

Role of Parasympathetic Inhibition in the Hyperkinetic Type of Borderline Hypertension

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SUMMARY

Eleven patients with borderline hypertension and high cardiac output were compared to 16 paid healthy volunteers. Cardiac output, heart rate, and intraarterial blood pressure were determined at rest, after administration of 0.2 mg/kg of propranolol i.v., and after administration of an additional 0.04 mg/kg of atropine. In four additional patients, response to infusion of isoproterenol before and after administration of 0.2 mg/kg of propranolol i.v. was evaluated. Resting heart rate and cardiac output in patients with borderline hypertension were elevated. After propranolol infusion, the values decreased more in the patients with borderline hypertension, but remained significantly elevated. After atropine administration, the difference in cardiac output and heart rate between the two groups disappeared. Consequently, patients with borderline hypertension and hyperkinetic circulation simultaneously exhibit an increase of sympathetic and a decrease of parasympathetic tone.

Additional Indexing Words:

Arterial pressure Cardiac output
Isoproterenol Parasympathetic tone

Heart rate Hemodynamics
Sympathetic tone

IT IS NOW well documented that many young patients with borderline hypertension have an increased resting cardiac output.¹⁻⁶ Heart rate in patients with borderline hypertension also tends to be elevated,⁴⁻⁶ but the reports on that topic are not unanimous.^{2,3} Recently, a condition of concurrent elevation of heart rate and cardiac output but normal, labile or established high blood pressure has been described under the name of hyperdynamic beta-adrenergic circulatory state.⁷

The mechanism by which the heart rate and blood pressure are elevated in borderline

hypertension still remains to be explained. Increased venous tone has been implicated as a factor producing elevation of the cardiac output,³ but it cannot easily explain the increased heart rate. Emotional hyperreactivity⁸ and adrenomedullary hypersecretion⁹ have also been postulated as possible mechanisms for blood pressure lability and the increased cardiac output. Finally, Frohlich and coworkers⁷ postulated a specific hypersensitivity of beta-adrenergic receptors. This was criticized by Bourne et al.¹⁰ who pointed out that the original study failed to prove specific hypersensitivity of the beta receptors.

Another hypothetical explanation of the hyperkinetic circulation may be given if one postulates that patients with borderline hypertension have a diminished vagal tone. This study examines the role of the parasympathetic inhibition in such patients. The investigation was prompted by our previous finding that heart rate in borderline hypertension

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Supported by grants from the Rackham Faculty Research Project no. FRR-851, University of Michigan, Ann Arbor, Michigan; and Mr. Leo Fields.

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Received November 30, 1970; revision accepted for publication May 5, 1971.

Table 1

Mean and Standard Error of Hemodynamic Measurements

		Patients (N = 11)	Control subjects (N = 16)	Significance of difference between groups
At rest	Mean blood pressure	92.2 \pm 2.5	79.2 \pm 1.4	<0.0001
	Cardiac index	4.55 \pm 0.28	3.10 \pm 0.12	<0.0001
	Heart rate	80.5 \pm 3.9	63.0 \pm 2.1	<0.0001
On propranolol	Mean blood pressure	93.6 \pm 3.3	80.8 \pm 2.1	<0.0001
	Cardiac index	3.23 \pm 0.20	2.61 \pm 0.10	<0.01
	Heart rate	65.0 \pm 2.5	57.2 \pm 2.3	<0.05
On atropine after propranolol	Mean blood pressure	98.6 \pm 2.7	85.7 \pm 2.0	<0.0001
	Cardiac index	3.63 \pm 0.22	3.45 \pm 0.14	NS
	Heart rate	98.4 \pm 3.6	101.0 \pm 3.6	NS
Change: Rest to propranolol	Mean blood pressure	+ 1.4 \pm 2.0	+ 1.6 \pm 1.0	NS
	Cardiac index	- 1.32 \pm 0.11	- 0.49 \pm 0.1	<0.0001
	Heart rate	- 15.4 \pm 1.1	- 6.2 \pm 1.1	<0.01
Change: Propranolol to atropine	Mean blood pressure	+ 5.1 \pm 1.2	+ 5.6 \pm 0.9	NS
	Cardiac index	+ 0.40 \pm 0.17	+ 0.83 \pm 0.2	<0.05
	Heart rate	+ 33.4 \pm 3.7	+ 43.9 \pm 5.0	<0.06

