SCIENTIFIC LETTER

Different effects of atenolol and nebivolol on coronary flow reserve

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Atenolol and nebivolol are commonly used antihypertensive agents. Nebivolol increases both stimulated and basal release of endothelial nitric oxide, thereby improving flow-mediated dilatation of the brachial artery in patients with essential hypertension.¹ However, it is believed that atenolol has no effect on arterial vasoreactivity.¹

Pharmacological stress transthoracic second harmonic Doppler echocardiography (TTDE) is a useful tool in evaluating coronary flow reserve (CFR). Several studies have evaluated its feasibility.²

We hypothesised that in patients with essential hypertension, nebivolol can reverse coronary microvascular dysfunction and improve CFR.

METHODS

After one month of lifestyle changes, 63 consecutive patients with hypertension had 24 h ambulatory blood pressure monitoring. Hypertension was diagnosed in 30 of these who had average daytime blood pressure > 135/85 mm Hg and average night-time blood pressure > 125/75 mm Hg. These 30 patients constituted the study population. For the control group, 30 healthy volunteers were enrolled. Patients with known cardiovascular risk factors, those who were taking any vasoactive or hypertension drug, and those with ECG changes specific for myocardial ischaemia were excluded from the study. Written informed consent was obtained from each participant, and the institutional ethics committee approved the study protocol.

In a prospective, randomised, single-blind crossover study, each participant had TTDE examination including CFR measurement. The participants were individually randomly assigned to receive either 5 mg nebivolol or 50 mg atenolol daily for eight weeks. After the first eight weeks, the TTDE examination was repeated, and each participant had a 15-day washout. At the end of the washout period the echocardiographic examinations were repeated, and the study arms were crossed over. In the second run, each participant took the other hypertension drug for eight weeks. At the end, the echocardiographic examinations were again repeated.

Each participant was examined with an Acuson Sequoia C256 echocardiography system (Acuson, Mountain View, California, USA) equipped with a 5V2c high-resolution transducer with second harmonic capability. Each participant underwent Doppler recording of the left anterior descending coronary artery. Coronary diastolic mean peak flow velocity (DPFV) was measured at baseline and after dipyridamole infusion (0.84 mg/kg over 6 min) by averaging the highest three Doppler signals for each measurement. CFR was defined as the ratio of hyperaemic to baseline diastolic peak velocities.²

Left ventricular mass was calculated from M mode recordings taken in the parasternal long axis.

Data were analysed with SPSS V.9.0 (SPSS Inc, Chicago, Illinois, USA). The hypertension and control groups were compared by Student's *t* test. Before treatment and after treatment analyses were compared by paired samples *t* test. Pearson's or Spearman's correlation test was used to test the

associations between coronary flow measurements and the study variables when appropriate. Values of *p* < 0.05 were considered significant.

RESULTS

The hypertension and control groups were similar in demographic and biochemical measurements (table 1). At the end of the one-month lifestyle change period, 24 h average blood pressure was 138.0 (SD 17.8)/88.2 (13.2) mm Hg in the hypertension and 110.9 (6.5)/69.6 (6.5) mm Hg in the control groups. Baseline DPFV was higher in the hypertension group. Hyperaemic DPFV was similar between the two groups (table 1). Therefore, CFR was significantly lower in the hypertension group (2.45 (0.76) *v* 2.97 (0.54), *p* < 0.01).

Nebivolol and atenolol similarly and significantly decreased heart rate (table 2). During the eight weeks of nebivolol treatment, baseline DPFV and hyperaemic DPFV significantly decreased. Therefore, nebivolol treatment slightly improved CFR (from 2.45 (0.48) to 2.56 (0.52), *p* = 0.09). The eight-week atenolol treatment significantly decreased baseline DPFV and hyperaemic DPFV. Therefore, treatment with atenolol for eight weeks significantly impaired CFR (from 2.46 (0.44) to 2.21 (0.40), *p* = 0.006). Nebivolol and atenolol did not alter mitral E:A ratios, and consequently left ventricular diastolic function.

DISCUSSION

Our study showed that CFR is impaired in essential hypertension, and eight-week treatment with 5 mg nebivolol slightly improves CFR. Patients with hypertension may benefit from nebivolol's vasodilator effect, which may be explained by release of nitric oxide in the resistance vasculature.³ Angiographically normal epicardial coronary arteries in patients with hypertension have been shown to have endothelial dysfunction, an abnormality that is now known to precede atherosclerosis.⁴ While we were designing the

Table 1 Comparison between the hypertension and control groups before treatment of hypertension

	Patients with essential hypertension (n = 30)	Normotensive controls (n = 30)
Women	18	17
Age (years)	41.4 (6.0)	40.9 (5.8)
Body mass index (kg/m ²)	27.1 (2.6)	27.5 (1.7)
Average 24 h BP (mmHg)	138.0 (17.8)/88.2 (13.2)	110.9 (6.5)/69.6 (6.5)
LVMI (g/m ²)	100.6 (15.9)*	91.7 (13.3)
Baseline DPFV (cm/s)	26.45 (5.03)**	23.0 (3.61)
Hyperaemic DPFV (cm/s)	66.82 (18.43)	68.26 (15.15)
CFR	2.45 (0.76)**	2.97 (0.54)

Data presented as mean (SD).

