Heart rate responses during treatment of hypertension with propranolol

The clinical usefulness of the nitroglycerin test

Increments in heart rate during the TNG test (sublingual nitroglycerin with assumption of upright posture), passive head-up tilt, and postrecumbency standing were compared to the effects of intravenous isoproterenol in 15 mild hypertensives during administration of placebo and two dosage levels of propranolol. TNG test results correlated with responsiveness to isoproterenol, but nitroglycerin tachycardia was reduced only about 50% during propranolol treatment. The TNG response was almost maximally inhibited by 160 mg/day of propranolol while the response to postrecumbency standing was inhibited only by a dose of 320 mg/day. The results indicate that: (1) the TNG test is of limited value in the assessment of beta adrenergic blockade in hypertensive patients, and (2) propranolol in a dose of 160 mg/day induces near-maximal cardiac blockade.

Andrew J. Zweifler, M.D., and Lennart Hansson, M.D.* *Ann Arbor, Mich.*
Department of Internal Medicine, Hypertension Section, University of Michigan Medical Center

The clinical effects of beta adrenergic blocking drugs have been investigated extensively and there has been an expansion of the uses of beta receptor blocking drugs, e.g., in the treatment of angina pectoris and hypertension.[7, 9, 10, 18]

Intravenous infusion of the specific beta receptor agonist, isoproterenol, has been used to test the degree of blockade during administration of beta adrenergic blockers.[2, 17] Fitzgerald[6] suggested that the increase of heart rate following sublingual nitroglycerin provides a simpler means for clinical estimation of the degree of beta receptor blockade.

In our study, two indirect methods for estimation of the degree of beta adrenergic blockade have been compared to the effects of intravenous administration of isoproterenol: the effect on heart rate of (1) sublingual nitroglycerin with assumption of upright postures, and (2) 10 min of 45° head-up tilt. These maneuvers have been compared during administration of placebo and two dosage levels of propranolol to 15 male subjects with mild essential hypertension. The findings were also

Supported by grants from the Michigan Heart Association, Ayerst Laboratories (Dr. Roger G. Mazlen), United States Public Health Service Nos. 5-MO1-RR-42 and 2-P11-GM-155559. Dr. Hansson was the recipient of a travel grant from the Swedish Medical Research Council and a grant from the Swedish National Association Against Heart and Chest Diseases.

Received for publication Oct. 16, 1975.

Accepted for publication Jan. 15, 1976.

Reprint requests to: Dr. Andrew J. Zweifler, Department of Internal Medicine, Hypertension Section, University of Michigan Medical Center, Ann Arbor, Mich. 48104.

*Present address: Department of Internal Medicine V, Sahlgrenska Hospital, University of Göteborg, Göteborg, Sweden.

Table I. *Patient information*

Patient No.	*Age (yr)*	*Race**	*Eye grounds†*	*Serum creatinine (mg/100 ml)*	*LVH‡*	*Initial BP§ (mm Hg)*
1	50	C	I	0.9	–	159/ 98
2	50	B	II	1.1	–	150/110
3	55	B	I	1.0	–	155/110
4	53	C	I	1.0	–	180/120
5	66	C	I	1.2	–	169/ 86
6	40	C	II	1.6	–	174/137
7	27	B	0	1.1	–	134/ 95
8	52	C	I	0.9	–	155/108
9	49	C	II	1.1	+	200/128
10	45	C	II	1.2	–	161/111
11	44	C	I	1.0	–	177/107
12	41	C	II	1.1	+	184/105
13	43	C	II	1.0	–	140/ 96
14	35	C	II	0.9	–	162/110
15	26	C	I	1.1	–	165/ 90

*C: Caucasian; B: Black.

†Keith, Wagner, and Barker classification.

‡Left ventricular hypertrophy in ECG or chest x-ray.

§Measured after 15-min recumbency in the clinic following 4 wk of placebo treatment.

Table II. *Change in heart rate (beats/min ± SEM) during various stimulating maneuvers*

	Placebo		*Propranolol (2 wk)*		*Propranolol (4 wk)*	
Stimulus	*N*	*Heart rate*	*N*	*Heart rate*	*N*	*Heart rate*
Nitroglycerin and standing	14	+37 ± 3.8	13	+21 ± 3.1*	12	+17 ± 2.5†
Isoproterenol (3.0 μg/min × 3 min)	15	+41 ± 3.5	—	—	14	+ 5 ± 1.1†
Tilt (45° × 10 min)	14	+ 8 ± 2.2	—	—	11	+ 3 ± 1.0
Standing (2 min)	13	+ 9 ± 2.8	15	+ 6 ± 1.3	15	+ 4 ± 1.8

Heart rate responses in all patients during the different treatment periods.

