

Autonomic and Non-Autonomic Circulatory Components in Essential Hypertension in Man

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SUMMARY

The circulatory effects of blocking cardiac and peripheral autonomic effectors were studied in 32 subjects with established essential hypertension, and in 15 normotensives. The mean resting arterial pressure, heart rate and total peripheral resistance index (TPRI) were significantly higher in the hypertensives, but cardiac index was the same in both groups. In subjects with blocked cardiac effectors (atropine + beta-blocking drugs, i.v.) the sympathetic constrictor effects on TPRI were estimated from the changes after giving i.v. guanethidine + phentolamine. The autonomic component of TPRI was higher in hypertensives than in normotensives. The residual resistance after 'total' autonomic block (non-autonomic TPRI) was higher in hypertensives, accounting for 60 to 80% of the initial difference in resting TPRI between the two groups. With an increase in non-autonomic TPRI, the increased autonomic TPRI effect in hypertension is not necessarily due to increased sympathetic nerve activity. Vagal and cardiac sympathetic effects on heart rate were compared in the two groups. Each estimate was based on the average of the responses to the appropriate blocking drug (1) in subjects not previously given a blocking drug, and (2) in subjects with the other cardiac effector pathway already blocked. The higher heart rate in established hypertension was predominantly due to change in vagal rather than cardiac sympathetic effects.

Additional Indexing Words:

Cardiac sympathetic effects
'Total' autonomic block

Vagal effects

Cardiac autonomic block

PRESENT EVIDENCE suggests that both autonomic and non-autonomic mechanisms contribute to the development and maintenance of essential hypertension but there is still no general agreement as to their relative importance.¹⁻³ One approach to the latter question used by Smirk et al.^{4, 5} is to compare the blood pressure responses to complete autonomic effector blockade in hypertensive and normotensive subjects. They found that hexamethonium produced greater lowering of blood pressure in the former group, and considered this as

evidence of autonomic hyperactivity in hypertension. Smirk and colleagues studied the effects only on arterial pressure, but did not measure the changes in cardiac output and total peripheral resistance in the two groups. Such measurements have been made in comparisons of the effect of guanethidine between hypertensive and normotensive subjects.⁶ However, this drug blocks only sympathetic cardiac and peripheral constrictor nerves. It leaves unblocked reflex adrenal medullary secretions and vagal effectors, through which some reflex compensation could still take place in response to the primary blood pressure reduction. In the above studies⁴⁻⁶ changes are determined between the completely unblocked and fully blocked states, so that it is not possible to assess even with detailed hemodynamic measurements which circulatory effects are mediated through cardiac and which through peripheral autonomic effectors. This information seems desirable, since effects on cardiac output are mediated not only through the cardiac sympathetic and vagus, but also through the sympathetic constrictor nerves via venomotor mechanisms.⁷ As regards the cardiac

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effectors, recent comparisons between subjects with borderline hypertension and normotensives have indicated differences in sympathetic and parasympathetic function,⁸⁻¹¹ but whether these are also abnormal in established hypertension remains to be determined.

The purpose of this paper was to investigate these differences in cardiac and peripheral autonomic effects between subjects with established hypertension and normotensives, and to examine also the residual differences in non-autonomic effects after acute 'total' autonomic blockade. In each subject cardiac autonomic block was induced intravenously with atropine and beta-blocking drugs, and this was followed by peripheral constrictor block by means of guanethidine and phentolamine.

Materials and Methods

Subjects

Thirty two patients (17M and 15F) with essential hypertension, and 15 healthy male normotensive volunteers were studied. Their ages ranged from 18 to 58 years. Fifteen hypertensives had never received any anti-hypertensive therapy, while the others had been without therapy (including diuretics) for 2 to 3 weeks before the study. Both showed identical responses and have been considered together. All subjects were placed on a diet containing approximately 100 mEq/day Na⁺, and 80 mEq/day of K⁺, for at least two weeks preceding the study. All the hypertensives had diastolic blood pressures greater than 95 mm Hg, at three consecutive measurements at intervals of one week and at the time of the study. Sixteen hypertensive patients were asymptomatic while the remainder gave a history of mild headache. None gave a history or had any signs suggestive of cardiac failure, or had X-ray evidence of cardiac enlargement. Most had normal electrocardiograms, but in some there were slight voltage abnormalities.¹² All patients showed only mild vascular changes in their retinal vessels and none had papilloedema, retinal hemorrhage or exudates.¹³ Intravenous pyelograms were performed only in hypertensives and were all normal, as were the renal arteriograms in the 13 patients having this test. All hematological (RBC, WBC and Hb) and biochemical tests (serum Na⁺, K⁺, Cl⁻, HCO₃⁻, BUN, creatinine and uric acid) were within normal limits.

The normotensives had diastolic pressures below 90 mm Hg on two occasions before and at the time of the study. All were clinically healthy as assessed by history, full physical examination, chest X-ray, ECG, and hematological and biochemical tests.

Procedures

The subjects were admitted to hospital one day before the study. The protocol had been fully explained to them and their informed consent obtained to participate in the study. The subjects received an antibiotic (penicillin or erythromycin) 30 minutes

before the study, but were not sedated. A number 5 or 6 Cournand catheter was introduced through the median cubital vein, using 0.5% lidocaine anesthesia, and was advanced under fluoroscopy into the pulmonary artery. The catheter was closed, and had a small thermistor mounted at its tip. A second catheter was introduced through the same vein, and positioned in the right atrium.

Cardiac output was measured by thermodilution, following rapid right atrial injection of 8.5 ml of 5% dextrose solution in distilled water, at room temperature. The formula used was $CO = (60 V_i d_i s_i (T_b - T_i) K) / [d_b s_b \int_0^\infty \Delta T(t) dt]$, where V_i = volume of

injectate (ml) corrected for catheter dead space from arm to atrium; d_i, d_b = density of injectate and blood; s_i, s_b = specific heat of injectate and blood; T_i, T_b = temperatures of injectate and arterial blood before each curve (°C); K = heat transfer correction factor, allowing for heat transfer between catheter wall and injectate during each injection,^{14, 15} which has a value of 0.84 ± 0.02 (SE) with the present catheter system. Cardiac index (CI) was obtained by dividing cardiac output by body surface area. The accuracy of the thermodilution method for measuring cardiac output is now well established¹⁶ and has been previously examined in our laboratory in animal and model experiments.^{14, 17} In 11 patients it was compared with the direct Fick method by recording 3 thermodilution curves at 1 min intervals, during the time necessary for collecting expired gas, and arterial and right atrial blood samples. The regression line calculated from 17 such comparisons was $CO(TD) = 0.5 + 0.94 CO(F)$, each cardiac output being expressed as liters/min. The standard error of a thermodilution estimate (i.e., mean of 3 curves) was $\pm 4\%$ of the mean value, giving the SE of a single curve of $\pm 7\%$ (i.e., $4 \times \sqrt{3}$).^{14, 16}

Arterial and right atrial pressures were measured, using Sanborn 1287 AC transducers. Zero pressure was referred to the midpoint of the PA chest diameter. Mean arterial and atrial pressures were obtained by electronic damping, and the total peripheral resistance index (TPRI) calculated from the formula (mean arterial - right atrial pressures) / cardiac index. The ECG was monitored continuously, and the mean heart rate was displayed on a digital ratemeter.

Protocol

During each experimental period measurements of cardiac index, heart rate, arterial and right atrial pressures, and total peripheral resistance index were made in each subject every 2 min for 5 consecutive readings. There were 5 periods during the study, providing 25 sets of measurements per subject: (1) The first resting period began 15-20 min after cardiac catheterization. (2) The second resting period followed about 60 min later. (3) The period of partial cardiac autonomic block with either atropine or beta-blocking drug, the choice of drug being allocated at random, began 5 min after drug injection. (4) The period of cardiac autonomic block began 5 min after the injection of the second drug and a booster dose of the first drug. (5) The period of 'total' autonomic

block, where the subject received an injection of guanethidine + phentolamine, followed by a second injection of phentolamine, and booster doses of the cardiac blocking drugs (see below); measurements began 5 min after the second phentolamine injection, and approximately 25 to 30 min from the first injection of guanethidine + phentolamine, by which time the arterial pressure had reached a stable supine minimum value. The protocol was approved by the Clinical Investigation Committee of the Royal Prince Alfred Hospital.

Tests of Reflex Function

The Valsalva test was performed after the first resting period, after cardiac autonomic block, and after 'total' autonomic block. The subject blew a mercury column to a height of 30 to 35 mm Hg for a period of 20 to 30 seconds, while blood pressure and heart rate were recorded.

The effects of posture were studied with the patient sitting on the catheter table, with feet hanging over the edge, for a period of 2 to 3 min. Hemodynamic variables were measured over 2 consecutive min while supine, and over 2 consecutive min immediately after sitting up.

Drugs

All drugs were administered intravenously, each drug being diluted to 1 to 20 ml 5% dextrose in distilled water and given over a period of 2 to 10 min. The initial dose of atropine was 0.04 mg/kg, followed by 0.008 mg/kg every 20 min. Three beta blocking drugs were used in the following doses: (1) propranolol, 0.2 mg/kg initially, followed by 0.04 mg/kg every 20 min; (2) oxprenolol, 0.08 mg/kg initially and 0.015 mg/kg every 20 min; (3) prindolol, 0.015 mg/kg initially followed by 0.004 mg/kg every 20 min. All three beta blockers produced identical effects and the results have accordingly been considered together. The doses of atropine and propranolol have been found by Jose and Taylor¹⁸ to produce, respectively, maximum cardiac acceleration and slowing when given intravenously to resting subjects and this was confirmed in the present study. The doses of the other beta-adrenergic blocking drugs also fulfilled the last criterion. In 6 subjects, two with each beta blocking drug, the above doses were adequate to block the effects on heart rate produced by an infusion of isoproterenol which, prior to the drugs, raised the heart rate by 20 to 25 beats/min.

The initial injection of guanethidine (1 mg/kg) and phentolamine (10 mg) was made slowly, over a period of 5 to 10 min, and was followed after 10 to 15 min by the second injection of 10 mg of phentolamine plus the booster dose of cardiac blocking drugs. Phentolamine was given to obviate any rise in arterial pressure following intravenous administration of guanethidine.¹⁹ In the presence of the cardiac blocking drugs no rise in heart rate was ever observed after injection of guanethidine + phentolamine or phentolamine alone.²⁰

Statistical Methods

The timing of the various measurements was the same in all subjects. To compare the significance of the

changes in mean values in any variable of a particular group, between two consecutive treatment periods A and B, standard errors were calculated based on the variation within subjects plus a measure of uniformity of the responses between subjects. These standard errors were calculated by analysis of variance as described previously.^{15, 21} Briefly the total sums of squares (SS) of the results obtained for the particular variable during periods A and B were partitioned into 'between subjects SS,' 'between means of periods (A-B) SS,' 'between time intervals A SS,' 'between time intervals B SS,' and into 'subjects \times time intervals A SS,' 'subjects \times time intervals B SS,' and 'subjects \times (mean of all periods A - mean of all periods B) SS,' the last interaction assessing uniformity of the response of the group. The SEM at a single time interval during period A, $SE(A) = [(\text{'subjects } \times \text{ time intervals A SS'} / (m-1)n)]^{0.5}$, for m time intervals and n subjects. The SEM of the entire period A, $SE(A) = SE(A) / (m)^{0.5}$. The SEM response, within subjects, during period B, $SE(B) = \{[\text{'subjects } \times \text{ time intervals B SS'} + \text{subjects } \times (\text{mean of all periods A} - \text{mean of all periods B}) \text{ SS'}] / (m+n-1)n\}^{0.5}$, the last term in the numerator accounting for difference in responses among the different subjects. The SEM difference between A and B, within subjects, averaged over all time intervals, $SE(A-B) = [(SE^2(A) + SE^2(B)) / m]^{0.5}$. When comparing the difference in responses between two groups of n_1 and n_2 subjects, $SE_{diff} = [SE^2(A-B)_1 + SE^2(A-B)_2]^{0.5}$, with $(n_1 + n_2 - 2)$ degrees of freedom.

The mean results of individual subjects were calculated for each period from the 10 resting measurements available, and from the 5 measurements available during each subsequent period, i.e., partial and complete cardiac block periods, and 'total' autonomic block. To compare difference in means between groups of subjects (e.g., of different ages) the SE between subjects was calculated for each group using one averaged result per subject as indicated above and then assessing the significance by t -test.²² The data from individual subjects was also used to examine relationships (e.g., between arterial pressure and TPRI) by standard linear regression analysis.²²

Results

Effects of Cardiac and 'Total' Autonomic Block

In the hypertensive subjects the resting mean arterial pressure, total peripheral resistance index (TPRI) and heart rate were all significantly higher than in normotensives, but the cardiac index (CI) was similar in both groups (table 1). The differences in circulatory variables between hypertensive males and females of similar ages were small and mostly not significant (table 1; except for heart rates of youngest subjects). We have therefore considered it reasonable to compare the responses to autonomic blocking drugs of the

Table 1
Resting Values of Different Groups of Normotensive and Hypertensive Subjects

	Normotensive male			Hypertensive male			Hypertensive female		
	< 30 yr	31 - 40 yr	> 41 yr	< 30 yr	31 - 40 yr	> 41 yr	< 30 yr	31 - 40 yr	> 41 yr
Number	5	5	5	6	7	4	5	6	4
Age	23.4 ± 1.9	35.4 ± 2.2	45.6 ± 1.3	23.5 ± 1.4	35.7 ± 1.0	45.8 ± 2.5	27.6 ± 1.5	36.3 ± 0.8	53.0 ± 2.4
Height (cm)	183.0 ± 2.2	170.0 ± 3.0	171.0 ± 3.4	175.0 ± 1.82	174.0 ± 1.78	174.0 ± 5.2	160.0 ± 2.4	162.0 ± 2.9	162.0 ± 1.7
Weight (kg)	76.4 ± 3.0	67.7 ± 3.0	67.6 ± 4.5	73.5 ± 4.3	73.6 ± 2.3	73.1 ± 8.4	56.8 ± 4.5	58.8 ± 4.0	63.3 ± 8.0
BSA (m ²)	1.93 ± 0.06	1.77 ± 0.05	1.78 ± 0.07	1.88 ± 0.06	1.88 ± 0.04	1.87 ± 0.10	1.55 ± 0.08	1.62 ± 0.06	1.67 ± 0.10
ECG score†	0	0	0	2.7 ± 0.95	1.00 ± 0.53	2.0 ± 1.41	0.60 ± 0.60	1.17 ± 0.75	3.25 ± 1.11
Retinal score‡	0	0	0	0.5 ± 0.34	0.57 ± 0.37	0.75 ± 0.48	0.40 ± 0.24	1.50 ± 0.34	1.75 ± 0.25
BP mm Hg	103.7 ± 1.92*	100.0 ± 2.52	100.6 ± 4.5	135.4 ± 5.1	131.2 ± 3.2	144.1 ± 10.9	131.7 ± 6.2	138.2 ± 6.2	148.9 ± 6.8
SP mm Hg	144.0 ± 2.0	139.0 ± 5.0	132.0 ± 7.0	180.0 ± 7.0	173.0 ± 3.0	194.0 ± 13.0	171.0 ± 8.0	186.0 ± 12.0	219.0 ± 11.0
DP mm Hg	85.0 ± 1.0	78.0 ± 3.0	75.0 ± 3.0	107.0 ± 7.0	105.0 ± 3.0	103.0 ± 10.0	106.0 ± 4.0	110.0 ± 5.0	114.0 ± 9.0
RAP mm Hg	6.0 ± 0.4	5.5 ± 0.5	5.3 ± 0.7	5.4 ± 0.6	6.4 ± 0.4	4.7 ± 0.1	4.8 ± 0.8	5.0 ± 0.4	4.4 ± 0.5
CI (liters/min·m ²)	3.45 ± 0.23	4.31 ± 0.53	2.92 ± 0.23	3.53 ± 0.23	3.60 ± 0.23	3.48 ± 0.36	4.0 ± 0.51	3.57 ± 0.27	3.35 ± 0.20
TPRI (units/m ²)	29.2 ± 1.70	23.9 ± 3.05	33.1 ± 3.0	38.1 ± 1.53	35.9 ± 2.13	42.6 ± 5.1	33.3 ± 2.74	39.0 ± 2.73	44.9 ± 2.89
HR/min	70.0 ± 6.0	68.0 ± 5.0	67.0 ± 4.0	71.0 ± 6.0	84.0 ± 6.0	92.0 ± 6.0	85.0 ± 3.0	85.0 ± 4.0	81.0 ± 10.0

*The result for each subject is the mean of 10 observations taken during the first and second resting periods; the SEM of each group is the SE between subjects.

†Scoring system is that of Estes, as outlined in Marriott, 1968¹².

‡Score 0 = no abnormality; 1 = arterial narrowing; 2 = nicking of veins; there were no hemorrhages, exudates or papilloedema.

Abbreviations: BSA = body surface area; BP = mean blood pressure; SP = systolic pressure; DP = diastolic pressure; RAP = right atrial pressure; CI = cardiac index; TPRI = total peripheral resistance index; HR = heart rate.

combined group of hypertensives, with the all male group of normotensives (table 2).

In the normotensive subjects the mean values of the different variables remained approximately constant during the two resting periods (fig. 1). Production of cardiac autonomic block with atropine plus beta-blocking drugs resulted in a small rise above the mean resting value, within subjects, in mean arterial pressure ($P < 0.001$) and in CI ($P = 0.001$), while the heart rate increased by 39 ± 1.2 (SE) beats/min ($P < 0.001$) (table 2). In addition there was a small reduction in TPRI ($P < 0.005$). When 'total' autonomic block was completed with guanethidine plus phentolamine the arterial pressure fell by 28 ± 0.8 mm Hg below the mean value during cardiac block, while TPRI was reduced by 3.6 ± 0.5 units/m² below this value ($P < 0.001$ for both variables). In addition there were significant reductions in CI, heart rate, and right atrial pressure and a fall in body temperature of $0.4 \pm 0.1^\circ\text{C}$.

In the hypertensive subjects the resting measurements also remained stable between the two resting periods (fig. 1). After cardiac autonomic block the arterial pressure rose slightly above resting as in normotensives, but there were no significant changes in CI and TPRI (table 2). The rise in heart rate from resting value was only 23 ± 1.0 beats/min, significantly smaller than in normoten-

sives ($P < 0.001$), but after cardiac autonomic block the heart rates were closely similar in both groups. After 'total' autonomic block the fall in hypertensive subjects from their mean cardiac block value, in mean arterial pressure (46 ± 1.1 mm Hg) and in TPRI (8.4 ± 0.6 units/m²) were significantly greater than in normotensive subjects ($P < 0.001$). When the TPRI changes in each group were expressed as percentages of the cardiac block value, the fall in hypertensives (22 ± 1.4 ; SE within subjects %), was still greater than in normotensives ($14 \pm 1.7\%$; $P_{\text{diff}} < 0.005$), though the difference was now smaller than when expressed in absolute units. The changes in CI, right atrial pressure and heart rate, and the fall in body temperature ($0.4 \pm 0.06^\circ\text{C}$) were approximately similar in both groups.

After 'total' autonomic block the absolute levels of mean arterial pressure and TPRI of the hypertensives were still significantly above corresponding levels in normotensive subjects (table 3; $P < 0.001$). Although the differences between the two groups was now smaller than at rest or during cardiac autonomic block, it was still substantial. Thus, after 'total' autonomic block the TPRI of hypertensives was on the average 7.4 units/m² above the level of normotensives, i.e., 82% of the initial resting difference, and 61% of the difference in this variable in subjects with cardiac autonomic

Table 2

Average Values During Resting Period, Complete Cardiac Block and 'Total' Autonomic Block in Normotensive and Hypertensive Subjects

		Normotensive		Hypertensive			
		Male (N = 15)		Male (N = 17)	Female (N = 15)	Combined (N = 32)	
		Mean	SE diff*	Mean	Mean	Mean	SE diff*
BP (mm Hg)	R	102	± 0.51	136	139	138	± 0.56
	CB	106	± 0.83	141	146	144	± 1.10
	TB	78		99	96	98	
CI (liters/min. m ²)	R	3.56	± 0.09	3.55	3.65	3.58	± 0.054
	CB	3.91	± 0.08	3.59	3.73	3.67	± 0.041
	TB	3.28		3.08	3.16	3.11	
TPRI (units/m ²)	R	29.8	± 0.55	38.3	39.5	38.8	± 0.53
	CB	27.2	± 0.46	39.6	39.1	39.4	± 0.56
	TB	23.6		32.0	30.2	31.0	
RAP (mm Hg)	R	5.6	± 0.10	5.6	4.8	5.2	± 0.08
	CB	4.5	± 0.09	4.9	4.5	4.7	± 0.07
	TB	4.2		4.5	4.2	4.3	
HR (beats/min)	R	68	± 1.15	81	84	83	± 1.03
	CB	107	± 0.46	108	104	106	± 0.23
	TB	98		98	95	96	

Abbreviations: BP = mean blood pressure; CI = cardiac index; TPRI = total peripheral resistance index; RAP = right atrial pressure; HR = heart rate; R = resting period; CB = cardiac block; TB = total autonomic block.

*SE diff = SE (A - B), within subjects, as explained under Statistical Methods.

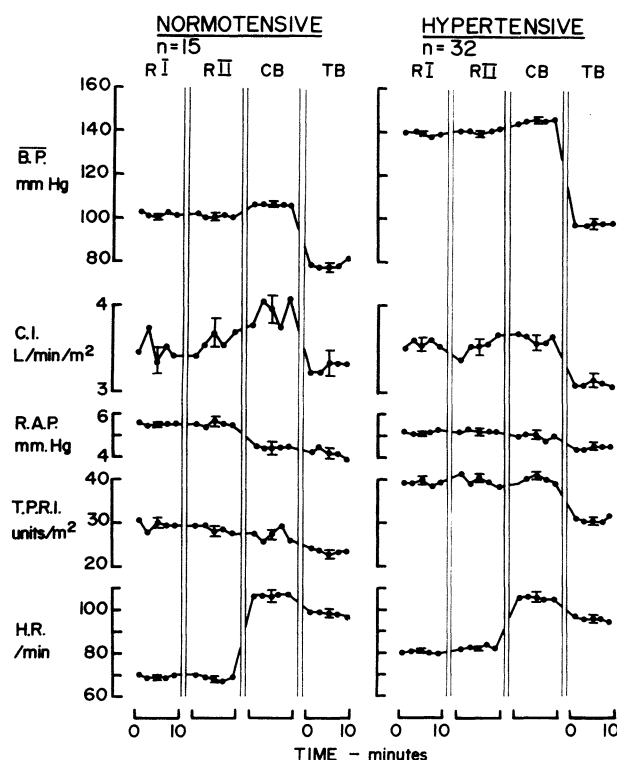


Figure 1

Mean values of the different circulatory variables obtained during first and second resting periods. (RI and RII), and periods of 'complete' cardiac (CB) and 'total' autonomic (TB) block in 15 normotensive and 32 hypertensive subjects. \overline{BP} and \overline{RAP} = mean arterial and right atrial pressures; CI = cardiac index; $TPRI$ = total peripheral resistance index; HR = heart rate. Each point is the mean of all observations of each group at that time interval. The symbol in the middle of each period is ± 1 SE, of the mean response at a single time interval, within subjects. For resting period I the standard error is calculated as $SE(A)$ in Statistical Methods, while at other periods it is calculated as $SE(B)$.

block. Assuming that the block is effective (see below), the results suggest that non-autonomic influences on TPRI make a large contribution to the elevation of blood pressure in essential hypertension.

We plotted the relationship between arterial pressure during cardiac block and TPRI during 'total' autonomic block using the results of both the hypertensive and normotensive subjects (fig. 2.). The results suggest that the higher the mean pressure before constrictor block, the greater the magnitude of the nonautonomic component of TPRI (i.e., the TPRI after block). The slope of the regression line (0.18 ± 0.035) differed from that relating arterial pressure during cardiac block with TPRI during cardiac block (0.32 ± 0.04 TPRI units/mm Hg, $P_{diff} = 0.05$). Since TPRI during cardiac block is a function of the sum of sympathetic constrictor + non-autonomic components, the divergence of the regression lines suggests that the absolute sympathetic constrictor components also increases *pari passu* with arterial pressure during cardiac block. Since the latter is closely related to the resting blood pressure (being about 5 mm Hg higher throughout the range), it seems that the higher the resting pressure the greater the magnitude of both non-autonomic and autonomic TPRI components.

Cardiac Sympathetic and Vagal Effects on Heart Rate

Cardiac sympathetic effects were assessed from the response to beta blockade of a group of resting subjects (fig. 3) and another group of previously atropinized subjects (fig. 4). In each of these

Table 3

Main Hemodynamic Differences between 32 Hypertensives and 15 Normotensives During Resting, Cardiac Autonomic Block and 'