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Bisoprolol improved endothelial function and myocardium survival of hypertension with stable angina: a randomized double-blinded trial

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Abstract. – AIM: This study was designed to determine the effect of bisoprolol on endothelial function of brachial artery and the myocardium survival in hypertensive patients with stable angina.

PATIENTS AND METHODS: 222 subjects with hypertension who had received coronary angiography examination were involved in the study, 162 in bisoprolol therapy group (96 men, 59%) and 60 in non-bisoprolol group (39 men, 65%). In accordance with results of angiography (coronary stenosis ≥ 50%), the patients in bisoprolol group were divided into three sub-groups: (1) single-vessel coronary disease group (n=42); (2) double-vessel coronary disease group (n=44); (3) multi-vessel coronary disease group (n=39) and hypertension-only group (n=37). All the subjects were treated with conventional drugs plus bisoprolol and followed up for 12 months. Parameters of clinical features, echocardiography, radionuclide ventriculographic and laboratory findings were measured and analyzed.

RESULTS: After 12 months bisoprolol treatment, the flow-mediated vasodilatation (FMD) and 99Tcm-sestamibi ($^{99}Tc^m$-MIBI) uptake fraction which reflects the survival of myocardium were improved markedly in bisoprolol group (all $p < 0.05$). Interestingly, a more significant improvement in FMD and $^{99}Tc^m$-MIBI uptake fraction were observed in severe coronary disease sub-groups (double-vessel group and multi-vessel group) when compared with single-vessel sub-group ($p < 0.05$).

CONCLUSIONS: Hypertensive subjects with stable angina might get benefit from the treatment of bisoprolol in improving endothelial function and the survival of myocardium.

Key Words:
Bisoprolol, Hypertension, Stable angina, Endothelial function, Survival of myocardium.

Introduction

Coronary artery disease (CAD) continues to be a leading cause of morbidity and mortality in patients with hypertension, because these patients are at increased risk for CAD as compared with normotensive patients[1-3]. Uncontrolled and prolonged elevation of blood pressure (BP) can lead to a variety of changes in the myocardial structure, coronary vasculature, and conduction system of the heart. The main benefit of therapy is the lowering of blood pressure. The different classes of antihypertensive agents have specific mechanisms of action that can favourably or unfavourably affect different organs or systems. An example of this is the effect of antihypertensive agents on endothelial function. It is proved that patients with symptomatic coronary artery disease can have benefit from the improvement of endothelium function[4]. Currently, it arouse concerns a role for early intervention of endothelial dysfunction to prevent irreversible vascular and organ damage in hypertensive patients.

Flow-mediated endothelial-dependent vasodilation (FMD) of the brachial artery is a method capable of detecting changes in endothelial function. The method was first described and implemented in clinical practice by Celermajer et al[5]. For more than two decades, the method has been used to evaluate early atherosclerotic changes in patients with various risk factors for coronary atherosclerosis. Recently, radionuclide myocardial perfusion imaging providing information on perfusion abnormalities has been proved to be a sensitive test for diagnosing ischaemia. $^{99}Tc^m$-sestamibi ($^{99}Tc^m$-MIBI) which is a lipophilic cation, distributes in the myocardium proportionally to the myocardial blood flow and is used mainly for evaluating myocardial perfusion.

Over the decades, β blockers were used as safe and effective antihypertensives[6]. In 1967, Lands et al[7] found evidence for the existence of two types of β-Adrenergic receptors (βARs), β1 and

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β2 – by measuring the relative potency of sympathomimetic amines in different tissues. In the cardiovascular system, β1ARs are found predominantly in the heart, where they increase heart rate (positive chronotropy) and force of contraction (positive inotropy), as well as increasing the rate of relaxation (positive lusitropy). Some β-blockers have been shown to have vasodilatory properties that are NO-dependent[8,9]. Bisoprolol is cardioprotective because it selectively and competitively blocks catecholamine (adrenalin) stimulation of beta-1 adrenergic receptors (β1 adrenoreceptor) which is mainly interested in hypertension[10,11]. Bisoprolol minimizes the side effects that might occur from administration of a nonspecific beta blockers where the blockage of the other adrenoreceptors (β2, β3, α1, α2) occurs[12]. It can lower blood pressure, protects the target organs and reduces the risk of cardiovascular events[10]. Bisoprolol was proved to increase the survival rate in high dosage[13]. In this study, the dose can be increased as tolerated to a maintenance dose of 10 mg/d.

