Does the β-Blocker Nebivolol Increase Coronary Flow Reserve?

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Abstract

Introduction Nebivolol, a highly selective β1-adrenergic receptor-blocker, increases basal and stimulated endothelial nitric oxide (NO)-release. It is unknown, whether coronary perfusion is improved by the increase in NO availability. Therefore, we sought to evaluate the effect of nebivolol on coronary flow reserve (CFR) and collateral flow.

Methods Doppler-flow wire derived coronary flow velocity measurements were obtained in ten controls and eight patients with coronary artery disease (CAD) at rest and after intracoronary nebivolol. CFR was defined as maximal flow during adenosine-induced hyperemia divided by resting flow. In the CAD group, collateral flow was determined after dilatation of a flow-limiting coronary stenosis. Collateral flow index (CFI) was defined as the ratio of flow velocity during balloon inflation divided by resting flow.

Results CFR at rest was 3.0±0.6 in controls and 2.1±0.4 in CAD patients. After intracoronary doses of 0.1, 0.25, and 0.5 mg nebivolol, CFR increased to 3.4±0.7, 3.9±0.9, and 4.0±0.1 ($p<0.01$) in controls, and to 2.3±0.7, 2.6±0.9, and 2.6±0.5 ($p<0.05$) in CAD patients. CFI decreased significantly with intracoronary nebivolol and correlated to changes in heart rate ($r=0.75$, $p<0.001$) and rate-pressure product ($r=0.59$, $p=0.001$).

Discussion Intracoronary nebivolol is associated with a significant increase in CFR due to reduction in resting flow (controls), or due to an increase in maximal coronary flow (CAD patients). CFI decreased with nebivolol parallel to the reduction in myocardial oxygen consumption.

Key words coronary artery disease · nebivolol · coronary flow reserve · coronary collateral flow

Introduction

The phenomenon of hypoxemia-induced increase in coronary flow was first described by Hilton and Eicholtz in 1925 [1]. Their findings were confirmed by Katz and Lindner in 1939 who reported a quantitative relation between reactive hyperemia and myocardial ischemia [2]. However, it was not until 1960 that the concept of coronary flow reserve was introduced by Coffman and Gregg [3] to assess the capacity of coronary circulation to conduct maximal hyperemic blood flow. Subsequently, coronary flow reserve has been used as a clinical parameter for assessing the functional significance of intermediate coronary stenoses. Three types of stimuli have been used to elicit maximal coronary blood flow in humans: (1) transient coronary occlusion during angioplasty (reactive hyperemia) [4]; (2) pharmacologic agents such as papaverine [5–7], adenosine [6–8], and dipyridamole [8]; (3) dynamic exercise [9].

Coronary flow reserve is defined as the ratio of coronary blood flow during maximal vasodilatation divided by resting flow, and measures the ability of the two components of myocardial perfusion, namely, epicardial stenosis resistance and microvascular resis-

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tance, to achieve maximal blood flow. In the absence of epicardial coronary artery lesions, the pressure–flow relationship is linear and steep during maximal vasodilatation and, therefore, peak flow is a function of coronary resistance [10]. Therapeutic interventions may affect coronary flow reserve by changing resting or maximal flow. A small increase in resting flow leads, however, to a large decrease in coronary flow reserve, and vice versa.

Beta-blockers reduce oxygen consumption of the myocardium and thus, diminish myocardial ischemia (=reduced demand). In addition, metoprolol has been shown to improve myocardial perfusion [11, 12] by increasing coronary flow reserve (=increased supply). This effect was mainly due to an increase in hyperemic flow rather than a decrease in resting flow. Nebivolol, a highly selective β1-adrenergic receptor-blocker with nitric oxide-modulating properties [13], might be especially useful for improving coronary flow reserve due to its vasodilating properties on the small and large coronary arteries. Thus, the purpose of the present study was to evaluate the effect of intracoronary nebivolol on coronary flow velocity reserve and coronary flow reserve in controls and in patients with coronary artery disease using adenosine as stimulus for maximal flow increase. In addition, the effect of intracoronary nebivolol on collateral flow was assessed in patients with coronary artery disease during balloon inflation by calculating the collateral flow index.

Methods

Patient population Ten patients with angiographically normal coronary arteries (controls) and eight patients with one-vessel and one-lesion coronary artery disease (coronary artery disease group) were included in the present analysis (Table 1). Exclusion criteria were: untreated hypertension, know allergy or intolerance to beta-blocking agents, alcohol or drug abuse, renal insufficiency, clinically significant extracardiac disease, as well as diffuse or two and three vessel coronary artery disease. Diagnostic coronary angiography and left heart catheterization were performed with standard techniques. Aortic and left ventricular pressures were measured with a pigtail catheter. Biplane left ventricular angiography was performed at the end of diagnostic coronary angiography.

