Symposium

The Effects of Verapamil SR and Bisoprolol on Reducing the Sympathetic Nervous System's Activity

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To assess the response of the sympathetic nervous system (SNS) to the handgrip test in essential hypertensive patients and to evaluate the effects of verapamil SR and bisoprolol on the reduction of the SNS's activity. Seventy eight essential hypertensive patients (50 receiving verapamil SR treatment and 28 receiving bisoprolol treatment) took the handgrip test while the SBP, DBP, and HR were measured on three occasions during the test (before test, 3 min after the patients squeezed the handgrip, and 2 min after the handgrip was released). Before and after the patients received Verapamil SR or Bisoprolol treatment, the plasma concentrations of epinephrine(E), norepinephrine (NE), angiotensin-II (AII), aldosterone (ALD), endothelin-1 (ET-1) and renin activity (RA) were measured post-test. 1) In about 70% of the essential hypertensive patients, SNS activity was above normal. Their HR and BP exceeded 20% when responding to stress. 2) In these patients, the baseline plasma concentrations of E, NE, AII, ET-1, ALD, and RA were higher than those whose SNS's activity was normal. 3) After 6 weeks of treatment, all the patients' BPs decreased remarkably. Verapamil SR could reduce the plasma concentrations of NE, AII, and ET-1 and increase RA. Bisoprolol could reduce E and RA. These two antihypertension drugs can both decrease BP and reduce the activity of SNS through different mechanisms. (*Hypertens Res* 2000; 23: 537-540)

Key Words: hypertension, sympathetic nervous activity, verapamil SR, bisoprolol

Introduction

Authoritative researchers have asserted that the autonomic systems of patients with a risk of hypertension react in a unique way to emotional stress, thereby demonstrating a psychophysiological neurovegetative hyperdysreactivity. The plasma concentrations of catecholamine, Angiotensin-II (AII), and endothelin (ET-1) are strong indicators of the state of the sympathetic nervous system. Hypertensive patients react to stimuli such as the cold pressor test (immersion of a limb in ice water for 1 min) and the handgrip test (isometric contraction at 30% of the maximum individual contractile capacity) with a higher significant cardiovascular response (1). This response was studied through the handgrip test in our research. Furthermore, pharmacological therapy employing a calcium

channel blocker — Verapamil SR or the β receptor blocker bisoprolol which was applied to the subjects, definitely encouraged us to assess the different efficiency of the two antihypertensive agents. In other words, the handgrip test was used as a tool to study the effects of the two antihypertensive drugs on the cardiovascular and neurovegetative systems.

Subjects and Methods

Subjects

Seventy-eight essential hypertensive patients were recruited from our hospital outpatient clinics or infirmary during a one-year period (Feb. 1998-Feb. 1999). The patients were allocated to one of two treatment groups (starting with verapamil SR or bisoprolol). Group A, 50

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patients (26 males, 24 females), aged 30–68 (an average of 56.2 ± 8.2), received the verapamil SR treatment. The other 28 patients (16 males and 12 females), aged 32–62 (an average of 52.6 ± 8.2) took bisoprolol as Group B. All patients suffering from secondary hypertension were excluded. After an initial physical examination, the antihypertensive medication was discontinued one week before the study. Hypertension was defined as systolic blood pressure (SBP) higher than 140 mmHg and diastolic blood pressure (DBP) higher than 90 mmHg on three occasions during the week before the study. The study was approved by the institutional ethical committee and the subjects gave informed consent.

Protocol

Blood Pressure Measurement and Handgrip Test

At each visit, which was arranged between 8 and 10 AM, the same arm of the patient (rather than the one the patient chose to grip with) should be used for the blood pressure measurements in a sitting position. The handgrip test was conducted by using a Martin Vigorimeter. After a 30-min rest, blood pressure and heart rate were measured and recorded as pre-grip measurements. The same measurements were then taken when the patients squeezed the handgrip continuously for 3 min using 30% of his/her maximum strength. Two minutes after the patient had stopped the handgrip test, his/her blood pressure and heart rate were measured again and recorded as post-grip measurements.

Measurement of Plasma CA Concentration

Seven microliters of venous blood for catecholamine measurements were drawn into a polypropylene syringe during the pre-grip and post-grip tests before the patient had taken any antihypertensive drugs and during the post-grip test six weeks after the patient had received medication. The blood samples were immediately mixed with 2% EDTA and centrifuged at 4°C for 20 min at a velocity of 2,500 cycles per minute. The plasmas were frozen at -70°C until the catecholamine measurements were taken within a few weeks. Plasma catecholamines were measured using high performance liquid chromatography according to Ma Xueyi as previously reported (2).

