Br. J. clin. Pharmac. (1982), **13**, 381S–390S

ELEVATED PLASMA CATECHOLAMINES IN YOUNG HYPERTENSIVE AND HYPERKINETIC PATIENTS: EFFECT OF PINDOLOL

P. DOMINIAK & H. GROBECKER

Department of Pharmacology, University of Regensburg, D-8400 Regensburg, West Germany

1 The sympathetic nervous system plays an important role in the regulation of blood pressure. Plasma catecholamine concentrations are considered to be reliable indices of sympatho-neuronal (noradrenaline) and sympatho-adrenal (adrenaline) activity and reactivity in man.

2 Sympathetic and adrenal activity and reactivity in young patients with essential hypertension or hyperkinetic heart syndrome were compared with an appropriate control group matched for age. The groups of hypertensive patients and patients with hyperkinetic heart syndrome could be clearly distinguished from control subjects on the basis of circulating catecholamine levels at rest.

3 A clear-cut increase in circulating noradrenaline and adrenaline was observed in young patients with essential hypertension and hyperkinetic heart syndrome at rest. Clinically, hypertensive patients were characterized by elevated systolic and diastolic blood pressure and increased heart rate, whereas patients with hyperkinetic heart syndrome had increased heart rate and increased systolic blood pressure, whereas diastolic blood pressure was normal. At rest, there was a significant positive correlation between heart rate and circulating catecholamines in both groups of patients. In hypertensives a positive correlation between heart rate and plasma adrenaline concentrations, in patients with hyperkinetic heart syndrome a positive correlation between heart rate and plasma noradrenaline concentrations could be observed. In addition a positive correlation between plasma noradrenaline concentrations and systolic blood pressure in all groups of patients studied, was obtained.

4 Sympatho-neuronal and sympatho-adrenal reactivity during mental stress or physical exercise increased in both groups of patients, mirrored by an increase in blood pressure and heart rate.

5 Pindolol, a potent non-selective β-adrenoceptor blocking drug with intrinsic sympathomimetic activity and minimal membrane stabilizing properties, administered in a single oral dose of 10 mg, diminished the exaggerated sympathetic tone in both groups of patients by attenuating circulating catecholamine levels at rest or during mental stress, but not during physical exercise.

Introduction

The hypothesis that the sympathetic nervous system could be implicated in the development and maintenance of human and experimental hypertension was until recently only supported by indirect evidence (c.f. Axelrod, 1976). The degree of involvement of sympathetic nerves and the adrenal medulla may vary with different types of hypertension and during different phases of the development of experimental and human hypertension (Grobecker *et al.*, 1975, 1977; Saavedra *et al.*, 1976, 1978; de Champlain *et al.*, 1977). An increased sympathetic neuronal activity reflected by elevated circulating noradrenaline concentrations and dopamine-β-hydroxylase activity was demonstrated in young spontaneously hypertensive rats (Nagatsu *et al.*, 1974; Grobecker *et al.*, 1975). Also in patients with essential hypertension a significant elevation of plasma catecholamines was found (for review see Axelrod, 1976). However, in these studies the control groups were not matched for age and the controls tended to be younger than the hypertensives. In age-matched hypertensive subjects there was no difference in circulating noradrenaline concentrations between controls and hypertensives (Lake *et al.*, 1976; Grobecker, 1977; Sever, 1978). Therefore the aim of the present study was to evaluate the activity and reactivity of the sympathetic nerves and adrenal medulla in young hypertensive patients, both under resting and stimulated conditions by determination of plasma noradrenaline and adrenaline concentrations. The effect of pindolol, a

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potent β-adrenoceptor blocking drug in the treatment of hypertension, on circulating catecholamines, blood pressure and heart rate was also investigated.

Methods

Forty-four male patients, aged 20.3 ± 1.1 (mean ± s.d.) years (soldiers), were studied during their admission in an army hospital. The diagnosis of essential hypertension or hyperkinetic heart syndrome was made after careful clinical and laboratory examinations excluding other forms of hypertension or hyperthyroidism. They had not been treated with antihypertensive drugs including β-adrenoceptor blocking agents before the study. The patients were informed of the nature and the risks of the study and their consent was obtained. Every patient was allowed to withdraw at any time.