Stent implantation Of the eight coronary artery disease patients, three had an RCA lesion (two segment 2 and one segment 3), two an LAD lesion (both segment 13) and two an LCX lesion (both segment 20). Stent implantation was performed according to standard technique. Only bare-metal stents were implanted. Three patients received a BX-SONIC™ stent (Cordis), three patients an AVE™ stent (Medtronic), and two patients a Vision™ (Guidant) stent. Lesion length was 8.1±2.1 mm, preprocedure minimal lumen diameter was 0.57±0.45 mm, mean stent length was 14±5 mm, nominal stent diameter 3.0±0.2 mm and acute gain in-stent was 2.53±0.34 mm.

Table 1 Patient characteristics

	Controls (%)	n	CAD (%)	p value
Number of patients	10	–	8	
Age (year)	57±6	–	55±10	0.68
Men	7	(70)	6	(75)	0.81
Smoking	3	(30)	6	(75)	0.06
Diabetes mellitus	2	(20)	1	(12.5)	0.67
Family history of CAD	4	(40)	4	(50)	0.67
Hypertension	6	(60)	3	(37.5)	0.34
Hypercholesterolemia	7	(70)	7	(87.5)	0.38
Cholesterol (mmol/l)	5.1±0.6		5.2±0.6	0.8
LVEDP (mmHg)	11±3		10±2	0.58
LV-EF (%)	63±7		60±6	0.67
Aspirin	7	(70)	8	(100)	0.09
Betablockers (metoprolol)	5	(50)	5	(62.5)	0.6
Calcium antagonists	1	(10)	1	(12.5)	0.87
Lipid lowering agents	7	(70)	6	(75)	0.81
ACE inhibitors	5	(50)	8	(100)	0.02
Nitrates	1	(10)	3	(37.5)	0.16

LVEDP Left ventricular end-diastolic pressure; *LV-EF* left ventricular ejection fraction; *CAD* coronary artery disease

Doppler-flow velocity measurements Doppler-flow velocity was measured with a 0.014 in. Doppler-guide wire with a 12-MHz piezoelectric crystal at its tip (FloWire®, Volcano Therapeutics Inc., Rancho Cordova, CA, USA). The validation of this Doppler-guide wire has been described previously [14]. In *coronary artery disease* patients, the tip of the Doppler guidewire was placed distal to the stent. Coronary flow velocity reserve was calculated from hyperemic peak flow velocity averaged over two cardiac cycles (averaged peak velocity=APV, cm/sec) divided by resting flow velocity. Pharmacologic modulation of coronary flow velocity reserve was induced by an intracoronary bolus of 18 μg adenosine for the left and 12 μg for the right coronary artery, respectively [7]. Coronary vascular resistance was calculated from mean aortic pressure divided by mean coronary flow velocity (mmHg×sec/cm). Coronary resistance ratio was calculated from coronary resistance during hyperemia divided by resistance at rest. Coronary flow was calculated from coronary flow velocity multiplied by cross-sectional area of the artery at the tip of the flow wire measured by quantitative coronary angiography using the ACA package of Philips DC/Integris system. Flow data were normalized by a factor of 0.5 assuming a parabolic flow profile and by a factor of 0.6 converting cm/sec into ml/min [14]. From these measurements coronary flow reserve was determined. In patients with coronary artery disease, after treatment of a flow-limiting stenosis with stent implantation, collateral flow velocity was calculated during subsequent balloon inflations. The collateral flow index (CFI) was determined as the ratio of the flow velocity time integral distal to the occluded artery during balloon inflation divided by baseline flow velocity obtained at the same location prior to balloon inflation.