Resting measurements are taken after 10 min. Cardiac index after propranolol and atropine is an average of two readings taken 5 and 7 min after the injection. Heart rate and blood pressure after propranolol and atropine represent readings after 7 min.

Cardiac index = liters/min/m²; heart rate = beats/min; blood pressure = mm Hg.

remains elevated in spite of extensive beta-adrenergic blockade with intravenous propranolol.¹¹ To put the hypothesis to the maximum test, we chose patients with high cardiac index (>3.6 liters/min/m², i.e., one standard deviation outside of the normal mean). Such a selected group of patients also had significantly increased resting heart rate. We also gave higher doses of propranolol than in our previous studies so that the amount given was equal to that employed by Jose.¹²

Materials and Methods

Fourteen patients with hyperkinetic borderline hypertension and 16 paid healthy normotensive volunteers were studied. The patients were from 18 to 32 years of age (23.4 \pm 0.9), whereas the control subjects were from 18 to 28 (24.0 \pm 0.8). Patients with borderline hypertension were defined as those having, out of five auscultatory casual readings within the last year, at least one with a diastolic value of 90 mm Hg or more and at least one below 90 mm Hg. Every patient underwent a thorough clinical examination and was thought not to have any signs of secondary hypertension. The examination involved taking medical history pointed at renal disease, pheochromocytoma, hyperthyroidism, and renal trauma. During the physical examination, special care

was given to weak femoral pulses, abdominal bruits, goiter exophthalmos, and fine tremor. None was found. All patients had a normal urine, serum creatinine, and intravenous pyelogram.

Cardiac output was measured by indocyanine green, blood pressure was measured intraarterially, and the heart rate was calculated from the arterial pressure curves. Details of the methodology are described elsewhere.¹³

All patients rested comfortably on an examining table. A short Teflon tubing was inserted percutaneously in the brachial artery, and from an antecubital vein a polyethylene catheter was advanced up to the level of the subclavian vein. The arterial catheter was connected to a Statham P23D strain gauge and a Gilson polygraph. Cardiac output curves were inscribed by a Gilford densitometer. Two different procedures were performed.

Procedure A: Eleven patients with borderline hypertension and all control subjects took part in this experiment. Two minutes after all catheters were introduced, the first measurements of cardiac output were performed, followed by another determination during the tenth minute. After the resting measurement, propranolol (0.2 mg/kg, i.v.) was injected slowly over 4 min. Cardiac output was again measured 5 and 7 min after completion of the injection. This was followed immediately by injection of 0.04 mg/kg of atropine sulfate i.v., which was completed

within 2 min. Finally, 5 and 7 min after atropine infusion, the cardiac output was again determined. The resting values after 10 min and the average values of two determinations after propranolol and after atropine infusion are presented. Averaging of the two values was considered permissible since in none of the cases did the consecutive readings differ more than 10%.

Procedure B: Four patients with hyperkinetic borderline hypertension took part in this experiment. After all catheters were introduced and the 10-min resting determination of cardiac output completed, slow infusion of 2 mg of isoproterenol in 500 ml saline was started by a Buretrol infusion set. The rate was adjusted to increase the heart rate for at least 20 beats over 2 min. Infusion was stopped, and time was allowed for the heart rate to stabilize at preinfusion levels. Then an intravenous injection of 0.05 mg/kg of propranolol was given, followed 5 min later by determination of the heart rate from ECG tracings. This was successively repeated three times more until, at the final measurement, a cumulative dose of 0.2 mg/kg of propranolol was given. At this point, infusion of isoproterenol was started at the same rate as before propranolol infusion, and heart rate was determined 2 min later. In three cases, another measurement of the heart rate was taken 2 min after the infusion rate of isoproterenol was approximately doubled.

The significance of difference of means and of paired averages between groups was determined by Student's *t*-test.

Results

Results for procedure A are given in table 1 and illustrated in figure 1.

Resting cardiac index, heart rate, and blood pressure were significantly elevated in patients with borderline hypertension. After propranolol infusion, cardiac output and heart rate decreased more in patients than in control subjects, but the initial significant difference between the two groups was still maintained. After injection of atropine, however, patients showed less of a rise of the cardiac index and heart rate than the control subjects; consequently, the difference between the two groups was abolished. Blood pressure in both groups did not change after propranolol infusion, whereas after atropine was administered a small and practically identical rise occurred in both groups. Therefore, a highly significant blood pressure difference between

the two groups was maintained throughout the whole experiment.

Results for procedure B are given in figure 2 and table 2. In all cases, the maximal effect on the resting heart rate appeared after the second dose of propranolol. The cumulative dose of propranolol at this point was 0.10 mg/kg. Further injections increased the cumulative dose to 0.2 mg/kg but produced minimal further decrease of the heart rate. Before the injection of propranolol, isoproterenol infusion in three patients was adjusted to produce an exact increase in the heart rate of 20 beats/min. In the fourth patient, the increase was 36 beats/min. When exactly the same dose of isoproterenol was repeated after infusion of 0.2 mg/kg of propranolol, no increase of heart rate was observed. In the three patients in whom the first dose produced an initial increase of 20 beats/min but failed to accelerate the heart after propranolol, the infusion rate of isoproterenol in the beta-blocked state was approximately doubled but produced very little response.

Discussion

Compared to normal subjects, after intravenous injection of 0.2 mg/kg of propranolol patients with high output borderline hypertension maintained significantly higher heart rate and cardiac output. We take this as

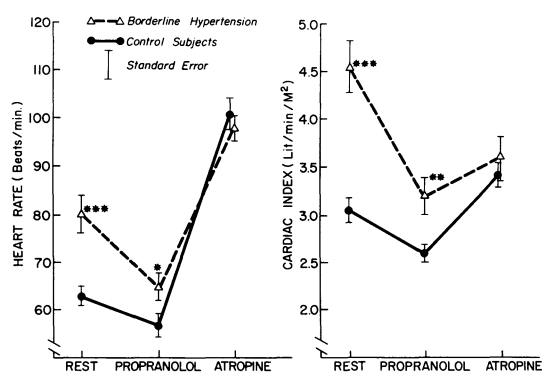


Figure 1

Mean and standard error of hemodynamic measurements at rest, after administration of propranolol, and after administration of atropine. Three, two, and one asterisks denote significance of difference at 0.001, 0.01, and 0.05, respectively.

Table 2

Change in Heart Rate of Four Patients with Hyperkinetic Borderline Hypertension

Patient	Initial infusion		First infusion after propranolol		Second infusion after propranolol	
	Isoproterenol ($\mu\text{g}/\text{min}$)	Change in heart rate (beats/min)	Isoproterenol ($\mu\text{g}/\text{min}$)	Change in heart rate (beats/min)	Isoproterenol ($\mu\text{g}/\text{min}$)	Change in heart rate (beats/min)
1	1.30	+20	1.30	0	3.20	+6
2	1.06	+20	1.06	0	2.12	+2
3	1.13	+20	1.20	0	1.86	+4
4	2.67	+36	2.67	0	—	—