The purpose of this study was to determine the effect of highly selective β1 receptor blocker, bisoprolol, on the endothelial function and the myocardial function in hypertensive patients with stable angina.

Patients and Methods

Patients

It was a randomized and double-blinded trial. 222 in hospital cases (135 Males (61%), aged from 38 to 71, mean age 58±13) were selected and randomly assigned in equal proportions to either bisoprolol group (n=162) or matching non-bisoprolol group (placebo) (n=60). All studies were carried out during August 2009 to September 2010 at the Sun Yat-sen Cardiovascular Hospital, Shenzhen. The attending physician did not know the patient bisoprolol treatment. The follow up period was 12 months. The statistical calculation was calculated by the third part. All the patients took coronary angiography (for ethical reason, not including hypertension only group and instead of coronary computed tomography angiography), ECG and echocardiography at baseline and 12 months end point. Coronary arteries were reviewed in consensus by two experienced cardiologists. 50% luminal narrowing was used as a threshold for obstructive. Inclusion criteria: systolic blood pressure ≥ 140 mmHg and/or DBP ≥ 90 mmHg, atypical symptoms (with/without risk factors for CAD), typical angina, inconclusive stress test results. Exclusion criteria: the onset of cardiovascular and cerebrovascular events in the past three months, diabetes mellitus, multiple ectopic beats, atrial fibrillation, heart rate more than 75 beats per minute (bpm) despite therapy or less than 55 bpm, renal failure, severe lung disease, usage of statins in the past three months, a history of allergic reaction to 99Tcm-Sestamibi, any condition other than CAD that limited life expectancy, hypotension or uncontrolled hypertension. Written informed consents were obtained from all subjects. The study was approved by the Institution's Ethics Committee.

Study Design

Patients were routinely treated with ACEI, ARB, diuretics, anti-platelet aggregation and nitrates. Bisoprolol is from Merck Serono Co., Ltd., China. The starting dose is 1.25 mg/d. The dose can be increased as tolerated to a maintenance dose of 10 mg/d. The target heart rate is 55-60 bpm. Patients were under routine follow-up once per month and the follow up period is 12 months.

FMD

FMD (**F**low-**M**ediated endothelial-dependent vaso **D**ilation) testing was performed by the experienced investigator according to the guideline[14]. FMD measurements were performed between 07:00 and 09:00. Patients were asked to refrain from eating, consuming alcohol or smoking after 20:00 the day before. On the morning of the study, the patient was asked not to consume anything but water, refrain from vigorous physical activity and not to smoke. They were also requested to postpone taking the prescribed medication until after FMD measurements were taken. After 15 min of rest in a quiet and temperate room, the investigation started with BP measurements taken on the dominant arm. The cuff of the sphygmomanometer was placed on the forearm of the same arm with the patient supine. A longitudinal image of the brachial artery with optimal visualization of the intima using a linear array transducer at 3 MHz to 11 MHz and an echocardiograph (ACUSON 128 XP 10 Art Ultrasound OB/GYN Vascular Cardiac, Willowick, OH, USA) was obtained. A 5 s to 10 s recording of the baseline state of the brachial artery was captured on a video cassette recorder. The cuff was inflated to a pressure of 200 mmHg or 50 mmHg

above the systolic arterial pressure of the respective patient, whichever was higher, and maintained for 5 min. A new recording during the last 30 s of the ischemic phase (cuff inflated) and at 120 s after cuff deflation was obtained. The entire image was ECG-gated. The investigator was blinded to patient identity and medication regimen. The FMD was measured and expressed as a per cent value, derived by the formula:

$$\text{FMD}\ (\%) = \frac{\left(\begin{matrix}\text{Postischemic}\\ \text{diameter of the}\\ \text{brachial artery}\end{matrix}\right) - \left(\begin{matrix}\text{baseline}\\ \text{diameter}\end{matrix}\right)}{\text{baseline diameter}} \times 100$$

$^{99}Tc^{m}$-MIBI uptake fraction

ß blockers (BBs) and nitrates were stopped 24 hours before single-photon emission computed tomography (SPECT) (e.cam Siemens Medical Systems Inc., Malvern, PA, USA) measurement. A 2 day protocol (0.3 mCi/kg of technetium Tc 99m sestamibi during rest and the same amount during stress) was used. Supine gated SPECT images were acquired 45-60 minutes after the injection. One day later, nitroglycerin intravenous drip infusion start 5-10 ug/min then may be up to > 200 ug/min when: (1). The change of SBP ≥ 10 mmHg; (2). SBP < 90 mmHg; (3). HR < 60 bpm or ≥ 100 bpm (4). Nitroglycerin intravenous drip ≥ 200 μg/min. Rest and stress acquisitions by 8-frame gated SPECT (GSPECT) were done 60 to 90 minutes after the injection of the radiopharmaceutical. Two experienced physicians of Department of Nuclear Medicine performed analysis and interpretation of images respectively. The myocardial tomographic image of left ventricular was divided into 17 segments. According to local radioactivity, myocardial intake 99mTc-MIBI was scored as: normal intake/no perfusion defect = 0, decreased/mild perfusion defect=one score, significant decreased/severe perfusion defect = two scores, defect/absence of perfusion = three scores. Total score was divided by 17.

By comparison of the resting and stress images, the defects were identified as persistent or stress induced. The global perfusion defect for each examination was presented by the summed stress score defined as the sum of the stress scores for 17 segments and by the summed rest score defined as the sum of the rest scores. Single-photon emission computed tomography examination was repeated during the 12 months follow up using the same protocol.

Statistical Analysis

Categorical variables are expressed as percentages of the corresponding population and continuous variables as means ± standard deviation. Values of $p < 0.05$ were considered to indicate statistical significance. One-Way Analysis of Variance (ANOVA) was used for comparing of mean values of continuous variables among groups, and post-hoc analysis was performed by Scheffe's test to examine for inter-group differences. Changes between baseline and 12 months follow up was calculated by paired *t*-test. All statistical analyses were conducted with the SPSS statistical package for Vista version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline Characteristics

A total of 222 hypertensive patients were randomized (135 men). Bisoprolol treatment group consisted of 162 patients (125 with stable angina), whereas the non-bisoprolol group consisted of 60 patients (30 with stable angina). No demographic differences were found between groups, as presented in Table I except left ventricular ejection fraction, white blood cells and creatinine level. There was no significant difference of medical and PCI (percutaneous cardiovascular intervention) treatment between bisoprolol and non-bisoprolol groups in hypertensive with stable angina sub-groups (Table II). More than half of the hypertensive patients with stable angina underwent PCI treatment (Table II).

Increase of Endothelial Function and Survival of Myocardium in Bisoprolol Group After 12 Months Follow up

There were no significant differences of FMD and $^{99}Tc^{m}$-MIBI uptake fraction score between bisoprolol and non-bisoprolol groups at baseline (Table III). FMD increased significantly after 12 months treatment in both bisoprolol and non-bisoprolol groups. However, the percent increase of endothelial function in hypertensive with stable angina with bisoprolol treatment was significantly higher than that without bisoprolol treatment ($p < 0.05$, Figure 1A). The same findings were found in $^{99}Tc^{m}$-MIBI uptake fraction score (Figure 1B). A significant improvement of myocardial perfusion defect was observed in bisoprolol group. With bisoprolol therapy, the percent change was significantly higher in hypertensive patients with stable

Table I. Baseline characteristics of bisoprolol and non-bisoprolol groups.