An indwelling catheter (Abbocath-G18, Fa. Abbott) was placed in the vena cubitalis of the left arm and the patients remained in the supine position for 30 min. After measuring heart rate (radial pulse) and blood pressure (standard sphygmomanometer) three times, 2 ml of blood were withdrawn for assay of basal levels of circulating catecholamines. The subjects were then asked to perform a multiplication test (mental stress, MS) which lasted 2 min. Heart rate and blood pressure were determined again and 2 ml of blood obtained at the end of the procedure. Mental stress was followed by physical exercise on a bicycle ergometer in the supine position (150 Watt, 6 min). Four minutes after application of work load a plateau of heart rate was reached (steady state). Blood samples were obtained during the last minute of physical exercise and simultaneously heart rate (electrocardiogram) and blood pressure measured. Pindolol (Visken®) was given in a single oral dose of 10 mg and the procedure described above, repeated 90 min later. Controls were 16 subjects, 20.0 ± 1.6 (mean ± s.d.) years, blood pressure 131 ± 3/75 ± 2.1 mm Hg (mean ± s.e.mean), heart rate 68 ± 1.7 beats/min (mean ± s.e.mean). Hypertensives were 16 subjects aged 20.2 ± 0.5 years, blood pressure 154 ± 5.1/96 ± 2.1 mm Hg and heart rate 80 ± 3.9 beats/min.

Patients with hyperkinetic heart syndrome were 12 subjects aged 20.6 ± 1.2 years, blood pressure 149 ± 4.7/78 ± 1.9 mm Hg and heart rate 88 ± 3.4 beats/min (for details see Table 1).

Catecholamine assay

After centrifugation the plasma was packed in dry ice and kept frozen at −70°C until assayed for catecholamines. Catecholamines were assayed according to the methods of Da Prada & Zürcher (1976) and Peuler & Johnson (1977) using purified catechol-*o*-methyl-transferase.

Results

Blood pressure and heart rate

In the groups of young hypertensive patients and

Table 1 Haemodynamic variables (blood pressure = BP, heart rate = HR) and plasma catecholamine concentrations (noradrenaline = NA, adrenaline = A) in normotensive controls, hypertensive and hyperkinetic patients at rest, during mental stress and during physical exercise before treatment with pindolol.

		Normotensive controls	*Hypertensive patients*	*Hyperkinetic patients*		*Analysis of variance*
Resting	BP (mmHg)	131/75 ± 3.0/2.1	154/96 ± 5.1/2.1	149/78 ± 4.7/1.9	(mmHg)	*****/******
	HR (beats/min)	68 ± 1.7	80 ± 3.9	88 ± 3.4	(beats/min)	******
	NA (pg/ml)	239 ± 14.5	431 ± 47.7	441 ± 31.3	(pg/ml)	******
	A (pg/ml)	72 ± 15.4	131 ± 22.7	124 ± 11.6	(pg/ml)	*
Mental stress	BP (mmHg)	143/81 ± 4.5/3.3	171/99 ± 5.7/2.3	164/89 ± 4.8/2.6	(mmHg)	******/******
	HR (beats/min)	87 ± 3.7	93 ± 4.0	101 ± 3.5	(beats/min)	*
	NA (pg/ml)	288 ± 18.2	511 ± 65.1	513 ± 43.7	(pg/ml)	*****
	A (pg/ml)	125 ± 17.9	157 ± 19.2	207 ± 26.5	(pg/ml)	*
Physical exercise	BP (mmHg)	203/96 ± 5.7/3.5	224/113 ± 6.4/6.7	211/94 ± 6.4/5.9	(mmHg)	*/*
	(HR (beats/min)	142 ± 4.9	145 ± 5.0	158 ± 6.2	(beats/min)	
	NA (pg/ml)	784 ± 99.8	931 ± 101	1106 ± 85.8	(pg/ml)	(*)
	A (pg/ml)	193 ± 41.0	188 ± 21.9	285 ± 37.3	(pg/ml)	

Results are expressed as mean ± s.e.mean. Significance values: (*) = $P<0.1$, * = $P<0.05$, ***** = $P<0.005$, ****** = $P<0.001$. Work load: 150 Watts.

