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Abstract

Nipradilol is a newly synthesized beta-blocker which has a propranolol-like structure and contains a nitrate moiety. To examine the effect of nipradilol on venous blood flow, a single oral dose of nipradilol (6 mg) and propranolol (20 mg) was administered in the same 15 normal volunteers on separate days. Peak flow velocities, flow velocity integrals, and the diameter of the right brachiocephalic vein were measured before and 2 h after drug administration using Doppler echocardiography. These two beta-blockers significantly decreased systolic blood pressure to the same extent as they did heart rate. Nipradilol dilated the venous diameter by 8% and decreased peak flow velocity by 8% during systole and 9% during diastole. The flow velocity integral in one cardiac cycle also decreased significantly by 14%. Propranolol, however, failed to modify these parameters. These results suggest that nipradilol decreased venous return through its nitroglycerin-like direct vasodilating action.

KEYWORDS: Doppler echocardiography, venous return, nipradilol

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Effects of Nipradilol on Venous Hemodynamics: Evaluation with a Doppler Blood Flow Method

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Nipradiol is a newly synthesized β-blocker which has a propranolol-like structure and contains a nitrate moiety. To examine the effect of nipradilol on venous blood flow, a single oral dose of nipradilol (6mg) and propranolol (20mg) was administered in the same 15 normal volunteers on separate days. Peak flow velocities, flow velocity integrals, and the diameter of the right brachiocephalic vein were measured before and 2h after drug administration using Doppler echocardiography. These two β-blockers significantly decreased systolic blood pressure to the same extent as they did heart rate. Nipradilol dilated the venous diameter by 8% and decreased peak flow velocity by 8% during systole and 9% during diastole. The flow velocity integral in one cardiac cycle also decreased significantly by 14%. Propranolol, however, failed to modify these parameters. These results suggest that nipradilol decreased venous retern through its nitroglycerin-like direct vasodilating action.

Key words: Doppler echocardiography, venous return, nipradilol.

Nipradilol (K-351), 3,4-dihydro-8-(2-hydroxy-3-isopropylamino) propoxy-3-nitroxy-2H-1-benzopyran, is a recently synthesized agent with a propranolol-like structure and contains a nitrate moiety (1). Nipradilol demonstrates not only non-selective β-adrenoceptor antagonist effects but also a nitroglycerin-like vasodilating action, and this vasodilating effect is expected to act more profoundly on the venous than on the arterial bed (2). Previous experimental study demonstrated that nipradilol produced vasodilation of isolated canine mesenteric vein (1). However, few reports have appeared concerning the effect of nipradilol on the venous system of human subjects.

Pulsed wave Doppler echocardiography is an easy non-invasive technique used to assess the flow velocity in the central veins, and it is considered to be useful for evaluating the hemodynamics of the venous system (3, 4). In the present study, we thus attempted to evaluate directly the effects of nipradilol on the venous system of healthy volunteers using Doppler echocardiography.

Subjects and Methods

Study Subjects

Fifteen healthy male volunteers (23 to 27 years of age) with no history of cardiovascular disease were enrolled in this study. All subjects were asymptomatic and normotensive, and the results of physical examinations were all normal. Laboratory examinations, and two-dimensional and routine Doppler echocardiographic examination were also normal. All subjects had a normal sinus rhythm and none were taking concurrent medication.

Two-dimensional echocardiogram and Doppler flow velocities were recorded using a Hitachi EUB-450 ultrasonograph with simultaneous recordings of a lead II electrocardiogram and phonocardiogram. All subjects were requested to rest in the supine position for at least 30 min before examination and remained in this position during measurement. A 5-MHz ultrasonic transducer was positioned on the right supraclavicular fossa. This position allowed the right brachiocephalic vein to be clearly visualized in all subjects. The diameter of the right brachiocephalic vein was measured about 1 cm proximal to the junction of the right subclavian and internal jugular veins. The venous flow velocity of 4 to 5 consecutive heart beats was recorded by the pulsed wave Doppler method positioning the sampling point in the center of the right brachiocephalic vein where the angle between the

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direction of beams and the long axis of the vessel was maintained at around 30 degrees.