Baseline	Bisoprolol		Non-bisoprolol		
Characteristic	Hypertensive with stable angina (n = 125)	Hypertension-only (n = 37)	Hypertensive with stable angina (n = 30)	Hypertension-only (n = 30)	ANOVA p
Age(yrs)	58.62 ± 12.62	57.80 ± 12.71	60.25 ± 10.23	59.12 ± 6.6	0.742
Gender(male)	75 (60%)	21 (57%)	20 (67%)	19 (63%)	0.253
Current Smokers	25 (20%)	8 (21%)	6 (20%)	5 (16%)	
Medical history					
Hyperlipidemia	18 (14%)	5 (13%)	4 (13%)	5 (16%)	0.527
Clinic					
LVEF (%)	55.36 ± 13.84*	65.58 ± 11.25	54.76 ± 10.43*	64.22 ± 4.23	< 0.001
SBP (mmHg)	136.25 ± 12.81	137.31 ± 13.6	135 ± 19	137 ± 10.12	0.845
DBP (mmHg)	82.32 ± 9.61	83.61 ± 9.32	81.76 ± 13.45	82.65 ± 8.34	0.775
HR (/minute)	75.13 ± 7.12	73.91 ± 6.70	77.45 ± 11.91	75.34 ± 9.23	0.687
BMI	24.32 ± 2.45	23.56 ± 3.56	25.11 ± 2.91	23.9 ± 3.41	0.629
Laboratory					
Fasting glucose (mmol/l)	5.91 ± 0.73	5.24 ± 0.31	6.01 ± 1.7	5.26 ± 0.78	0.021
TC (mmol/l)	5.01 ± 1.14	5.18 ± 0.77	4.98 ± 1.25	5.12 ± 0.52	0.691
LDL-C (mmol/l)	2.9 ± 0.84	3.05 ± 0.33	2.84 ± 1.32	2.91 ± 1.01	0.317
TG (mmol/l)	1.45 ± 0.58	1.32 ± 0.45	1.56 ± 0.47	1.45 ± 0.87	0.542
HDL-C (mmol/l)	1.41 ± 0.27	1.53 ± 0.54	1.45 ± 0.47	1.51 ± 0.63	0.471
WBC (10^9/l)	13.14 ± 3.57*	8.78 ± 3.14	12.47 ± 3.74*	8.51 ± 1.81	0.023
Creatinine (μmol/l)	156 ± 51	90 ± 21	158 ± 97	92 ± 15	0.002

*$p < 0.05$ vs hypertension-only group. LVEF = left ventricular ejection fraction; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; BMI = body mass index; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; WBC = white blood cells.

angina than that of hypertensive only. Furthermore, this improvement was more markedly under stress than rest status (Figure 1B).

Severe Coronary Artery Disease in Hypertension Subjects Could Get Benefit From Bisoprolol Therapy

In all bisoprolol treatment sub-groups, systolic blood pressure, diastolic blood pressure and heart rate were markedly decreased after 12 months follow up, as well as FMD improvement (Table IV, all $p < 0.05$). The $^{99}Tc^m$-MIBI uptake fraction score was also decreased significantly in all four bisoprolol therapy sub-groups, but there was no significant difference in hypertensive-only (1.35 ± 0.41 vs 1.21 ± 0.15, $p > 0.05$) and single-vessel (1.62 ± 0.33 vs 1.53 ± 0.37, $p > 0.05$) sub-groups (Table IV). On the contrary, no significant differ-

Table II. Discharge medications and in hospital percutaneous cardiovascular intervention (PCI) in different groups.