Statistical comparisons within the group, compared to the placebo value (paired t test).

*$p < 0.01$; †$p < 0.001$.

compared with increases in heart rate induced by standing during clinic visits and with plasma propranolol concentrations.

Methods

Material. The subjects were 15 male patients with mild to moderate essential hypertension (Table I), average age 44 yr (range, 26 to 66). Before entering the study all patients but two were receiving antihypertensive therapy, usually alpha methyldopa with or without diuretics. Secondary causes of hypertension were excluded by thorough clinical examination, rapid-sequence intravenous urography, and laboratory studies (serum electrolytes, creatinine clearance, plasma renin activity, and urinary excretion of aldosterone, epinephrine, and norepinephrine).

Heart rate response tests.

Nitroglycerin and standing. Pulse rate was measured at the wrist by one of the investigators (L. H.) after at least 15 min of recumbent

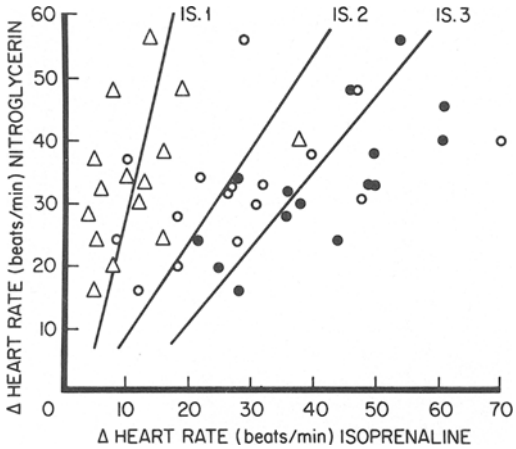

Fig. 1. Correlations between increase of heart rate in response to sublingual nitroglycerin and isoproterenol infusions during placebo therapy. Δ, Isoproterenol, 1.0 μg/min ($r = 0.351$, $p > 0.05$). ○, 2.0 μg/min ($r = 0.510$, $p < 0.05$). ●, 3.0 μg/min ($r = 0.633$, $p < 0.005$).

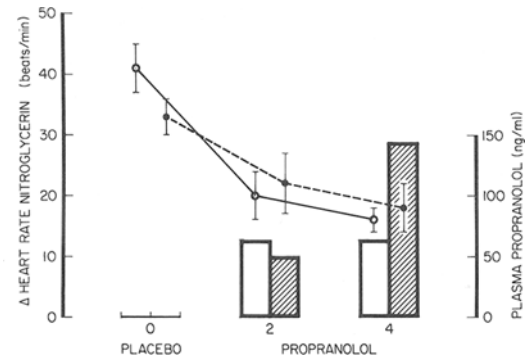

Fig. 2. TNG test results (± SEM) before and during propranolol therapy. Patients treated with 160 mg/day throughout (open circles) compared to those increased to 320 mg/day during weeks 3 and 4 (closed circles). Clear bars refer to low-dose propranolol group and cross-hatched bars, the high-dose group.

rest in a quiet, comfortable room. A tablet containing 0.4 mg of nitroglycerin was then given sublingually and the patient assumed upright posture. Pulse rate was counted for 6 min and the highest rate during any 30-sec interval was used for comparison with the initial recumbent rate.

Isoproterenol infusion. Isoproterenol was administered into the superior vena cava utilizing a constant infusion pump while monitoring heart rate electrocardiographically. A solution of 1.0 μg/ml of isoproterenol in saline (0.8%) was used. During the period of placebo treatment three rates of infusion were tested, 1.0, 2.0, and 3.0 μg/min, each for 3 min. Heart rate at the end of each 3 min period was compared to the heart rate before infusion.

Passive tilt. Heart rate was measured from a continuously recorded electrocardiogram. Basal readings were obtained during horizontal rest for at least 15 min on a tilt table with a saddle. The table was then tilted for 10 min to a 45° head-up position. Heart rate at the end of this period was compared to the basal rate.

Standing. Pulse rate was measured at the wrist by the same two nurses in the clinic throughout the study. Visits were always in the morning. Basal heart rate was determined after 15 min of recumbent rest. Pulse rate was measured again after 2 min of quiet standing. Heart rate after standing was compared to the basal rate.

Plasma propranolol determinations. Plasma propranolol concentration was measured by fluorometry.*[15] Blood samples were drawn approximately 90 min after the last dose of propranolol following 2 and 4 wk of oral therapy. The plasma was separated by centrifugation and chilled at 4° C before being sent for analysis.