Study protocol

1. *Baseline*: Vasoactive medication (including beta-blockers) was discontinued at least 48 h before catheterization. After coronary angiography and stent implantation for clinical purpose (only in coronary artery disease group), an interval of at least 15 min was allowed for dissipation of the effect of nonionic contrast medium. Two hundred micrograms of nitroglycerin was administered intracoronary for maximal vasodilation. Heart-rate, mean aortic pressure as well as coronary cross-sectional area at the tip of the flow wire were determined in all patients. Baseline coronary flow velocity and flow measurements were performed. Intracoronary adenosine was administered for assessment of coronary flow velocity and flow reserve, followed by a 1 min balloon inflation within stented segment (only in coronary artery disease group) for calculation of collateral flow index (Fig. 1).
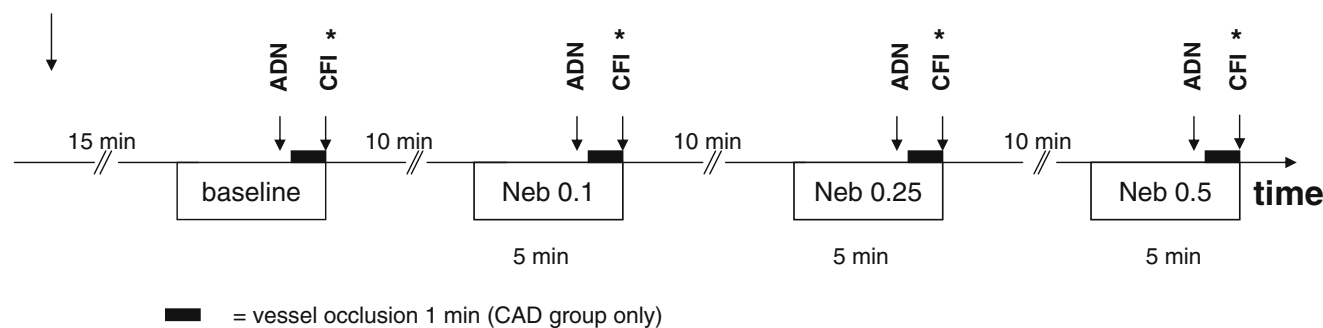
Study protocol

Fig. 1 Study protocol: After coronary angiography and stent implantation (only in CAD group), an interval of at least 15 min was allowed for dissipation of the effect of nonionic contrast medium. Two hundred micrograms of nitroglycerin was administered i.c. for maximal vasodilation. Baseline coronary flow velocity and flow measurements were performed. Intracoronary adenosine (*ADN*) was administered for assessment of coronary flow velocity and flow reserve (*CFR*), followed by a 1 min balloon inflation within stented segment (only in CAD group) for calculation of collateral flow index (*CFI*). Three intracoronary nebivolol infusions were performed over a period of 5 min with increasing doses (0.1, 0.25, and, 0.5 mg) separated by intervals of 10 min to allow coronary flow reach baseline level. At the end of each infusion period ADN was administered for CFR calculation followed by a 1 min balloon inflation (only in CAD group) for CFI calculation. *Asterisk* = procedures and measurements performed only in CAD group

2. *Infusion of intracoronary nebivolol*: Three intracoronary nebivolol infusions were administered over 5 min with increasing doses (0.1, 0.25, and, 0.5 mg/min) separated by intervals of 10 min to allow coronary flow reach baseline level. These doses adhere to comparable intra-arterial infusions into the brachial artery reported previously [15]. Doppler flow velocities were measured continuously. At the end of each infusion period, hyperemia was induced with adenosine for calculation of coronary flow and flow velocity reserve, followed by a 1 min balloon inflation (only in coronary artery disease group) for coronary flow index calculation (Fig. 2).

Ethics

The study protocol was approved by the local ethics committee, and written informed consent was obtained from all patients.

Statistical analysis

Comparison of angiographic, hemodymamic, and Doppler-flow velocity data was performed by an unpaired Student *t*-test (continuous variables) and by a χ^2-test (categorical variables). A two-way analysis of variance for repeated measurements was performed for comparison of hemodynamic and Doppler-flow data during nebivolol administration. Multivariable logistic regression analysis was performed to determine the effect of cardiovascular risk factors (hypertension, smoking) and baseline medication (ACE inhibitors and nitrates) as covariates on coronary flow velocity and coronary flow (including coronary flow velocity reserve and coronary flow reserve) response to nebivolol application. Correlation between coronary flow index and heart rate as well as rate-pressure product was performed using the square method. The correlation coefficient (*r*) and the regression equation were calculated from these data. Statistical significance was defined at a *p* value of <0.05.

Results

Baseline patient characteristics Patients in the two groups were well matched with regard to age, gender, presence of risk factors (diabetes mellitus, family history, and hypercholesterolemia) as well as medication (beta-blockers, calcium-antagonists). There was an imbalance with regard to history of smoking (higher incidence of smokers in the coronary artery disease group, *p*=0.06) and medication with ACE inhibitors (all coronary artery disease patients on ACE-inhibitor medication as opposed to only 50% in the control group, *p*=0.02) (Table 1).