Peak flow velocities and flow velocity integrals of 3 consecutive beats in each recording were averaged and used for analysis. One cardiac cycle was divided into systole and distole (Fig. 1). Flow velocity integrals were obtained as the area under the flow velocity curve, and measured separately during systole and distole. Blood pressure was measured over the left brachial artery using a sphygmomanometer.

Study Protocol

Effect of respiration. We studied the effect of respiration on the venous diameter and the flow velocity in eight subjects. In this study, the subjects were requested to remain quiet for at least 30 min before study, and recordings were made during a brief breath holding at the end of quiet inspiration. Following this, the subject was allowed to continue quiet respiration for 1 min and then the second recording was repeated with a breath holding at the end of expiration. All recordings were completed within 10 sec.

Effects of nipradilol and propranolol on venous hemodynamics. The effects of a single oral administration of β-adrenoceptor antagonists, propranolol and nipradilol, were compared. Propranolol 20 mg and nipradilol 6 mg were administered to 15 subjects on separate days, 7 days apart. Before and 2 h after the administration of each drug, the diameter and flow velocity of the brachiocephalic vein were recorded along with simultaneous measurement of arterial blood pressure and heart rate.

Data Analysis

Group data were expressed as the mean ± standard deviation (SD). Student's t-test was used for comparing the data within a group, and a P value less than 0.05 was considered significant.

Results

Effects of respiration on diameter and blood flow velocity of the brachiocephalic vein. Fig. 1 shows actual records obtained at end-

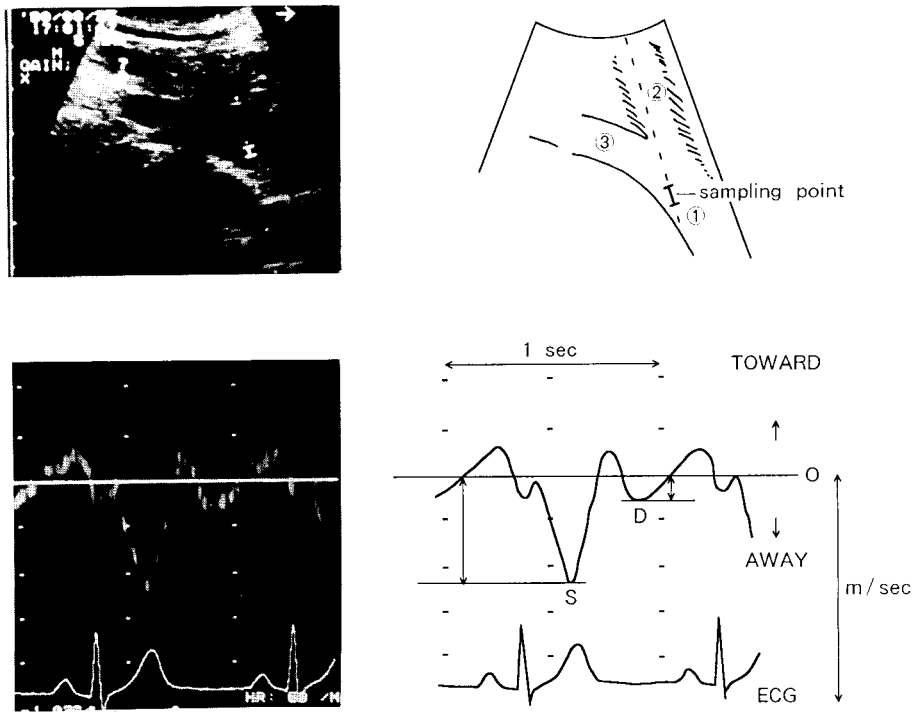

Fig. 1 Upper panel: Actual record and schematic illustration of the right brachiocephalic vein. Sampling point is within the brachiocephalic vein. ① = Brachiocephalic vein; ② = Internal jugular vein; ③ = Subclavian vein. Lower panel: Blood flow pattern of the brachiocephalic vein before drug administration. O = zero line; S = peak flow velocity in systole; D = peak flow velocity in diastole; ECG = electrocardiogram.

expiration and schematic illustrations of brachiocephalic vein flow. The normal flow pattern exhibited two peaks which appeared in the systole and diastole of the ventricle. The peak flow velocity and flow velocity integral of each phase in one cardiac cycle were greater during systole.

Respiration modified the vein flow velocity significantly with an increase in velocity during inspiration and a decrease during expiration. The systolic peak flow velocity in the eight subjects averaged 41 ± 2 cm/sec during inspiration and 37 ± 6 cm/sec during expiration, and peak diastolic flow velocity was 23 ± 4 cm/sec during inspiration and 18 ± 2 cm/sec during expiration, though these changes did not reach a significant level.

Effects of nipradilol and propranolol on the venous hemodynamics. The effects of the β-blockers on arterial blood pressure and heart rate are summarized in Table 1. Systolic blood pressure was significantly decreased with propranolol (7 %, $P < 0.01$) and nipradilol (9 %, $P < 0.01$), but diastolic blood pressure was not affected by either drug. Heart rate was significantly decreased with both propranolol (11 %, $P < 0.01$) and nipradilol (17 %, $P < 0.01$). The extent of the inhibitory effects on systolic blood pressure and heart rate did not significantly differ between these two agents.

Table 2 summarizes the changes in the vessel diameter and blood flow velocity of the brachiocephalic vein before and after drug administration. Propranolol affected neither the diameter of the vein nor venous flow velocity. Peak flow velocities and flow velocity integrals remained unchanged after the administration of propranolol.

Unlike propranolol, nipradilol significantly increased the vessel diameter by 8 % and decreased the flow velocity of the brachiocephalic vein. Peak flow velocity decreased significantly during systole, but did not change during diastole 2 h after the administration of nipradilol.

Fig. 2 shows the percent changes in the flow velocity integrals after nipradilol administration. Nipradilol decreased the flow velocity integral during systole ($P < 0.05$), but not during diastole. The flow velocity integral in one cardiac cycle also decreased significantly ($P < 0.05$).

Table 1 Changes in arterial blood pressure and heart rate following administration of β-blockers

Drug	Blood pressure (mmHg)				Heart rate (beats/min)	
	Systole		Diastole			
	Before	2 h	Before	2 h	Before	2 h
Propranolol	116 ± 8	110 ± 11*	62 ± 10	63 ± 9	69 ± 6	61 ± 7*
Nipradilol	115 ± 7	105 ± 6*	69 ± 9	66 ± 8	60 ± 9	58 ± 5*

Values are expressed as mean ± standard deviation.
Difference from pre-administration values was statistically significant at * $P < 0.01$.

Table 2 Changes in diameter and peak flow velocity of the brachiocephalic vein

Drug	Diameter (mm)		Peak flow velocity (cm/sec)			
			Systole		Diastole	
	Before	2 h	Before	2 h	Before	2 h
Propranolol	11.8 ± 1.9	12.2 ± 1.7	34 ± 5	36 ± 8	20 ± 7	21 ± 5
Nipradilol	12.5 ± 1.6	13.4 ± 1.8*	34 ± 10	31 ± 8*	19 ± 5	16 ± 5

Values are expressed as mean ± standard deviation.
Difference from pre-administration values was statistically significant at * $P < 0.05$.