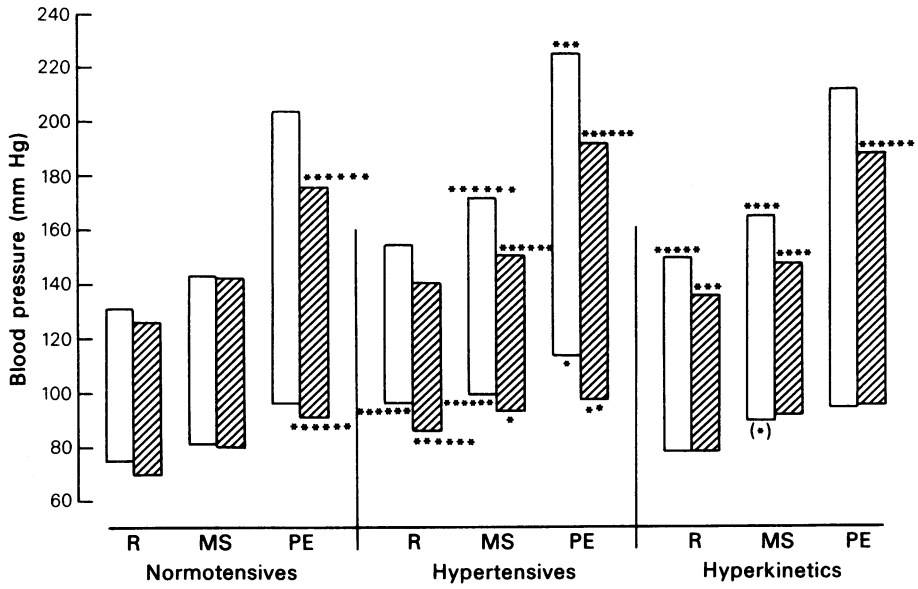

Figure 1 Changes in blood pressure (BP) in young hypertensive patients, in young hyperkinetic patients and in the respective controls at rest (R), during mental stress (MS) and during physical exercise (PE, 150 Watt, 6 min), before (open columns) and 90 min after acute blockade of β-adrenergic receptors with pindolol (10 mg, p.o., hatched columns). Significance (*t*-test): (*) = $P<0.1$, * = $P<0.05$, ** = $P<0.025$, *** = $P<0.02$, **** = $P<0.01$, ***** = $P<0.005$, ****** = $P<0.001$. The significance values on the open columns mean the difference between the groups of patients and the control groups, and the significance values on the hatched columns express the difference before and after treatment with pindolol.

patients with hyperkinetic heart syndrome distinct and significant changes of diastolic and systolic blood pressure at rest could be observed, when compared with the control group (Figure 1). The diastolic blood pressure was elevated in young hypertensive patients, but was normal in young hyperkinetic patients and in the control group. In contrast the systolic blood pressure in both groups of patients was signific-

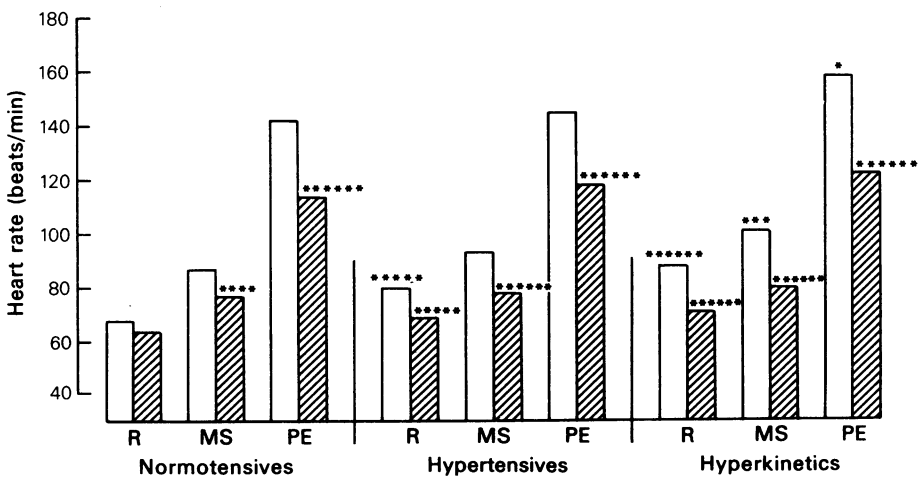

Figure 2 Changes in heart rate (HR) in young hypertensive patients, in young hyperkinetic patients and in the respective controls at rest (R), during mental stress (MS) and during physical exercise (PE, 150 Watt, 6 min), before (open columns) and 90 min after acute blockade of β-adrenergic receptors with pindolol (10 mg, p.o., hatched columns). Significance (*t*-test): see Figure 1.

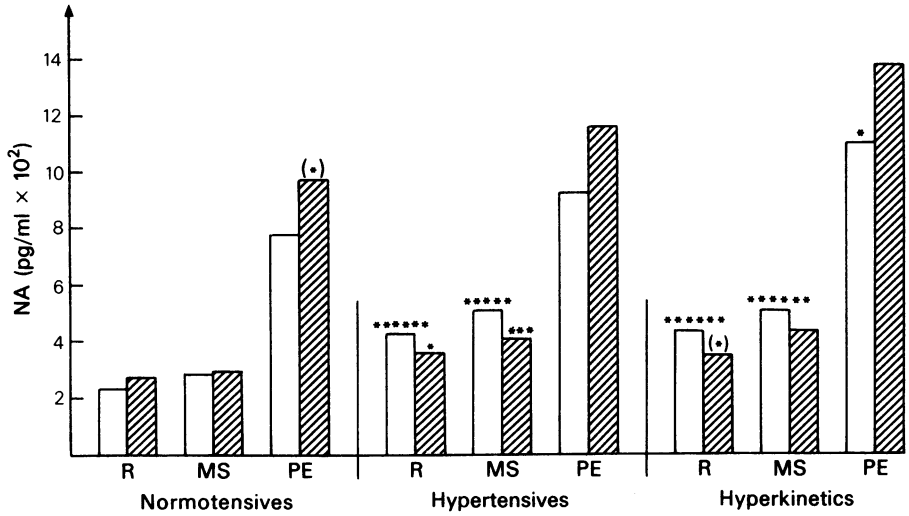

Figure 3 Changes in plasma noradrenaline concentrations (NA) in young hypertensive patients, in young hyperkinetic patients and in the respective controls at rest (R), during mental stress (MS) and during physical exercise (PE, 150 Watt, 6 min), before (open columns) and 90 min after acute blockade of β-adrenergic receptors with pindolol (10 mg, p.o., hatched columns). Significance (*t*-test): see Figure 1.

antly enhanced at rest. Moreover in hyperkinetic patients the amplitude of blood pressure was increased. Ninety minutes after administration of a single oral dose of pindolol, diastolic and systolic blood pressure was reduced in the group of hypertensive patients, but only the systolic blood pressure in hyperkinetic patients was decreased. β-adrenergic receptor blockade also reduced the increments in both systolic and diastolic blood pressure in the groups of patients with hypertension during mental stress and physical exercise, whereas in the group of patients with hyperkinetic heart syndrome only the systolic blood pressure was decreased. In controls as reported earlier by several laboratories (see discussion) blockade of β-adrenergic receptors resulted in diminished response of systolic and diastolic blood pressure during physical exercise (Figure 1).

Heart rate (Figure 2) measured in the supine posi-

Table 2 Haemodynamic parameters (blood pressure = BP, heart rate = HR) and plasma catecholamine concentrations (noradrenaline = NA, adrenaline = A) in normotensive controls, hypertensive – and hyperkinetic patients at rest, during mental stress and during physical exercise 90 min after single oral treatment with pindolol (10 mg p.o.).

		Normotensive controls	*Hypertensive patients*	*Hyperkinetic patients*		*Analysis of variance*
Rest	BP (mmHg)	126/70 ± 2.5/2.6	140/86 ± 4.4/2.9	135/78 ± 3.7/3.6	(mmHg)	**/*****
	HR (beats/min)	64 ± 1.5	69 ± 3.0	71 ± 1.9	(beats/min)	(*)
	NA (pg/ml)	283 ± 28.0	365 ± 36.6	355 ± 38.2	(pg/ml)	
	A (pg/ml)	71 ± 11.6	96 ± 16.5	95 ± 13.6	(pg/ml)	
Mental stress	BP (mmHg)	142/81 ± 3.2/2.5	150/93 ± 5.1/2.5	147/91 ± 4.1/2.9	(mmHg)	NS/*****
	HR (beats/min)	77 ± 1.9	78 ± 3.8	80 ± 2.0	(beats/min)	
	NA (pg/ml)	299 ± 30.6	413 ± 48.9	441 ± 48.1	(pg/ml)	(*)
	A (pg/ml)	90 ± 14.8	132 ± 22.5	137 ± 23.1	(pg/ml)	
Physical exercise	BP (mmHg)	175/91 ± 4.6/3.4	191/97 ± 5.5/3.8	187/95 ± 5.7/5.8	(mmHg)	(*)/NS
	HR (beats/min)	114 ± 2.5	118 ± 3.2	122 ± 4.2	(beats/min)	
	NA (pg/ml)	976 ± 194	1166 ± 197.3	1382 ± 217.7	(pg/ml)	
	A (pg/ml)	274 ± 82.3	260 ± 38.8	361 ± 57.5	(pg/ml)	

Results are expressed as mean ± s.e.mean. Significance values: (*) = $P<0.1$, ** = $P<0.025$, ***** = $P<0.005$. Work load: 150 Watts.

tion for 30 min was significantly increased in patients with hypertension and hyperkinetic heart syndrome, when compared with controls. A further increase of heart rate occurred only in hyperkinetic patients during mental stress or physical exercise. Pindolol reduced the heart rate significantly at rest in the two groups of patients with cardiovascular disease, but not in control patients. During mental stress or physical exercise pindolol diminished the increase in heart rate significantly in all groups of patients (Table 2).

Noradrenaline and adrenaline concentrations in plasma

At rest noradrenaline concentrations were significantly elevated in young patients with high blood pressure and hyperkinetic heart syndrome, when compared with controls at the same age (Figure 3). During mental stress a further significant increase in circulating noradrenaline was seen in hypertensive and hyperkinetic patients. A large increase of noradrenaline concentrations occurred in all groups of patients during physical exercise, most pronounced in patients with hyperkinetic heart syndrome. Administration of pindolol decreased the circulating noradrenaline levels at rest or during mental stress only in hypertensive patients.

As with noradrenaline, significantly elevated levels of circulating adrenaline were detected in patients with hypertension and hyperkinetic heart syndrome in supine position (Figure 4). In contrast to the effect of pindolol on circulating noradrenaline in patients with hypertension, pindolol decreased circulating adrenaline only in patients with hyperkinetic heart syndrome at rest or during mental stress.

Correlations between catecholamines and haemodynamic parameters at rest

Combining all the groups studied, a positive significant correlation was obtained between circulating noradrenaline and systolic blood pressure at rest (Figure 5). However, no correlations could be shown between the two variables if each group was analysed separately. Also combining all the patients the heart rate showed a significant positive correlation to both circulating noradrenaline and adrenaline (Figure 6). In normotensive and hypertensive patients adrenaline concentrations were shown to be related to heart rate (Figure 7), whereas in patients with hyperkinetic heart syndrome noradrenaline concentrations were shown to be related to heart rate (Figure 8). After oral administration of pindolol the observed relationships were reduced.

Discussion

With the catechol-*o*-methyl transferase (COMT) assay used in the present study the recumbent plasma concentrations of noradrenaline and adrenaline were in good agreement with the values reported by several laboratories (Louis *et al.*, 1974; Cryer *et al.*, 1974; Pedersen & Christensen, 1975; Da Prada & Zürcher, 1976; Peuler & Johnson, 1977). Normal values, however, may vary with age, sex, race etc. There are

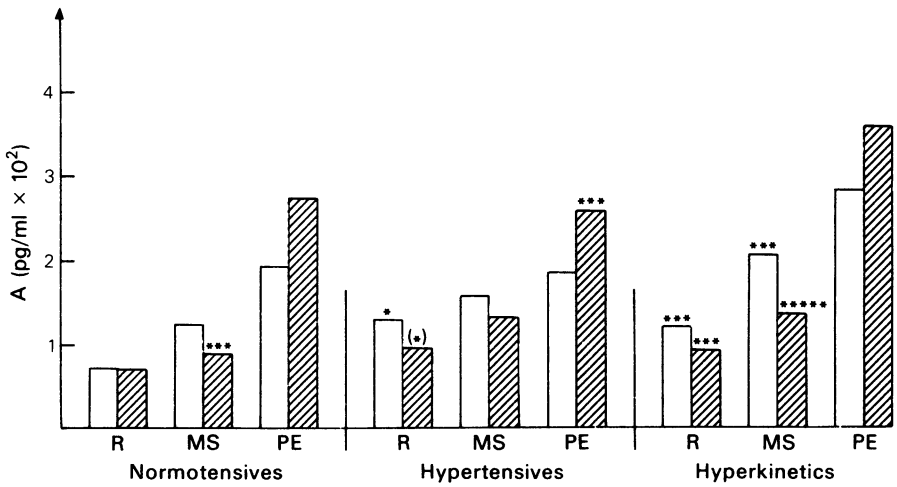

Figure 4 Changes in plasma adrenaline concentrations (A) in young hypertensive patients, in young hyperkinetic patients and in the respective controls at rest (R), during mental stress (MS) and during physical exercise (PE, 150 Watt, 6 min), before (open columns) and 90 min after acute blockade of β-adrenergic receptors with pindolol (10 mg, p.o., hatched columns). Significance (*t*-test): see Figure 1.