Hemodynamics There was a significant decrease in heart rate after nebivolol administration in both groups. Mean aortic pressure remained unchanged after nebivolol in controls as well as in coronary
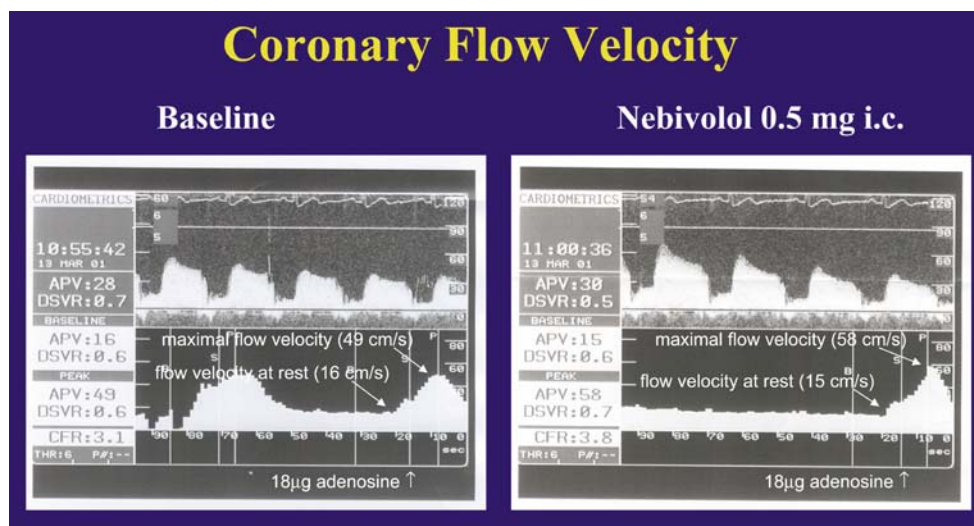

Fig. 2 Representative recordings of coronary flow velocity in a coronary artery disease patient before (*left*) and after 0.5 mg intracoronary nebivolol (*right*). Coronary flow velocity at rest remained unchanged (from 16 to 15 cm/sec after 0.5 mg nebivolol), whereas maximal flow velocity increased from 49 to 58 cm/sec, respectively. As a consequence, coronary flow velocity reserve increased from 3.1 to 3.8

Table 2 Hemodynamics

	Baseline	Nebivolol 0.1 mg	Nebivolol 0.25 mg	Nebivolol 0.5 mg
Controls:				
HR (beats/min)	73±16	68±15	66±14**	64±11**
Systolic blood pressure (mmHg)	142±15	143±14	140±11	139±11
Diastolic blood pressure (mmHg)	82±8	83±9	80±8	81±7
RPP (mmHg×10³/min)	10.4	9.7	9.2	8.9*
CAD group:				
HR (beats/min)	71±9	70±11	65±7*	63±9*
Systolic blood pressure (mmHg)	140±21	140±26	135±17	135±16
Diastolic blood pressure (mmHg)	84±10	82±11	75±13	76±14
RPP (mmHg×10³/min)	9.9	9.8	8.8*	8.5*

HR Heart rate; *RPP* rate-pressure product
$*p<0.05$, $**p<0.01$

artery disease patients. As a consequence, the rate-pressure product (RPP) decreased after intracoronary nebivolol from $10.4×10^3$ to $8.9×10^3$ mmHg/min ($p<0.05$) in controls and from $9.9×10^3$ to $8.5×10^3$ mmHg/min ($p<0.05$) in coronary artery disease patients (Table 2).