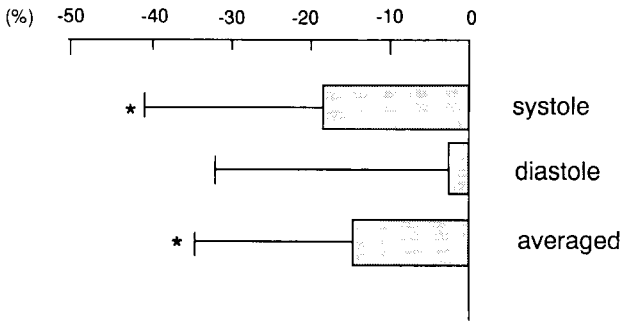

Fig. 2 Percent changes in flow velocity integral after nipradilol administration. Systole = % changes during systole; diastole = % changes during diastole; averaged = changes in flow velocity integral in one cardiac cycle.
* $P < 0.05$ before nipradilol administration.

Discussion

The present study demonstrates that in normal subjects, nipradilol reduced peak flow velocities and dilated the diameter of the brachiocephalic vein, while propranolol failed to modify either the venous flow velocity or diameter. These results suggest that nipradilol affects venous flow through a mechanism unrelated to β-adrenoceptors.

In normal subjects, venous return is affected by respiration possibly due to changes in intrathoracic pressure. Several investigators (5) reported that during inspiration, intrathoracic pressure registers below zero and venous flow return increases in association with the negative intrathoracic pressure, and that during expiration a decrease occurs in venous flow return. The present results concerning the effect of respiration on the central veins were consistent with the previous findings: the peak flow velocity of venous return increased with inspiration and decreased with expiration. Therefore, to avoid the effects of respiration, we investigated the effects of each drug on venous diameter and flow through breath holding at the end of quiet expiration.

In this study, we measured only the transverse diameter of the vein. Sakai *et al.* (6) demonstrated using ultrasonography that there were high correlations between anteroposterior diameter and cross-sectional area of the inferior vena cava. Therefore, the transverse diameter could well reflect the cross-sectional area of the brachiocephalic vein.

In the present results, two β-blockers, propranolol and nipradilol, decreased heart rate to the same extent. Therefore, the dose of each drug was sufficient to block the β-adrenoceptors to similar extent. It is known that β-blockers decrease the cardiac output, and that in the experimetal studies in the dog (7, 8), the decrease in cardiac output by the β-blocker due to decreased venous return. The difference between our results and the previous data regarding the venous system (7, 8) may be mainly due to the different methods used in the venous flow analysis. The previous investigations estimated venous return as the volume per min, but we measured the effects of β-blockers on venous return within one cardiac cycle. In the previous studies (7, 8), the decrease in venous return per min mainly results from the decrease of heart rate. Therefore, the venous return in one cardiac cycle may not necessarily decrease.

On the other hand, nipradilol significantly decreased the flow velocities. Nipradilol was shown to have a weak α-adrenoceptor blocking action (9, 10), which may decrease venous return. It is unlikely that the α-adrenoceptor blocking action of nipradilol is involved in the decreased venous flow velocity because this blocking action is negligible. Nipradilol has a nitroxy moiety in its chemical structure and this structural difference may account for the difference between the vasodilatory effect produced by propranolol and nipradilol. Nipradilol is expected to produce nitroglycerin-like direct vasodilating action (1) in addition to non-selective β-adrenoceptor blockade. It is known that nitroglycerin directly dilates peripheral vessels and that its effect is more profound on the venous bed than on the arterial, resulting in a reduction in venous return (11). In fact, in an experimental study (9), nipradilol caused a striking decrease in venous return due to the direct vasodilating action. Inoue *et al.* (12) observed in humans that nipradilol reduced the pulmonary artery wedge pressure after a single oral administration. These reports are consistent with the present results which indicate that nipradilol has a vasodilatory action.

The product of the cross-sectional area and mean flow velocity represents the blood flow volume of the vessel (13). However, since the cross-sectional shape of the vein is oval, the changes in the transverse diameter of the

vein do not quantitatively represent the cross-sectional area of the vessel. In the present study, we did not attempt to calculate the flow volume in the brachiocephalic vein, because it was technically difficult to measure the exact cross-sectional area of the vessel.

In conclusion, our results demonstrated the venous vasodilatory effect of nipradilol in addition to its β-adrenoceptor blocking action.

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