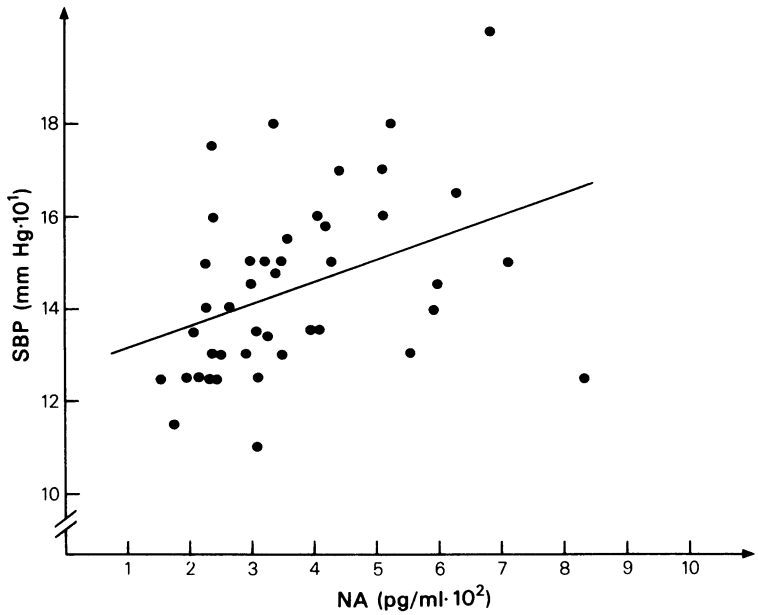

Figure 5 Correlations between plasma noradrenaline concentrations (NA) and systolic blood pressure (SBP) at rest in all three groups studied. $r = 0.40$, $P < 0.001$.

several reports that plasma noradrenaline concentrations rise with age (Lake *et al.*, 1977; Pedersen & Christensen, 1975; Sever *et al.*, 1977). Other laboratories could not observe this relationship between age and plasma noradrenaline (de Champlain & Cousineau, 1977; de Quattro & Chan, 1972). Therefore we selected a sub-group of younger subjects with essential hypertension and age-matched controls. In these young patients with elevated blood pressure a clear-cut increase in circulating norad-

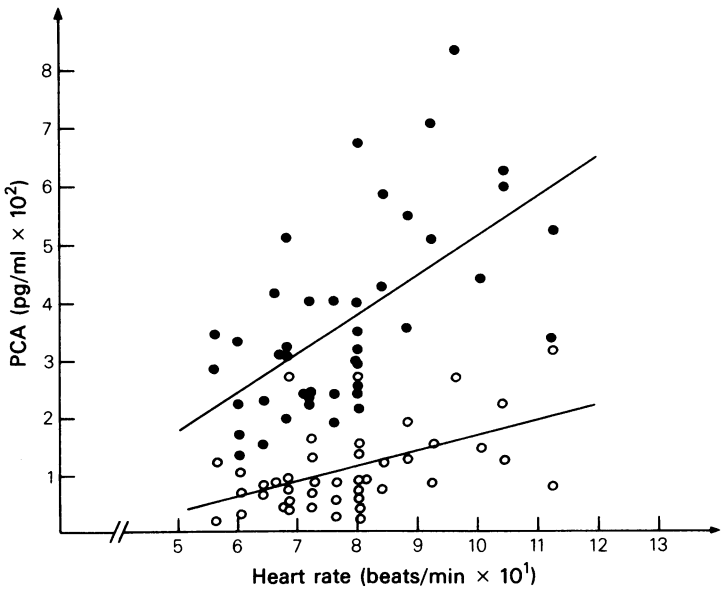

Figure 6 Correlations between plasma catecholamine concentrations (PCA, noradrenaline = ●, adrenaline = ○) and heart rate (HR) at rest in all groups studied. For adrenaline $r = 0.53$, $P < 0.001$, for noradrenaline $r = 0.60$, $P < 0.001$.

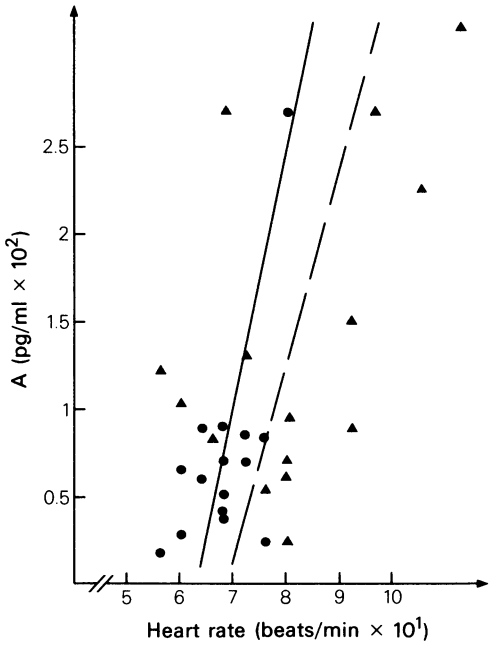

Figure 7 Correlations between plasma adrenaline concentrations (A) and heart rate (HR) in young hypertensive patients (▲) and the control normotensive group (●) at rest. For hypertensives $r=0.52$, $P<0.05$, for normotensives $r=0.57$, $P<0.05$.

renaline was seen, indicating enhanced sympathoneuronal activity associated with the early stages of the development of essential hypertension. In addition significantly increased levels of plasma adrenaline were measured in young patients with essential hypertension. This seems to be in agreement with earlier results of elevated circulating adrenaline in hypertensive patients (Franco-Morselli *et al.*, 1979). However, in this study the age range of the patients was 18–70 years and therefore comparison is difficult.

In animal models of hypertension e.g. young spontaneously hypertensive rats (SHR), both noradrenaline concentrations and dopamine-β-hydroxylase activity were significantly increased over those of the controls (WKY), indicating increased sympathetic neuronal activity in spontaneously hypertensive rats at the beginning of the development of high blood pressure in genetic hypertension (Grobecker *et al.*, 1975; Nagaoka & Lovenberg, 1976). Also in DOCA-salt hypertensive rats plasma noradrenaline and plasma adrenaline levels were significantly raised (Reid *et al.*, 1975; de Champlain *et al.*, 1977; Grobecker *et al.*, 1977; Franco-Morselli *et al.*, 1977). In addition sympatho-neuronal and sympatho-adrenal reactivity in genetic and experimental hypertensive rats were greater than in controls during stress (McCarty & Kopin, 1978). From the results obtained in young patients with essential hypertension and in animal models of hypertension it can be concluded that peripheral sympathetic nerves and the adrenal medulla are directly involved in the development of high blood pressure. For the first time we have been able to distinguish hypertensive patients from normotensive controls on the basis of catecholamine levels. Further support for this assumption came from animal experiments demonstrating that increased circulating levels of adrenaline can result in a chronic elevation of blood pressure (Majewski & Rand, 1981). At rest and especially during periods of stress, secretion of adrenaline from the adrenal glands is increased in patients (see Figure

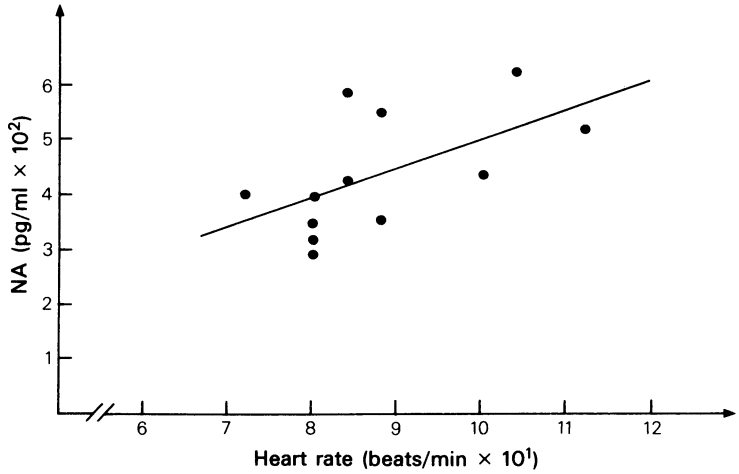

Figure 8 Correlations between plasma noradrenaline concentrations (NA) and heart rate (HR) in young hyperkinetic patients at rest. $r=0.58$, $P<0.05$.

4), as well as in animals (McCarty & Kopin, 1978). Increased circulating levels of adrenaline can lead to an increased uptake of adrenaline into sympathetic nerve endings. Subsequently the stored adrenaline can be released by nerve stimulation and may modulate its own release or alternatively, by activation of facilitatory prejunctional β-adrenoceptors, enhance the amount of noradrenaline released by the nerve endings (Majewski & Rand, 1981). A prolonged facilitatory effect of adrenaline on sympathetic transmission, thereby increasing the release of noradrenaline, may considerably contribute to elevation of blood pressure in the initiation and/or maintenance of certain forms of human essential hypertension. In accordance with this hypothesis, we observed a positive correlation between heart rate and circulating adrenaline in hypertensive patients and in normotensive controls at rest. Thus, the facilitatory mechanism elicited by adrenaline on sympathetic transmission is probably operating preferentially in the heart (c.f. Figure 7).