Measurement of Plasma PRA and Angiotensin-II (AII)

Three microliters of blood for PRA and AII measurements were drawn from a forearm vein on the same three occasions mentioned above. The samples were mixed with 7 μl of 10% EDTA and Oxine Sulpate, and then centrifuged at 4°C similar to the CA measurement. Plasma PRA and AII were measured using a series of test kits provided by the Beijing Free Bioengineering Co., strictly according to the instructions given.

ET-1 Measurement

On the same occasions, we drew 2 μl of venous blood for ET-1 measurement. As soon as the samples were taken from the vein, they were mixed with 10% EDTA and aprotinin, each at 50 μl . They were then centrifuged below 4°C for 15 min at a speed of 3,000 cycles per minute. The variance was 5% in batch and <10% among batches.

Administration Design

Verapamil SR, which was provided by Knoll Pharmaceuticals (Batch No. 784), was given at 240 mg daily. On the other hand, bisoprolol, which was supplied by Merk Pharmaceuticals (Batch No. 12635 059), was given at 5 mg daily. Both of the two drugs were administered for six weeks. Throughout the study, the patients were closely followed up and took the handgrip test before and after the treatment.

Statistical Analysis

Data was expressed as mean $\pm$ SD. The change in each parameter from pre- to post-stress was analyzed within groups using paired tests. Such change was compared between the two different SNS's activation types using Fisher's exact test when the variance was regular or the rank sum test when it was not. A *p* value of less than 0.05 was considered statistically significant. All the calculations were executed using GPIS software on computers.

Results

1. Before treatment, the handgrips could induce an increase of blood pressure and heart rate. In Group A, 35 patients' (about 70%) BP and HR exceeded more than 20% of the baseline values from pre- to post-stress. So did 20 patients (about 71%) in Group B. Therefore, nearly 70% of the hypertensive patients in the study experienced hyperdysreactivity to stress while the other 30% of the patients were determined as normal (Table 1).
2. After six weeks of antihypertensive treatment, we found that stress could no longer evoke the rise of BP and HR in all the patients, regardless of the type of sympathetic activation. This phenomenon possibly suggested that the two antihypertensive drugs can lower the SNS's activity while decreasing BP (Table 1). Furthermore, the post-handgrip BP and HR decreased more significantly in those patients with hyperactivity after treatment. This suggested that the patients who had hyperactivity of SNS are more sensitive to the two medications than are others.
3. Throughout the study, we determined the plasma concentrations of CA, AII, PRA, and ET-1. On the basis of our observation, we found: (1) Before treatment, there was no significant change of vasoactive substances during stress. (2) The baseline values of those substances in pa-

Table 1. The Changes of BP and HR from Pre- to Post-Hand Grip Test before and after Therapy in Two Groups ($\bar{X} \pm SD$)

	SBP (mmHg)			DBP (mmHg)			Δ BP			HR (bpm)		
	0 week	6 week	Δ SBP	0 week	6 week	Δ DBP	0 week	6 week	Δ HR	0 week	6 week	Δ HR
Group A (Verapamil SR)												
Hyperactivity (n=35)												
Pre-grip	154.2 $\pm$ 4.6	138.4 $\pm$ 2.4**	16.0 $\pm$ 4.0	8.2 $\pm$ 1.8	85.8 $\pm$ 1.3**	13.4 $\pm$ 1.5	75.6 $\pm$ 2.4	72.0 $\pm$ 1.2	3.6 $\pm$ 2.0			
Post-grip	194.2 $\pm$ 4.1	150.2 $\pm$ 3.4**	44.0 $\pm$ 3.6 $\Delta\Delta$	124.2 $\pm$ 1.8	92.6 $\pm$ 1.3**	32.2 $\pm$ 1.6 Δ	96.0 $\pm$ 3.2**	77.2 $\pm$ 2.1	19.0 $\pm$ 2.7 Δ			
BP $\uparrow$ (%)	20.3	7.8		20.9	7.3		21.3	6.7				
Normoactivity (n=15)												
Pre-grip	159.3 $\pm$ 3.3	138.4 $\pm$ 3.2**	21.0 $\pm$ 3.3	95.0 $\pm$ 1.8	88.4 $\pm$ 1.2*	6.6 $\pm$ 1.6	76.4 $\pm$ 1.8	74.4 $\pm$ 1.8	2.0 $\pm$ 1.8			
Post-grip	168.6 $\pm$ 3.2**	144.0 $\pm$ 4.6**	24.6 $\pm$ 4.0	102.2 $\pm$ 2.0	94.2 $\pm$ 1.3*	8.0 $\pm$ 1.5	82.1 $\pm$ 2.1	78.2 $\pm$ 2.1*	4.0 $\pm$ 2.1			
BP $\uparrow$ (%)	5.5	3.8		7.0	6.1		6.9	4.8				
Group B (Bisoprolol)												
Hyperactivity (n=20)												
Pre-grip	158.8 $\pm$ 4.3	138.2 $\pm$ 4.6**	20.5 $\pm$ 4.4	95.2 $\pm$ 2.8	90.2 $\pm$ 2.4*	5.0 $\pm$ 2.6	80.2 $\pm$ 1.4	76.4 $\pm$ 1.8	3.8 $\pm$ 1.6			
Post-grip	198.8 $\pm$ 4.5	148.4 $\pm$ 3.8**	49.5 $\pm$ 4.0 Δ	120.2 $\pm$ 2.4	96.2 $\pm$ 2.1**	24.0 $\pm$ 2.2 $\Delta\Delta$	102.4 $\pm$ 2.1	88.2 $\pm$ 2.1*	14.2 $\pm$ 2.1 Δ			
BP $\uparrow$ (%)	20.1	6.8		20.7	6.2		21.6	13.3				
Normoactivity (n=8)												
Pre-grip	160.2 $\pm$ 4.2	138.4 $\pm$ 3.2**	22.6 $\pm$ 3.8	96.5 $\pm$ 2.4	90.4 $\pm$ 1.8*	6.1 $\pm$ 2.2	78.6 $\pm$ 1.8	72.2 $\pm$ 2.0	6.3 $\pm$ 1.9			
Post-grip	166.2 $\pm$ 4.1**	144.2 $\pm$ 4.1**	22.0 $\pm$ 4.1	104.6 $\pm$ 2.6**	95.6 $\pm$ 2.0**	9.0 $\pm$ 2.3	86.4 $\pm$ 2.0#	78.4 $\pm$ 1.8*	8.0 $\pm$ 2.0			
BP $\uparrow$ (%)		3.6	4.0	7.7	5.4		9.2	7.6				

Significant change of the post-grip from 0 weeks to 6 weeks: * $p < 0.05$, ** $p < 0.01$. Significant difference between hyperactivity and normoactivity: # $p < 0.05$, ## $p < 0.01$. Significant difference of Δ BP and Δ HR between hyperactivity and normoactivity: $\Delta p < 0.05$, $\Delta\Delta p < 0.01$ (Δ BP, Δ HR: the decrease of BP and HR after 6 week treatment).

tients with hyperdysreactivity were higher than in others. (3) Both the two drugs could decrease the plasma level of vascular substances. The difference could be due to Verapamil SR's ability to decrease NE, ET-1, and AII, and increase PRA, while Bisoprolol could lower the plasma levels of E and AII (Table 2).

Discussion

Sympathetic activity can be affected by many factors such as heredity, behavior, and social culture. These factors interact with each other, and in combination they exert a significant effect on the sympathetic nervous system. Various studies have demonstrated that sympathetic hyperactivation in essential hypertension is not rare. Moreover, other researchers have shown that sympathetic activation can be triggered by environmental stress through the baroreceptor (3). The nervous system, which regulates the cardiocirculatory system, is excited by the handgrip test. Through medullar-sympathetic centers and pathways, it stimulates the release of the neurotransmitters (such as NE and E) and thus increases cardiac output and peripheral resistance. As a result, the blood pressure increases and the heart rate decreases. According to our experience, a BP and HR exceed more than 20% of their baseline values during stress indicates hyperdysreactivity. The vasoactive substances in the circulation, especially NE, AII and ET-1, can indicate sympathetic reactivity (4). The higher the plasma levels of NE and AII are, the stronger the sympathetic activity is. In this study, we used handgrip tests to induce the subjects' sympathetic activation. As we observed, about 70% of the hypertensive patients' BP and HR exceeded more than 20% in the peak of the stress and returned to the baseline level 2 min after the stress. The sympathetic activities of the other 30% of the patients were normal. Their BP and HR showed increases of only 8-12% from pre- to post-stress. Furthermore, no subject showed a significant increase in plasma hormones following the handgrip test. But there were differences between the two hypertensive types with different sympathetic activities. In comparison, the patients with hyperdysreactivity had higher plasma baseline values of NE, ET-1, PRA, and AII ($p < 0.01$). On the basis of this data, we can conclude that the rise of the BP and HR during acute stress is the result of the abnormal regulation of the nervous system, yet a long-run process of response to chronic stress will result in high plasma substance levels. All these indications have led us to a conclusion, nevertheless, that it may be possible that stress is an important factor in the starting mechanism of hypertension.