Coronary flow velocity and flow reserve Coronary flow velocity reserve at rest was 3±0.6 in controls and 2.1±0.4 in coronary artery disease patients ($p<0.05$). Coronary flow velocity reserve increased after intracoronary doses of 0.1, 0.25 and 0.5 mg nebivolol to 3.1±0.6 (ns), 3.5±0.8 ($p<0.05$), 3.6±0.8 ($p<0.05$) in controls and
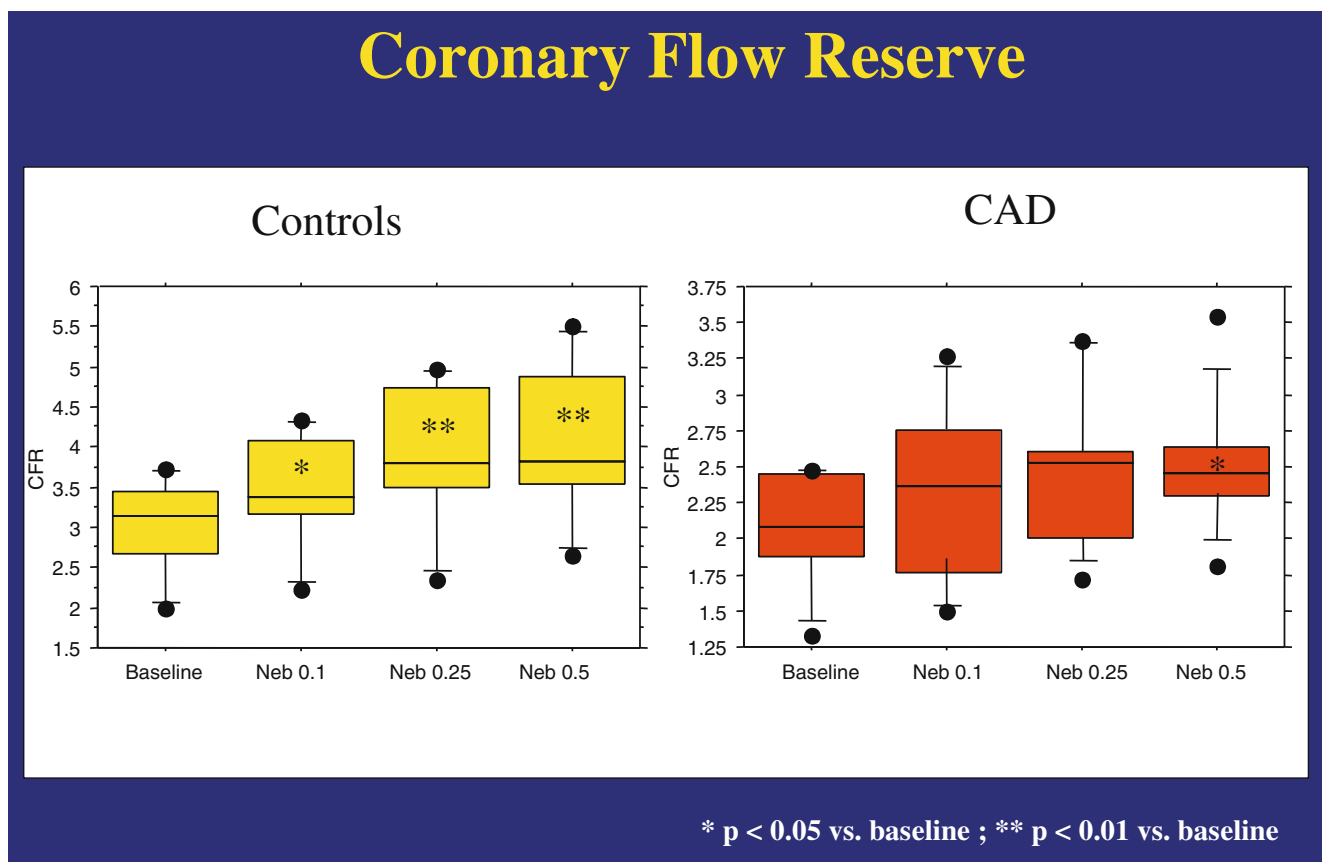

Fig. 3 Box plot of coronary flow reserve (*CFR*) at rest and after intracoronary nebivolol in controls (*left panel*) and in CAD patients (*right panel*). CFR increased after intracoronary doses of 0.1, 0.25, and 0.5 mg nebivolol from 3.0±0.6 to 3.4±0.7 ($p<0.05$), 3.9±0.9 ($p<0.01$) and 4.0±0.1 ($p<0.01$) in controls and from 2.1±0.4 to 2.3±0.7 (ns), 2.6±0.9 (ns), and 2.6±0.5 ($p<0.05$) in CAD patients, respectively (abbreviations as in Fig. 1)

Table 3 Coronary flow velocity

	Baseline	Nebivolol 0.1 mg	Nebivolol 0.25 mg	Nebivolol 0.5 mg
Controls:				
CFV rest (cm/sec)	18±2	16±2	15±2*	14±2**
CFV hyperemic(cm/sec)	54±8	50±7	50±7	49±7
CFVR	3±0.6	3.1±0.6	3.5±0.8*	3.6±0.8*
CSA (mm^2)	5.1±1.9	5.0±1.8	5.0±1.8	5.0±1.7
Coronary artery disease group:				
CFV rest (cm/sec)	24±7	25±7	26±7	24±8
CFV hyperemic (cm/sec)	49±17	54±13	61±20	56±13
CFVR	2.1±0.4	2.2±0.7	2.5±1	2.4±0.6
CSA (mm^2)	5.0±1.4	5.3±1.4	5.1±1.4	5.2±1.3

CFV Coronary flow velocity; *CFVR* coronary flow velocity reserve; *CSA* cross sectional area
sec*$p<0.05$; **$p<0.01$

to 2.2±0.7, 2.5±1.0, 2.4±0.6 (all ns) in coronary artery disease patients, respectively. The similar pattern was observed for coronary flow reserve in both groups. Precisely, coronary flow reserve at rest was 3.0±0.6 in controls and 2.1±0.4 in coronary artery disease patients ($p<0.05$). Coronary flow reserve increased after intracoronary doses of 0.1, 0.25, and 0.5 mg nebivolol to 3.4±0.7 ($p<0.05$), 3.9±0.9 ($p<0.01$), and 4.0±0.1 ($p<0.01$) in controls, and to 2.3±0.7 (ns), 2.6±0.9 (ns), and 2.6±0.5 ($p<0.05$) in coronary artery disease patients, respectively (Fig. 3) (Tables 3 and 4).