Moreover we observed a positive correlation between plasma catecholamines (noradrenaline and adrenaline) in all groups of patients studied as well as a positive correlation between plasma noradrenaline concentrations and systolic blood pressure at rest (c.f. Figures 5 and 6). This positive feedback mechanism mediated by presynaptic β-adrenoceptors, originally postulated by Langer *et al.* (1975) might be also a point of attack for β-adrenoceptor blocking drugs. We demonstrated that after acute blockade of β-adrenoceptors by pindolol both circulating adrenaline and noradrenaline levels were significantly decreased and concomitantly the blood pressure was reduced (c.f. Figures 1, 3 and 4). There is also experimental evidence for a blockade of presynaptic β-adrenoceptors by sotalol, which resulted in an inhibition of noradrenaline release into the coronary sinus blood after cardioaccelerator nerve stimulation at low frequencies (de Champlain *et al.*, 1977). Thus β-adrenoceptor blocking drugs like pindolol or sotalol may exert their antihypertensive activity partially by blockade of prejunctional β-adrenoceptors, preventing adrenaline from activating the facilitatory mechanism in sympathetic nerves. Another possible mode of action of pindolol in the hypertensive patients studied is an effect mediated through the central nervous system. Clinical side-effects of most of the β-adrenoceptor blocking drugs in current use, such as vivid dreams, hallucinations, insomnia and occasionally depression, occurring during antihypertensive therapy, give evidence of entry of the drugs into the central nervous system. As anticipated, during mental stress (calculation stress) an increase in heart rate and blood pressure as well as in circulating noradrenaline and adrenaline was observed in all patients studied (Table 1). Acute blockade of β-adrenoceptors by oral administration of a single dose (10 mg) of pindolol reduced significantly the changes in haemodynamic parameters and plasma catecholamines (Table 2). The mode of action of pindolol in this investigation is probably mediated through the central nervous system, however the precise mechanism of action e.g. blockade of β-adrenoceptors or other receptors in the central nervous system is still unknown. As a result of the central action of pindolol the decrease in sympathetic outflow could contribute to the reduction in circulating catecholamines (Lewis & Haeusler, 1975). Acute treatment with pindolol reduced the increase in heart rate and blood pressure during exercise in all groups of patients, but elevated in normotensive patients the increase in noradrenaline concentration in plasma to higher levels than obtained without blockade. This is in agreement with previous observations after acute and chronic blockade of β-adrenoceptors with either atenolol or penbutolol (Grobecker *et al.*, 1976, 1977). In the group of hypertensive patients the same phenomenon could be observed with circulating adrenaline (c.f. Figure 4). Since catecholamines can accelerate their own clearance through β-adrenergic mechanisms (e.g. receptors or systems regulated by β-adrenergic receptors, c.f. Cryer, 1980) antagonists at β-receptor sites should increase the ability of catecholamines at other receptor sites and stimulate for example α-adrenergic receptors (Palm & Grobecker, 1977). On the other hand, circulating noradrenaline at high concentrations may act as a hormone, in addition to its effect as a neurotransmitter. Adrenaline is about 10 times more potent than noradrenaline in producing metabolic effects (Hamburg *et al.*, 1979), but it may also be more potent in stimulating presynaptic β_2-adrenergic receptors (see above).

In the present investigation we could not only distinguish hypertensive patients from normotensive controls on the basis of circulating catecholamine levels, but also patients with hyperkinetic heart syndrome, who also had significantly increased levels of noradrenaline and adrenaline at rest (Figures 3 & 4). However, in contrast to the hypertensive patients, their diastolic blood pressure was normal and their heart rate clearly increased above the heart rate in hypertensive patients (Table 1). Therefore the hyperkinetic heart syndrome can be considered as a clinical and physiological entity. It has been suggested that the hyperkinetic circulation in part may be β-adrenergically mediated (Delius, 1967). Accordingly in the patients with hyperkinetic heart syndrome the increase in heart rate and circulating catecholamines were more pronounced than in the other groups of patients studied (Table 1). Blockade of β-adrenoceptors by pindolol significantly reduced heart rate during all experimental conditions in the

patients with hyperkinetic heart syndrome (Table 2). In addition the increase in blood pressure during the mental stress or physical exercise was attenuated by pindolol in these patients. Since there was a reduction in circulating noradrenaline at rest and a correlation between heart rate and circulating noradrenaline at rest in patients with hyperkinetic heart syndrome (c.f. Figure 8), the increased heart rate in these patients is probably due to enhanced release of noradrenaline in the heart. Therefore, β-adrenergic receptor blockade seems to be the best therapeutic approach for the treatment of hyperkinetic heart syndrome (c.f. Frohlich, 1971; Lydtin & Lohmöller, 1977).

In the present investigation we have demonstrated that in young patients with essential hypertension and hyperkinetic heart syndrome circulating levels of catecholamines can serve as biochemical indices of sympathetic function i.e. sympatho-neuronal and sympatho-adrenal activity. Pindolol as a potent non-selective β-adrenoceptor blocking drug with intrinsic sympathomimetic activity and minimal membrane stabilizing properties is able to diminish the altered sympathetic activity observed in patients with essential hypertension and hyperkinetic heart syndrome, thereby blocking a possibly important pathogenetic factor in the development of these diseases.

The skilful technical assistance of Miss E. Stocker is gratefully acknowledged.

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