Both of the therapeutic approaches induced a significant reduction of the blood pressure and heart rate. Furthermore, the BP and HR did not increase significantly when the hypertension responded to stress. In addition,

Table 2. The Changes of Post-Grip Plasma Concentrations of Cardiovascular Activity Substances from Pre- to Post- Therapy in Two Groups ($\bar{X} \pm \text{SD}$)

		Verapamil SR (n=50)		Bisoprolol (n=28)	
		Hyperactivity (n=35)	Normoactivity (n=15)	Hyperactivity (n=20)	Normoactivity (n=8)
NE (pg/ml)	0 week	592.4 $\pm$ 34.5	298.4 $\pm$ 27.6**	424.3 $\pm$ 40.7	274.6 $\pm$ 39.1*
	6 week	292.4 $\pm$ 31.2##	180.4 $\pm$ 27.4#,**	320.3 $\pm$ 27.1	230.6 $\pm$ 34.8*
E (pg/ml)	0 week	82.4 $\pm$ 4.4	48.4 $\pm$ 2.5**	72.4 $\pm$ 2.9	42.8 $\pm$ 3.6**
	6 week	71.5 $\pm$ 3.1#	41.8 $\pm$ 2.4**	38.8 $\pm$ 2.1##	22.1 $\pm$ 2.5**,**
ET-1 (pg/ml)	0 week	72.4 $\pm$ 1.8	51.2 $\pm$ 2.4**	67.2 $\pm$ 2.4	40.8 $\pm$ 2.4**
	6 week	34.4 $\pm$ 1.4##	30.2 $\pm$ 2.1##	56.3 $\pm$ 2.3#	38.7 $\pm$ 2.4**
PRA (ng/ml)	0 week	0.58 $\pm$ 0.2	0.42 $\pm$ 0.1**	0.54 $\pm$ 0.1	0.42 $\pm$ 0.08*
	6 week	1.34 $\pm$ 0.1##	0.68 $\pm$ 0.1#,**	0.21 $\pm$ 0.08##	0.26 $\pm$ 0.06##
AII (pg/ml)	0 week	92.6 $\pm$ 2.2	48.4 $\pm$ 2.6**	72.4 $\pm$ 2.3	30.4 $\pm$ 2.9**
	6 week	38.2 $\pm$ 1.6##	26.2 $\pm$ 2.0##,*	66.3 $\pm$ 2.2#	29.9 $\pm$ 2.8

Significant change of post-grip from 0 weeks to 6 weeks: # $p < 0.05$, ## $p < 0.01$. Significant difference between hyperactivity and normoactivity: * $p < 0.05$, ** $p < 0.01$.

the plasma levels of the vasoactive substances decreased remarkably, but they presented different profiles in the two groups. Verapamil SR induced a marked decrease of NE, AII, and ET. The possible mechanism might involved the drug blocking the calcium channel, with this reducing the calcium which is important in releasing neurotransmitters in nerve cells. These decreases are predominantly caused by central effects, presumably in the nucleus tractus solitarius, resulting in a decrease in sympathetic outflow. In addition, an inhibition of the energy-dependent catecholamine uptake into catecholamine vesicles, an induction of leakage of the amines from their vesicles, and an activation of the metabolic degradation of catecholamines via the catalyzing enzyme catechol-O-methyltransferase may contribute to an overall decrease in sympathetic activity (5). Therefore the BP and HR will be decreased when responding to stress, thus improving the whole cardiovascular conditions in hypertensive patients. At the same time, Verapamil can increase plasma renin activity. A possible mechanism is that the release of PRA is related to intracellular calcium. The increase of intracellular calcium concentration will inhibit the release of PRA. Verapamil is a kind of calcium ion channel blocker which can block the L-type calcium channel so that it can decrease the calcium concentration in the blood cells and thus increase the plasma level of PRA. On the other hand, Bisoprolol apparently reduces the levels of E and PRA. It is hypothesized that this agent will lower the excitations of the cardiovascular centers by blocking the cardiac and presynaptic β receptors (6). This leads to the same effects as does verapamil. These findings suggest that they can both restrain sympathetic overactivity and reduce responses to stress in hypertensive

patients.

In conclusion, verapamil SR should be administrated to those with high plasma levels of NE, AII, and ET-1 and with abnormal sympathetic nerve activities, while bisoprolol should be prescribed to patients with high E and PRA levels. Both of these two antihypertensive drugs can reduce sympathetic activation, thereby lowering the blood pressure steadily.

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