evidence that the beta-adrenergic system is not solely responsible for the resting hyperkinetic circulation in borderline hypertension. This conclusion is contingent on acceptance of the fact that the dose of propranolol utilized indeed produces substantial beta-adrenergic blockade. Other investigators have shown that 0.2 mg/kg of propranolol is quite a potent dose. Jose and Taylor¹² demonstrated its effectiveness in animal and human subjects. In dogs, 20 min after 0.2 mg/kg of propranolol was administered, stimulation of the stellate ganglion increased the heart rate by only 2% of the preblockade response. Similarly, a dose of isoproterenol sufficient to increase the heart rate by 46 beats/min, increased the rate by only 5% when given after 0.2 mg/kg of propranolol. In humans, Jose and Taylor¹² assessed the effectiveness of propranolol by giving increasing doses and observing the fall of the resting heart rate in 36 healthy subjects. Whereas there was still some additional slowing of the heart as the dose was increased from 0.1 to 0.15 mg/kg, no further decrease was observed with 0.2 mg/kg. Epstein et al.¹⁴ applied doses lower than 0.2 mg/kg to produce adequate blockade in human subjects. Bender et al.¹⁵ presented experimental evidence showing that lower doses are adequate. They gave a continuous infusion of isoproterenol sufficient to increase the heart rate to 120 beats/min (average dose, 0.07 $\mu\text{g}/\text{min}$). Additive doses of 0.1 mg of propranolol produced a continuous decrease of the heart rate until finally 1.1 mg totally abolished the effect. Evidence from the literature also indicates that measurements in our study were taken within the peak activity time of propranolol.^{12, 16}

Consequently, the dose applied in this

experiment is capable of producing an effective blockade in healthy subjects. However, theoretically, patients with hyperkinetic borderline hypertension might require larger doses of propranolol due to greater resistance to the drug. This was tested in four patients (fig. 2). When the dose of 0.2 mg/kg was split into four equal parts given consecutively, the resting heart rate substantially decreased between the first and second dose but failed to continue decreasing with subsequent injections. This indicates that the maximum effect in these patients was noticeable already at one-half of the total dose, a result very similar to data obtained by Jose and Taylor in normotensive subjects.¹² Furthermore, 0.2 mg/kg of propranolol totally abolished the effect of a dose of isoproterenol which was sufficient to increase the resting heart rate at

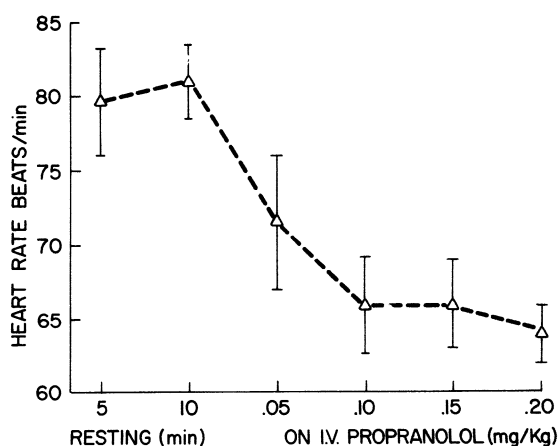


Figure 2

Mean and standard error of the heart rate in four patients given four consecutive doses of 0.05 mg/kg of propranolol intravenously. Measurement was taken 5 min after each injection. The amount of propranolol denoted on the abscissa is the cumulative dose of propranolol at each point.

least 20 beats/min before the adrenergic blockade. A further step-up of the dose of isoproterenol had very little effect on the heart rate. A dose of isoproterenol sufficient to increase the heart rate by about 20 beats/min was chosen to mimic the difference in resting heart rate between the patient and control groups (16 beats/min). If only the beta-adrenergic system is responsible for the resting difference of 16 beats/min between the two groups, the applied dose of propranolol most certainly was sufficient to abolish this difference. This was not the case in 11 patients and 16 control subjects undergoing procedure A. The question of how representative the four individuals in procedure B are of patients in procedure A could be brought up. Their 10-min resting heart rate (81.2 ± 2.5 beats/min) and cardiac output (4.1 ± 0.2 liters/min/m²) were similar to patients in procedure A. After propranolol, heart rate (64.2 ± 1.9 beats/min) fell to values closely approximating those in other patients. Therefore, the four patients selected to test the effectiveness of propranolol closely resembled the other 11 patients.