Coronary vascular resistance Coronary vascular resistance (CR) at rest increased after nebivolol in controls, whereas it did not change in coronary artery disease patients. Hyperemic coronary vascular resistance remained unchanged after nebivolol in controls, whereas it decreased significantly after 0.25 mg ($p<0.05$) and 0.5 mg ($p<0.05$) intracoronary nebivolol in coronary artery disease patients. Coronary resistance ratio at rest was 0.34±0.8 in controls and 0.5±0.1 in coronary artery disease patients, and decreased with 0.5 mg nebivolol to 0.29±0.6 in controls ($p<0.01$) and to 0.45±0.1 (ns) in coronary artery disease patients, respectively (Table 5).

Collateral flow index Coronary flow index decreased from 0.37±0.23 to 0.33±0.25, 0.28±0.3 ($p<0.05$), and 0.27±0.30 ($p<0.05$), respectively after 0.1, 0.25, and 0.5 mg intracoronary nebivolol. There was a significant correlation between heart-rate and coronary flow index ($r=0.76$, $p<0.0001$), as well as between rate-pressure product and coronary flow index ($r=0.59$, $p<0.001$), respectively (Figs. 4 and 5).

Discussion

The present study shows that: (1) Intracoronary nebivolol is associated with a significant increase in both coronary flow velocity reserve and coronary flow reserve in patients with angiographically normal coronary arteries due to a reduction in resting but no change in maximal flow. (2) In coronary artery disease patients, coronary flow velocity reserve and coronary flow reserve increase after nebivolol due to an increase in maximal but no change in resting coronary flow. (3) Collateral flow decreases after nebivolol due to the reduction in myocardial oxygen requirements.

Table 4 Coronary flow

	Baseline	Nebivolol 0.1 mg	Nebivolol 0.25 mg	Nebivolol 0.5 mg
Controls:				
CFR	3±0.6	3.4±0.7*	3.9±0.9**	4.0±1**
CF rest (ml/sec)	113±31	126±45	121±30	111±24
CF hyperemic(ml/sec)	239±83	276±78	297±79	277±54*
Coronary artery disease group:				
CFR	2.1±0.4	2.3±0.7	2.6±0.9	2.6±0.5*
CF rest (ml/sec)	83±35	74±29	68±30*	63±27**
CF hyperemic (ml/sec)	236±80	240±81	244±84	236±80

CF Coronary flow; *CFR* coronary flow reserve
*$p<0.05$; **$p<0.01$

Table 5 Coronary resistance

	Baseline	Nebivolol 0.1 mg	Nebivolol 0.25 mg	Nebivolol 0.5 mg
Controls:				
CR rest (mmHg×sec/cm)	5.6±0.8	6.3±0.6	6.9±0.6	7.5±0.5*
CR hyperemic (mmHg×sec/cm)	2.0±0.6	2.1±0.6	2.0±0.5	2.1±0.6
CRR	0.34±0.8	0.34±0.7	0.30±0.7**	0.29±0.6**
Coronary artery disease group:				
CR rest (mmHg×sec/cm)	4.6±1.7	4.8±2.1	4.3±1.9	4±1.4
CR hyperemic(mmHg×sec/cm)	2.2±0.6	2.1±0.7	1.8±0.6*	1.7±0.4*
CRR	0.5±0.1	0.47±0.2	0.47±0.1	0.45±0.1

CR Coronary resistance; *CRR* coronary resistance ratio
*$p < 0.05$; **$p < 0.01$

Changes in coronary hemodynamics associated with the administration of β-blockers have been extensively studied in the past [16]. Previous clinical studies using coronary flow measurements suggest that non-selective β-adrenergic antagonists are associated with an increase in coronary vascular resistance during hyperemia and, therefore, reduce coronary flow reserve [17, 18]. This phenomenon has been attributed to the unopposed alpha-adrenergic vasomotor tone. Selective β-adrenergic antagonists on the other hand are associated with an increase of coronary flow reserve [11]. The increase in coronary flow reserve with metoprolol administration is achieved by an increase in maximal coronary flow which is further enhanced by a decrease in resting flow [11, 12]. With metoprolol, coronary vascular resistance decreases during adenosine-induced hyperemia.