Experimental design. All patients were given placebo, 1 tablet 4 times daily, for 4 wk. After this period the effects of standing and of nitroglycerin tests were determined in the clinic. The tilt test and isoproterenol infusions were then carried out in the Clinical Physiology Laboratory.†

Patients then took propranolol orally in a dose of 40 mg, 4 times daily. After 2 wk they returned to the clinic where the effects of standing and nitroglycerin plus standing were determined again. Samples for plasma propranolol concentration measurement were also obtained. Those patients who demonstrated a satisfactory therapeutic response (a reduction

*Courtesy of Ayerst Laboratories, Montreal, Dr. Henry LeMien, Jr.

†Dr. Stevo Julius, Director.

Table III. *Heart rate increments in beats/min (± SEM) during stimulating maneuvers in high- and low-dose groups*

Group	Placebo				Propranolol (2 wk)		
	Nitro-glycerin	Isoproterenol	Tilt	Standing	Nitro-glycerin	Standing	PPL (ng/ml)
Low dose (160 mg propranolol/day)	41.3 (4.3)	42.1 (5.5)	8.3 (4.4)	9.8 (4.8)	20.0* (4.0)	5.6 (2.2)	63.4 (12.1)
High dose (160-320 mg propranolol/day)	32.6 (3.0)	39.1 (4.8)	8.6 (1.5)	8.5 (3.0)	22.2 (5.3)	6.8 (1.5)	50.1 (16.2)

PPL: plasma propranolol concentration (nanograms/ml).

Heart rate response in patients treated with propranolol, 160 mg/day throughout, and those observed in patients whose incomplete blood pressure change after 2 wk required an increase in dosage to 320 mg/day.

Statistical comparisons between high- and low-dose groups (Student's t test) were all $p > 0.05$.

Statistical comparisons within groups, compared to the immediately preceding values (paired t test), *$p < 0.05$; †$p < 0.01$.

of recumbent diastolic blood pressure in the clinic of at least 15 mm Hg or a recumbent clinic reading of less than 150/90) were advised to continue to take propranolol, 40 mg, 4 times daily, while in those with a poorer response the dose was increased to 80 mg 4 times daily.

Dosage was kept at 160 mg daily in 8 patients and increased to 320 mg daily in 7 patients, and all patients returned for final observations after 2 wk at these dosage levels. Tests performed at this visit included the effects of standing and of nitroglycerin plus standing in the clinic and the tilt test and isoproterenol infusion in the Clinical Physiology Laboratory. Finally, blood for plasma propranolol concentration was also obtained.

Statistical methods. Student's t test, the t test for paired observations and correlation coefficients were calculated using the Midas (Constat) Computer Program of the Statistical Research Laboratory at the University of Michigan.

Results

The effects on heart rate of the maneuvers used were as expected most pronounced during placebo treatment (Table II); the nitroglycerin and standing test (TNG test) caused an increase in heart rate of 37 beats/min. The various infusion rates of isoproterenol increased heart rate between 12 and 41 beats/min (Fig. 1). Correlations between TNG test and isoproterenol infusion were significant for infusion rates of 2.0 and 3.0 μg/min. Since the stronger correlation was after 3.0 μg/min ($r = 0.633$, $p < 0.005$), only this infusion rate was used after propranolol therapy, and heart rate response to only this dose are summarized in Table II. Heart rate increments during both passive tilt and quiet standing were similar, and considerably less than those observed after isoproterenol or TNG.

TNG test responses were halved during propranolol treatment, and most of this effect was established after 2 wk of therapy, whereas the isoproterenol response (after 4 wk) was reduced to 15% of control values by propranolol. On a percentage basis, modification of the responses to tilt and standing was quantitatively similar to that noted with the TNG test.

Analysis of data obtained from patients divided into subsets based on treatment protocol ("low" dose and "high" dose) revealed no statistically significant differences between the two groups (Table III) but within-group comparisons were significant. The blunting of TNG test response after 2 wk of propranolol achieved statistical significance in the low-dose but not in the high-dose group. The blockade of isoproterenol tachycardia was significant

Propranolol (4 wk)				
Nitro-glycerin	*Isoproterenol*	*Tilt*	*Standing*	*PPL (ng/ml)*
15.8 (1.8)	6.2† (1.4)	4.0 (2.0)	7.6 (3.1)	63.3 (14.8)
18.4* (4.2)	4.5† (1.6)	1.8* (0.5)	1.3* (1.5)	144.0 (72.3)

in both groups, while the impairment of responses to both tilt and standing was significant only in the high-dose subset during the 320 mg/day dosage. The small decrement in TNG response noted between weeks 2 and 4 of propranolol therapy (Fig. 2) was significant only in the group of patients switched from 160 to 320 mg/day. There was a correlation between the heart rate responses to TNG and isoproterenol after 4 wk of propranolol therapy ($r = 0.65$, $p < 0.03$).