In summary, we believe that patients in this study were not resistant to propranolol and that the dose applied was sufficient to achieve a blockade of physiologic stimuli operating under resting conditions. Consequently, elevation of cardiac output and heart rate observed in patients after propranolol infusion is not a sign of some residual sympathetic activity. Additional support for such a statement can be found in the results after injection of atropine. Addition of atropine effectively abolished the difference between the two groups. Consequently, the residual elevation of heart rate and cardiac output observed after propranolol infusion resulted from differences in parasympathetic cardioinhibitory tone. If the increased heart rate and cardiac output at rest and after propranolol administration were indeed caused by increased sympathetic sensitivity, normal response to such a condition would be a reciprocal increased vagal inhibition (particularly in view of increased blood pressure). Our data show that this is not the case. On the

contrary, after administration of atropine patients with borderline hypertension had less of an increase in cardiac output and heart rate than control subjects, which is indicative of decreased parasympathetic tone in the patient group (table 1).

The parasympathetic inhibitory influence is quite an important determinant of the resting heart rate. J. Hamilton Crawford¹⁷ demonstrated almost half a century ago that administration of 1.5 mg of atropine subcutaneously produces a substantial increase of the heart rate. Robinson et al.¹⁸ recently performed a stepwise sympathetic, parasympathetic, and combined blockade in four subjects. The decline of the heart rate after propranolol administration was minimal, but a substantial increase after administration of atropine or atropine combined with propranolol was observed. The data of Jose et al.¹² are similar. In addition to the influence at rest, changes in parasympathetic tone are responsible for alterations in heart rate during mild exercise.¹⁸

Since vagal tone plays such an important role in physiologic regulation of the heart rate, it is surprising to find that the role of the parasympathetic system in the hyperkinetic state of borderline hypertension was scarcely investigated. Frohlich et al.⁷ gave a submaximal dose to one control subject and three patients with borderline hypertension. Heart rate increased more than 35 beats/min in all cases. The authors drew no conclusions from these few observations, stating: "interrelationship of parasympathetic and beta-adrenergic function remains speculative." To our knowledge, no other reports of measurement of vagal tone in borderline hypertension have been published.

Patients with borderline hypertension in this study exhibited a greater fall of heart rate and cardiac output after propranolol infusion. It may, therefore, be supposed that both a heightened sympathetic tone and a reduced parasympathetic activity are present in borderline hypertension, a reciprocal relationship that is well recognized in baroreceptor-induced cardiac control.¹⁸ Our previous studies¹¹

have been confirmed in this report, namely that not all of the increase of cardiac output and heart rate in borderline hypertension is accounted for by sympathetic overactivity. The remainder can now be explained by a decrease of parasympathetic inhibition.

This investigation also further supports our earlier observations that higher blood pressure in borderline hypertension is not necessarily maintained by an elevation of the cardiac output.¹⁹ This now can be extended to patients with hyperkinetic circulation in whom a net increased beta-adrenergic stimulation can be demonstrated. These patients had very high resting cardiac outputs, but after blockade with propranolol and atropine their cardiac output was comparable to the normotensive controls. However, their blood pressure remained increased. It appears, therefore, that an intact beta-adrenergic system and an increased cardiac output are not the necessary prerequisites for maintenance of hypertension in these patients. Obviously the peripheral resistance is increased. Whether this increase stems from long-term autoregulation or from increased alpha sympathetic tone, remains unsolved at this point.

Conclusions

(1) Decreased parasympathetic cardiac inhibition can be demonstrated in patients with high output borderline hypertension.

(2) Evidence of increased sympathetic cardiac activity in these patients is also present.

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