Nebivolol combines potent β1-adrenoreceptor-blocking activity with nitric oxide-mediated vasodilating properties. *In vitro* studies have shown that

nebivolol dilates coronary resistance vessels in humans through an agonist effect on endothelial β3-adrenoreceptors to release nitric oxide and promote neoangiogenesis [19]. The nitric oxide-releasing and vasodilating properties of nebivolol in coronary microvessels may exert its beneficial effect in patients with ischemic and dilated cardiomyopathies [20], particularly those with diastolic dysfunction [21], given the direct lusitropic properties of nitric oxide on the myocardium. Diseases such as dyslipidemia, diabetes, and atherosclerosis are all associated with a decrease in eNOS expression, nitric
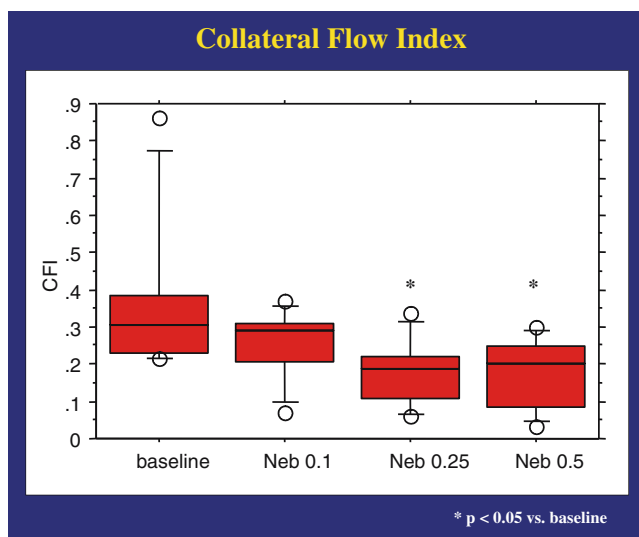

Collateral Flow Index

Fig. 4 Box plot of collateral flow index (*CFI*) at rest and after intracoronary nebivolol in CAD patients. CFI decreased from 0.37±0.23 to 0.33±0.25, 0.28±0.3 (*p*<0.05), and 0.27±0.3 (*p*<0.05), respectively, after 0.1, 0.25, and 0.5 mg of intracoronary nebivolol
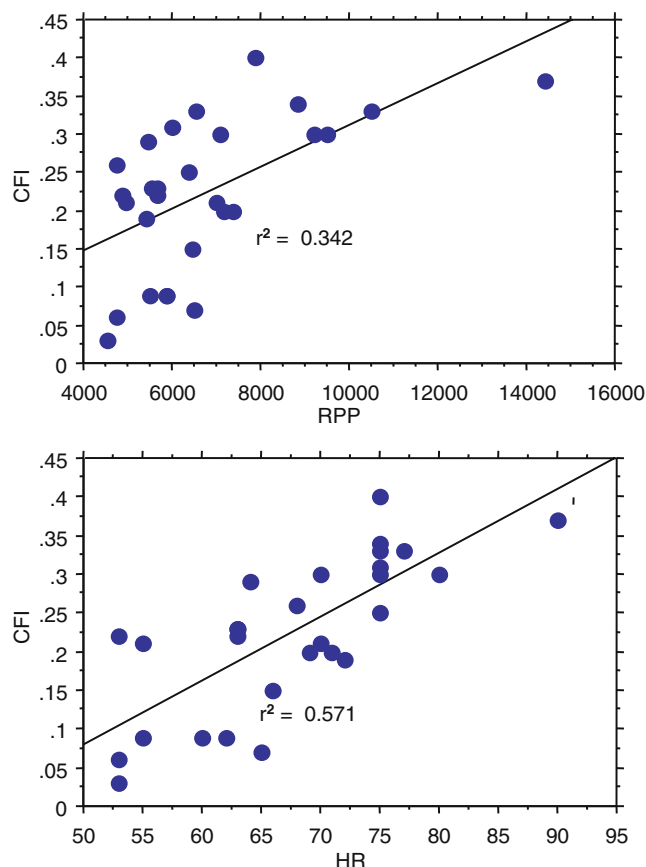

Fig. 5 Regression plot of collateral flow index versus heart rate (*top panel*) and rate-pressure product (*lower panel*), respectively

oxide bioavailability, or both, which could limit the clinical impact of a drug that depends on nitric oxide release. The marked vasodilating effect of nebivolol in human coronary microvessels is well established under *in vitro* conditions [13]. The present study compliments a recent *in vivo* investigation by Galderisi et al. who demonstrated improvement of coronary flow reserve in hypertensive patients without coronary artery disease [22]. Nebivolol increased coronary flow reserve through an increase in hyperemic flow without changing resting flow comparable to our findings in the coronary artery disease patients. However, the two studies differ substantially. In the work by Galderisi: (1) exclusively hypertensive subjects without coronary artery disease were investigated, (2) coronary flow reserve was assessed by non-invasive means (Doppler echocardiography), and (3) nebivolol was administered by the oral route over 4 weeks. Importantly, Galderisi was able to demonstrate that adequate nebivolol concentrations are reached in the coronary blood by conventional oral administration in order to obtain relevant effects on coronary flow. A comparable effect on the brachial artery flow-mediated vasodilation was shown by Lekakis with an oral dose of 5 mg of nebivolol [23].