*p < 0.05 *v* control; **p < 0.01 *v* control.

BP, blood pressure; CFR, coronary flow reserve; DPFV, diastolic mean peak flow velocity; LVMI, left ventricular mass index.

Table 2 Coronary flow values of patients with hypertension before and after treatment with nebivolol and atenolol

	Nebivolol (n = 30)		Atenolol (n = 30)	
	Before	After	Before	After
E:A ratio	1.10 (0.28)	1.17 (0.30)	1.11 (0.26)	1.13 (0.24)
Heart rate (beats/min)	73.13 (11.67)	65.10 (11.55)**	74.08 (11.45)**	61.77 (9.44)**
BP (mm Hg)	146 (7)/90 (4)	133 (16)/78 (8)**	149 (8)/89 (4)**	131 (15)/77 (5)**
Baseline DPFV (cm/s)	26.5 (4.7)	22.0 (3.8)*	26.2 (4.7)**	23.4 (5.3)**
Hyperaemic DPFV (cm/s)	65.8 (18.5)	56.7 (14.5)**	66.0 (18.6)**	52.1 (15.5)
CFR	2.45 (0.48)	2.56 (0.52)†	2.46 (0.44)**	2.21 (0.40)

*p<0.05 v before treatment (paired samples t test); **p<0.01 v before treatment (paired samples t test); †p=0.09. BP, blood pressure; CFR, coronary flow reserve; DPFV, diastolic mean peak flow velocity.

present study, we had hypothesised that treatment with nebivolol for essential hypertension might improve coronary microvascular function; however, it slightly improved CFR. On the other hand, atenolol significantly impaired CFR. Only one study⁵ to date has investigated the possible effect of nebivolol on CFR, and no study has investigated the effects of atenolol on CFR. Coronary microvascular dysfunction has been implicated in causing angina pectoris or silent ischaemia in patients with hypertension free of epicardial coronary artery narrowing.⁶ In our study, although no patient had microvascular angina, our results raise the suspicion that, in patients with hypertension and microvascular angina, atenolol may worsen coronary microvascular dysfunction. Our results are somewhat different from those of the only study⁵ investigating the effects of nebivolol on CFR. In a better-designed study we have found that the nebivolol-induced improvement in CFR is not so prominent. So far, the most established effect of nebivolol is an increase in endothelial nitric oxide bioavailability. The dipyridamole-induced increase in coronary flow velocity predominantly reflects coronary microvascular function. The preservation and slight increase in CFR by nebivolol may be attributed to its effect on vascular endothelium.

In patients with hypertension, in addition to the similar decrease in the rate–pressure product, the slight increase in CFR by nebivolol may be regarded as an advantage over atenolol. The most notable result of our study is that atenolol significantly impaired coronary microvascular function and CFR in patients with essential hypertension.

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REFERENCES

- 1 Tzemos N, Lim PO, MacDonald TM. Nebivolol reverses endothelial dysfunction in essential hypertension: a randomized, double-blind, crossover study. *Circulation* 2001;**104**:511–4.
- 2 Lambertz H, Tries HP, Stein T, et al. Noninvasive assessment of coronary flow reserve with transthoracic signal-enhanced Doppler echocardiography. *J Am Soc Echocardiogr* 1999;**12**:186–95.
- 3 Dawes M, Brett SE, Chowieńczyk PJ, et al. The vasodilator action of nebivolol in forearm vasculature of subjects with essential hypertension. *Br J Clin Pharmacol* 1999;**48**:460–3.
- 4 Brush JE Jr, Cannon RO 3rd, Schenke WH, et al. A. gina due to coronary microvascular disease in hypertensive patients without left ventricular hypertrophy. *N Engl J Med* 1988;**319**:1302–7.

- 5 Galderisi M, Cicala S, D'Errico A, et al. Nebivolol improves coronary flow reserve in hypertensive patients without coronary heart disease. *J Hypertens* 2004;**22**:2201–8.
- 6 Zeiher AM, Krause T, Schachinger V, et al. Impaired endothelium-dependent vasodilation of coronary resistance vessels is associated with exercise-induced myocardial ischemia. *Circulation* 1995;**91**:2345–52.

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