Discharge medications	Bisoprolol		Non-bisoprolol	
	Hypertensive with stable angina (n=125)	Hypertension-only (n=37)	Hypertensive with stable angina (n=30)	Hypertension-only (n=30)
ACEI	118 (84%)	34 (81%)	27 (80%)	26 (78%)
ARB	25 (20%)	8 (22%)	7 (23%)	5 (17%)
Ca channel blockers	61 (49%)	19 (51%)	17 (57%)	15 (50%)
Diuretics	35 (28%)	7 (18%)	7 (23%)	5 (16%)
Aspirin	115 (92%)	0	28 (93%)	0
Nitrates	98 (78%)	0	24 (80%)	0
Statins	72 (58%)	0	17 (57%)	0
PCI in hospital	71 (56%)	0	16 (53%)	0

ACEI: angiotensin-converting-enzyme inhibitors; ARB: angiotensin receptor blockers; PCI: percutaneous coronary intervention.

Table III. Discharge medications and in hospital percutaneous cardiovascular intervention (PCI) in different groups.

			Bisoprolol		Non-bisoprolol	
			Hypertensive with stable angina (n=125)	Hypertension -only (n=37)	Hypertensive with stable angina (n=30)	Hypertension-only (n=30)
FMDt improvemen	Baseline 12 m		5.15 ± 2.07 9.43 ± 2.94	7.82 ± 3.62 11.13 ± 3.73	5.31 ± 2.13 8.67 ± 2.64	7.74 ± 3.57 9.74 ± 3.54
$^{99}Tc^{m}$-MIBI uptake fraction	Baseline	Rest	1.28 ± 0.32*	0.64 ± 0.28	1.30 ± 0.32†	0.59 ± 0.38
		Stress	1.84 ± 0.58*	1.35 ± 0.41	1.79 ± 0.47†	1.42 ± 0.51
	12 m	Rest	1.01 ± 0.21*	0.59 ± 0.41	1.21 ± 0.21†	0.55 ± 0.41
		Stress	1.37 ± 0.25*	1.21 ± 0.15	1.62 ± 0.35†	1.31 ± 0.32

*$p < 0.05$ vs hypertension-only (bisoprolol group); †$p < 0.05$ vs hypertension-only (non-bisoprolol group).

ence of $^{99}Tc^{m}$-MIBI uptake fraction score improvement was observed in non-bisoprolol subgroups (data not shown).

Discussion

In clinical practice, coronary disease and hypertension often occur concurrently. Coronary heart disease continues to be the leading causes of illness and death in adults from developed countries. The prevalence of CAD is closely related to the blood pressure level (particularly the systolic), and the relationship between blood pressure and CAD appears to be linear, continuous, and independent of other risk factors[2,15-17]. Hight BP is the most prevalent cardiovascular risk factor and, consequently, is a leading cause of morbidity and mortality worldwide. There is unequivocal evidence that treatment of hypertension with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and dihydropyridine calcium channel antagonists could lead to an improvement of endothelial function. Coronary atherosclerosis is associated with progressive impairment of coronary endothelial