Differences in response to nebivolol between coronary artery disease and control group

In controls, endothelial function is normal with a normal coronary flow reserve value. In coronary artery disease patients, endothelial dysfunction is present and coronary flow reserve is reduced. Stimulation of the endothelium by nebivolol acts mainly in the diseased arteries with an increase in maximal coronary flow and almost normalization of coronary flow reserve. In the normal coronary artery, the beta-blocking effect of nebivolol predominates rather than the vasodilating effect on maximal flow. Thus, in the presence of normal endothelial function, the beta-blocking effect of nebivolol becomes evident, whereas in the diseased vessel the vasodilating effect of nebivolol prevails. These changes are reflected by the changes in coronary peripheral resistance with an increase in resistance in the controls at rest and a decreased resistance in coronary artery disease patients under hyperemic conditions.

The anti-ischemic effect of nebivolol in the presence of coronary artery disease is based on the following mechanisms: (1) reduction in oxygen demand through the β1-adrenoreceptor blocking properties as reflected by the decrease in heart rate and rate-pressure product, (2) maintained (not diminished) coronary flow at rest, (3) increased coronary flow reserve through the increase in hyperemic flow (=increased oxygen supply).

These three mechanisms influence the oxygen supply–demand balance of the myocardium favorably.

Collateral flow index and nebivolol The coronary collateral flow decreased significantly after nebivolol. Previous reports have shown a similar response of coronary collateral flow to the selective β1-blocker metoprolol [24]. The reduction in coronary collateral flow has been attributed to a vasoconstrictive response of the collateral vessel to metoprolol with an increase in vascular resistance. With nebivolol a similar response was observed with a decrease in coronary collateral perfusion. However, there was a close relation between heart rate and changes in collateral flow. This finding supports the hypothesis that collateral flow is mainly determined by the requirements of the collateral-dependent myocardium.

Limitations Several limitations have to be considered for this study:

(1) Changes in heart rate and mean aortic pressure may affect coronary flow and flow velocity. In controls, baseline flow decreased after nebivolol administration, and the rise in coronary flow reserve was attributed to the reduction in coronary flow at rest in the presence of a maintained hyperemic flow. In coronary artery disease patients, however, the decrease in heart rate and mean aortic pressure after nebivolol was not associated with a change in resting coronary flow. This finding could be explained by the beneficial effect of nebivolol on nitric oxide-release which may counteract the flow reduction induced by the presence of endothelial dysfunction in coronary artery disease patients.

(2) Comparisons with other selective β1-adrenoreceptor antagonists (i.e., metoprolol) were not performed. Previous studies from our group demonstrated a similar response of coronary flow and reserve capacity [12] as well as collateral flow [24] to metoprolol. However, study protocols differ substantially, and therefore, data may not be extrapolated for comparison purposes.

(3) The control group consisted of patients who underwent coronary angiography to exclude the presence of coronary artery disease. Therefore, the results of the control group do not reflect the response to nebivolol in normals.

(4) There was an imbalance between the two groups with regard to smoking and medication with ACE inhibitors. We therefore performed an multivariable regression analysis with covariates to determine the effect of medication and presence of risk factors (smoking, diabetes) on the effect of nebivolol on

coronary flow and flow reserve. The analysis of variance showed no effect of cardiovascular risk factors as well as baseline medication including ACE-inhibitors on the results obtained.

(5) Coronary flow reserve may have been affected by other factors apart form endothelial function such as left ventricular mass and cholesterol values. Cholesterol values were similar in the two study groups. Left ventricular mass was not determined and thus no comment on this relationship can be made, except that the incidence of hypertension was similar in both groups.

(6) The concomitant use of beta-blockers in the two groups may have affected the results of the present study. The only beta-blocker used was metoprolol and in a similar percentage in both groups. However, all cardiovascular medication was stopped at least 48 h prior to the study and all patients showed decrease in heart rate under nebivolol.

Conclusions

Nebivolol is associated with a significant increase in coronary flow reserve in controls as well as in patients with coronary artery disease. In controls, the rise in coronary flow reserve is mainly attributed to the decrease in resting coronary flow (β-blocking effect), whereas in coronary artery disease patients, this effect is mainly due to an increase in maximal coronary flow during adenosine infusion without a change in resting flow. The increase in coronary flow (supply ↑) and the reduction in rate-pressure product (demand ↓) after nebivolol explain the excellent anti-ischemic properties of this compound in patients with coronary artery disease. Coronary flow index decreased with nebivolol parallel to the reduction in oxygen requirements of the collateral-dependent myocardium.

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