Discussion

These data reveal that cardiac acceleration after administration of nitroglycerin and assumption of the erect posture (TNG test) is diminished during propranolol therapy. The findings are consistent with those of Fitzgerald with nitroglycerin[6] and with standing.[5] We were also able to demonstrate a significant correlation between cardiac response to isoproterenol infusion and TNG test results both in the control state and during propranolol therapy. Our data therefore provide support for Fitzgerald's suggestion that TNG testing is a means for assessing the degree of adrenergic beta receptor blockade. However, we did not observe obliteration of the TNG response during treatment with propranolol at a dose of 320 mg/day even though plasma propranolol concentrations were at full beta blocking levels.[2] We found almost maximal inhibition of tachycardia at the 160 mg/day dosage (Fig. 2). The slope of the dose-response curve suggests that complete blockade of this response would not have been attained even at much higher dosage. These latter observations cast doubt on the concept that the heart rate response to nitroglycerin is mediated purely by the sympathetic nervous system[6] and are supported by the recent report of Ekue, Shanks, and Walsh.[3] They conflict with the results of a study of reflex heart rate control in normal men,[12] which indicated that the change of heart rate due to hypotension induced by amyl nitrite is mediated largely by the parasympathetic nervous system. It appears more likely that the tachycardia induced by nitroglycerin in our hypertensive subjects is a result of both sympathetic stimulation and vagal withdrawal. This picture is compatible with the traditional view that heart rate responses are the result of a balance between sympathetic and parasympathetic systems[14] and is in agreement with recent work in dogs on the mechanism of baroreceptor-induced changes in heart rate.[16]

It is obvious, therefore, that the TNG test is of limited value in the assessment of beta adrenergic blockade, as responses to it are determined in some part by the parasympathetic nervous system. Only if the vagal component could be regarded as constant could changes in heart rate due to nitroglycerin be ascribed to changes in the degree of beta blockade. This test has been helpful in our study, however, in the assessment of the completeness of blockade in a group of subjects and thereby helped to provide information on the maximum dose of propranolol required when it is used in the treatment of hypertension.

The capability of propranolol to lower blood pressure in hypertensive patients is almost certainly related to its beta adrenergic receptor blocking activity.[11] There is some suggestion, however, that beta-blocking drugs in higher dose or after a longer period of time may have additional antihypertensive properties.[13] In a separate paper, based on additional data obtained from the same subjects in the present study,[8] we reported that in most patients the reduction in blood pressure observed at the dose of 320 mg of propranolol per day was the same as that seen at 160 mg/day. Coupled with the current finding that, based on the TNG test,

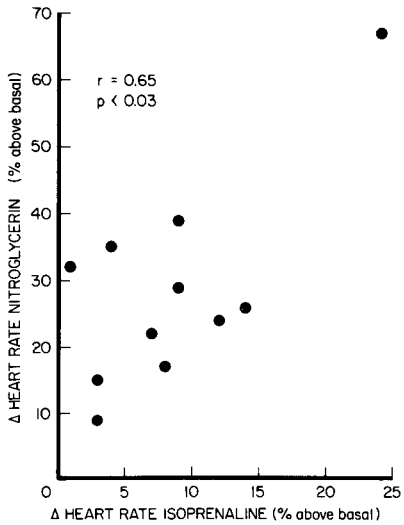

Fig. 3. Correlation between TNG-induced tachycardia and heart rate response to isoproterenol infusion after 4 wk of propranolol administration. Subjects from both high- and low-dose groups are included.

nearly complete cardiac beta blockade is present at the 160 mg/day dosage, this suggests that at least in the mild hypertensive propranolol lowers blood pressure primarily because of its action as a beta blocker. It also suggests that in treating such patients there is no need to administer more than a beta-blocking dose of propranolol.

Our data, from the TNG test and responses to quiet standing and tilt indicate that a slightly greater degree of beta blockade can be obtained with propranolol in a dose of 320 mg/day than with 160 mg/day. It is therefore justifiable to consider prescribing 320 mg/day to selected patients with hypertension who respond inadequately to the lower dosage.

A final point of interest is the fact that the TNG test response was inhibited significantly during the first treatment period only in the group of patients who required the lesser dose of medication for blood pressure control. The data suggest that the main reason for this difference is that those patients with the most substantial blood pressure responses to 160 mg propranolol per day had greater heart rate increments during the control TNG test. This finding hints at the often studied,[1, 8] but rarely substantiated[4] relationship between the ability of beta blockers to lower blood pressure and the activity of the sympathetic nervous system in hypertensive patients.

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