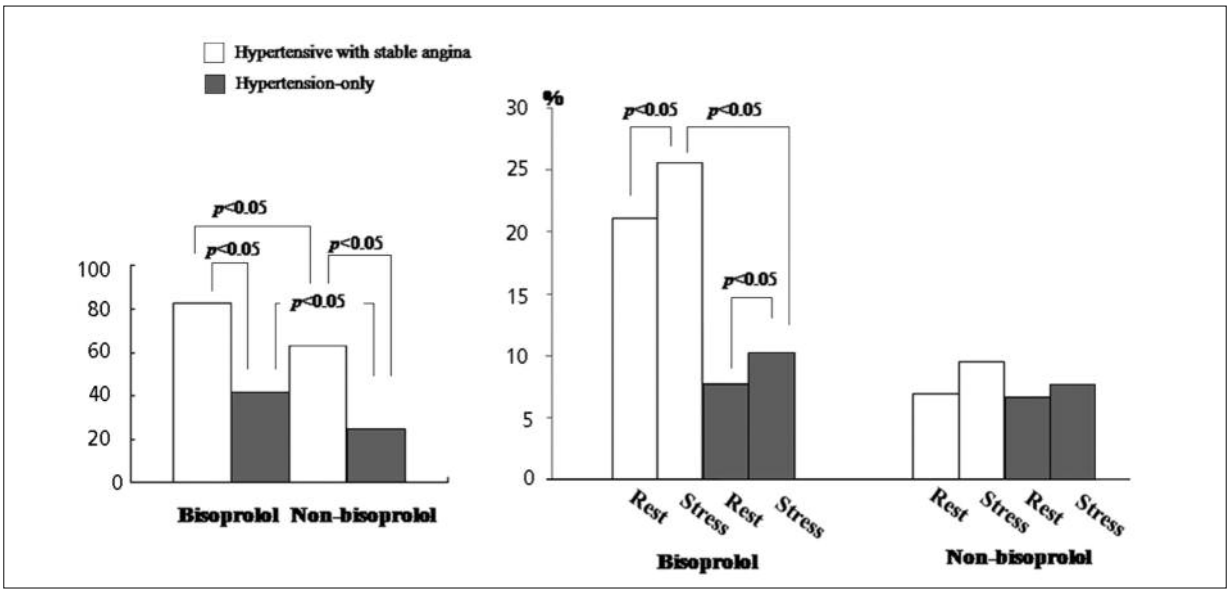

Figure 1. ***A,*** Percentage of FMD improvement during 12 months follow up. ***B,*** Percentages of 99Tcm-MIBI uptake fraction scores improvement during 12 months follow up. White: hypertensive with stable angina; Grey: hypertension-only.

Table IV. Comparison of FMD and $^{99}Tc^{m}$-MIBI uptake fraction between baseline and 12 months follow up (FU) in bisoprolol sub-groups.

	FMD improvement	$^{99}Tc^{m}$-MIBI uptake fraction (stress)	SBP (mmHg)	DBP (mmHg)	HR (minute)
Hypertension-only (n=37)					
Baseline	7.82 ± 3.62	1.35 ± 0.41	136.3 ± 13.6	83.6 ± 9.3	73.9 ± 6.7
12 months FU	11.13 ± 3.73	1.21 ± 0.15	122.5 ± 7.8	75.2 ± 7.4	63.1 ± 6.1
p value	< 0.05	> 0.05	< 0.05	< 0.05	< 0.05
Single-vessel (n=42)					
Baseline	6.17 ± 2.43	1.62 ± 0.33	135.7 ± 12.8	82.8 ± 9.6	75.1 ± 7.3
12 months FU	9.63 ± 2.94	1.53 ± 0.37	123.5 ± 9.5	74.3 ± 6.7	64.3 ± 5.7
p value	< 0.05	> 0.05	< 0.05	< 0.05	< 0.05
Double-vessel (n=44)					
Baseline	5.18 ± 3.23	1.75 ± 0.29	137.1 ± 13.3	81.7 ± 10.1	74.6 ± 6.5
12 months FU	7.93 ± 2.64	1.42 ± 0.36	124.3 ± 9.6	72.7 ± 7.5	62.8 ± 5.7
p value	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Multi-vessel (n=39)					
Baseline	4.23 ± 2.97	1.94 ± 0.23	136.7 ± 11.8	82.3 ± 8.8	75.3 ± 7.1
12 months FU	6.78 ± 3.54	1.57 ± 0.39	124.1 ± 8.7	71.6 ± 6.2	63.2 ± 5.5
p value	< 0.01	< 0.01	< 0.05	< 0.05	< 0.05

function. Angina pectoris is the most common symptom in patients with stable atherosclerosis coronary disease.

