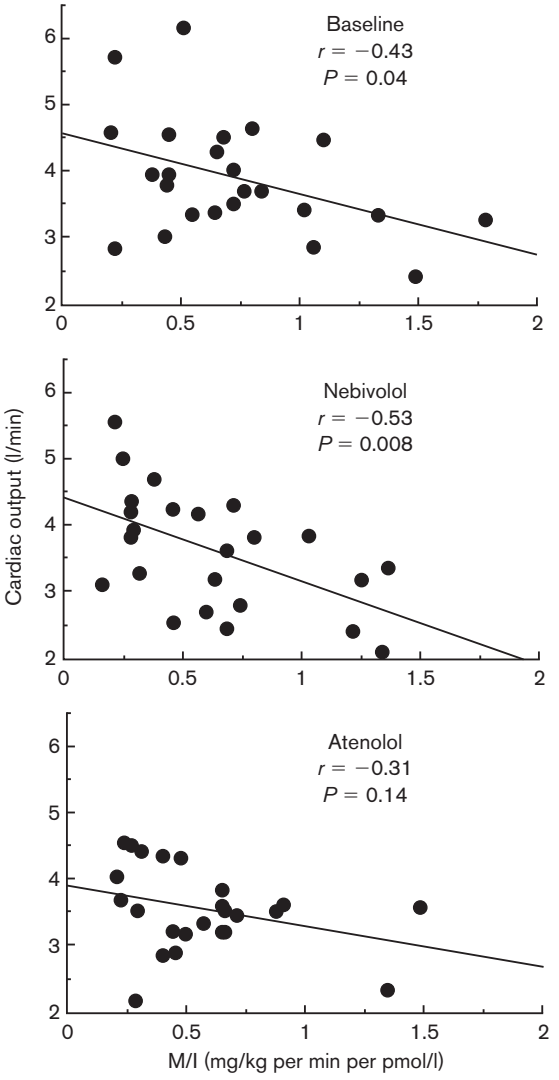
Variable	Placebo	Nebivolol	Atenolol
Regional hemodynamics			
Supine rest			
MAP (mmHg)	105 ± 9	100 ± 12*	97 ± 13***
FBF (ml/100 ml per min)	3.7 ± 1.7	3.8 ± 1.9	3.6 ± 1.7
FVR (mmHg/ml per 100 ml per min)	32.8 ± 14.3	32.1 ± 15.7	34.0 ± 19.0
Isometric hand grip			
MAP (mmHg)	129 ± 12	124 ± 16	124 ± 16
FBF (ml/100 ml per min)	4.1 ± 2.0	3.9 ± 2.0	3.5 ± 2.0
FVR (mmHg/ml per 100 ml per min)	37.9 ± 17.8	42.6 ± 34.5	47.0 ± 28.1
Systemic hemodynamics			
Seated rest			
MAP (mmHg)	111 ± 8	104 ± 13*	100 ± 13***
Cardiac output (l/min)	3.9 ± 0.9	3.6 ± 0.9*	3.6 ± 0.6*
Heart rate (beats/min)	81 ± 13	70 ± 10***	63 ± 7***†††
Stroke volume (ml)	49 ± 13	52 ± 12	58 ± 10***†
TPR (mmHg/l per min)	29.6 ± 6.8	30.3 ± 8.2	29.0 ± 7.8
Submaximal cycle exercise			
MAP (mmHg)	120 ± 10	112 ± 9***	107 ± 12***†
Cardiac output (l/min)	10.3 ± 3.2	9.8 ± 3.2	9.2 ± 2.4**
Heart rate (beats/min)	109 ± 15	96 ± 14***	85 ± 12***†††
Stroke volume (ml)	93 ± 29	103 ± 36*	111 ± 28***
TPR (mmHg/l per min)	13.3 ± 6.6	12.9 ± 5.2	12.8 ± 4.4

Data are means ± SD. MAP, mean arterial pressure; FBF, forearm blood flow; FVR, forearm vascular resistance; TPR, total peripheral resistance. * $P < 0.05$, ** $P < 0.01$ versus placebo; † $P < 0.05$, ††† $P < 0.001$ versus nebivolol.

propranolol were associated with a significant decrease in insulin sensitivity in the order of 20–25% [3,4]. In contrast with these results, β-blockers with β_2 agonistic properties such as celiprolol [19] and dilevalol [20] were associated with an improvement of 10% in insulin sensitivity. In keeping with these data, several hypotheses have been postulated to explain why conventional cardioselective or non-cardioselective β-blockers devoid of vasodilatory properties decrease insulin sensitivity. It has been demonstrated that the decrease in insulin sensitivity correlates with a reduced blood flow in peripheral tissue such as skeletal muscles [21].

In addition, blockade of β-adrenergic receptors further attenuates an already decreased insulin clearance in hypertensive patients [22]. This suggests that the extent of insulin resistance induced by these agents might be related to the degree of β-adrenergic blockade. In our study, atenolol decreased heart rate more than nebivolol, whereas blood pressure was reduced to a similar extent by both drugs. In keeping with the effects of β-blocking agents possessing intrinsic sympathomimetic activity, the fact that nebivolol induced a lesser degree of insulin resistance may be related to the lesser β-blocking action of this drug. This hypothesis is supported by the recent study of Fogari *et al*. [23] who showed an unaltered insulin sensitivity with a reduced dosage of atenolol (50 mg) that produced a similar reduction in heart rate compared to that induced by nebivolol. A nitric oxide-mediated vasodilatory effect of nebivolol was previously demonstrated in anesthetized animals [24] or *in vitro* with ring preparations of dog coronary arteries [7]. More recently, these findings were confirmed by hemodynamic studies in non-hypertensive human volunteers [8,25,26]. However, these experiments were realized using in-situ techniques with parenteral infusion of drugs. Moreover, in an earlier study, we were not able to discriminate the vasodilatory effect of l-nebivolol by comparing the antihypertensive effects of the β-adrenergic blocking portion of nebivolol, the D-isomer, with the racemic mixture, DL-nebivolol [27]. In order to further evaluate the clinical relevance of earlier findings in human hypertensives [8,25,26], we investigated systemic hemodynamics as well as regional blood flow to the forearm at steady state following oral administration of nebivolol and atenolol. Both nebivolol and atenolol reduced blood pressure mainly by a reduction in cardiac output at rest, whereas only atenolol reduced cardiac output significantly during submaximal bicycle exercise. This was associated with a lower blood pressure during submaximal exercise with atenolol compared to nebivolol and appears to be related to a more pronounced reduction in heart rate with atenolol because total peripheral resistance was unaffected with either drug compared to placebo. Neither nebivolol nor atenolol increased forearm blood flow at rest. Therefore, the present data support the assumption that the observed difference in insulin resistance in favour of nebivolol versus atenolol could be mainly related to a less pronounced blockade

Fig. 2



Relationship between cardiac output and insulin-induced glucose disposal rate/mean insulin concentration ratio (*M/I*) at the end of treatment with placebo, atenolol and nebivolol.

of β-adrenergic receptors by nebivolol and not to a lesser effect of nebivolol on the reduction in cardiac output and/or blood flow to skeletal muscles.

The reduced insulin sensitivity in hypertension was suggested to be related to high blood pressure-induced vascular changes in skeletal muscles [9]. In agreement with this hemodynamic hypothesis, Baron *et al*. found an inverse relationship between insulin-stimulated blood flow and blood pressure level within a group of normotensive individuals [21]. An inverse relationship between the severity of vascular changes in the forearm and insulin sensitivity [28] and, although by no means a uniform finding [29], a reduced insulin-induced vasodilatation were recently reported in hypertensive patients [30]. However, to the best of our knowledge, no study has investigated the relationship between cardiac output or forearm blood flow at rest and insulin sensitivity in hypertensive subjects. In the present study, the inverse relationship between cardiac output and insulin sensitivity may reflect compensatory hemodynamic adjustments for the reduced glucose delivery to peripheral tissues. Our results further suggest that the peripheral blood flow adaptation is unaffected by nebivolol but is altered by atenolol. This may be related to the more marked β-adrenergic blocking (vasodilatory) effect of atenolol compared to nebivolol as underlined above. Indeed, it may be speculated that with a lesser β-adrenergic blocking effect, nebivolol will have a decreased impact on heart rate but will also have a lesser effect on the ability of the β-adrenergic receptors to induce vasodilation. Thus, the significant correlations found in the present study indicate that compensatory increases in resting systemic blood flow occur in hypertensive patients with progressively more marked insulin resistance.

In conclusion, the results of the present study indicate that, at similar levels of blood pressure reduction, nebivolol did not induce a significant reduction in insulin sensitivity as opposed to atenolol. Our study did not confirm the vasodilatory effect which was proposed as the pharmacological mechanism for the neutral effect of nebivolol on insulin sensitivity. Nevertheless, in contrast to atenolol, nebivolol did not alter the inverse relationship between systemic blood flow and insulin sensitivity that may illustrate compensatory increases in blood flow in the face of a reduced glucose delivery to peripheral tissues.

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