Clinical trial evidence to date leads to the conclusion that beta blockers are strongly recommended in post-MI and in all patients with left ventricular dysfunction regardless of symptoms[18]. Their beneficial abilities include improvement of oxygen supply and demand (which can reduce myocardial ischemia), anti-arrhythmic properties, and beneficial effects on cardiac remodeling[18]. In this study, bisoprolol, also a highly selective β1-adrenoceptor antagonist[19], consistent with the well documented effects on the cardiovascular system, i.e slowing of the heart rate, lowing the blood pressure and decrease in myocardial contractility with previous reports[18,20]. In TRECE study, bisoprolol was proved more effective of reducing resting heart rate (RHR) than other BBs in CAD patients. Clinical benefit and prognosis improvement obtained by β-blockers treatment in CAD patients correlate closely with the grade of RHR reduction[21,22]. RHR is influenced by many clinical situations[23], but even taking those into consideration, RHR independently predicts the incidence of coronary events[24].

Additionally, bisoprolol markedly improved endothelial dysfunction in hypertensive patients, especially in those with CAD. Although bisoprolol might not improve the endothelial dysfunction directly[25], the benefits from bisoprolol might include: lowing blood pressure decreases the damage of endothelium; improving cardiac function increases blood supply to the blood vessels; improving of blood supply alleviate structural remodeling of the wall of blood vessels, etc. Currently, another β1AR blocker, Nebivolol is licensed for treatment of hypertension in Europe and the United Kingdom. Similarly, it has no intrinsic sympathomimetic or AR blocking activity at therapeutic doses[9] and it was proved possessing nitric oxide (NO)-mediated vasodilatory properties via its metabolite[26]. It is proved that endothelial function depends on the ability of endothelial cells to produce and release NO – a powerful endogenous vasodilator. Thus, another important mechanism of the improvement of the endothelial dysfunction by bisoprolol might due to the signaling pathway(s) through L-arginine/NO cascade just like nebivolol. In terms of βAR-mediated NO generation in hypertension, little work has been done and the results are still conflicting. Cockcroft et al[27] investigated forearm blood flow by venous occlusion plethysmography and found no difference in isoproterenol-mediated vasodilatation between hypertensive patients and normotensive controls. In the same year, Arribas et al[28] investigated endothelial β AR-mediated vasodilatation in isolated rat aorta and found impairment of the response in spontaneously hypertensive rats.

In this study, endothelium-independent vasodilation by nitroglycerin (GTN) was not measured. However, this vasodilation should not be the major effect although bisoprolol in particular

could affect mechanism different from the endothelial one[28]. Simova et al[30] demonstrated that bisoprolol had no significant improvement of FMD in hypertension. That might be due to the relative small sample size (25 subjects) and short treatment period (eight weeks). Another important difference is that they didn't focus on the hypertension with CAD. Bisoprolol might have efficient improvement in serious cardiovascular dysfunction. It could explain the higher improvement of FMD in hypertension with multivessel coronary artery disease than that of other sub-groups.

In this study, $^{99}Tc^{m}$-MIBI uptake fraction score was used to represent the survival of myocardium. SPECT imaging is certainly more available than Doppler echocardiography and allows a more complete evaluation. In the present study, SPECT was used to evaluate the myocardial function because of its finding intraluminal thrombi but with negative stress ECG. It is likely that the majority of improvement in endothelial function that we observed is due to the decrease of heart rate and blood pressure. Simultaneously, coronary artery dilation from the endothelial function improvement could increase the heart blood supply and heart's pumping power. All of these benefits are likely to contribute to the improvement of the $^{99}Tc^{m}$-MIBI uptake fraction. Similarly with FMD, $^{99}Tc^{m}$-MIBI uptake fraction score was significantly improved in those hypertensive patients especially with serious coronary artery disease. Thus, all the findings suggest that bisoprolol can improve endothelial function and the survival of myocardium in hypertension, especially those with CAD.

Conclusions

Bisoprolol can improve endothelial function and the survival of myocardium in hypertension, especially those with serious CAD.

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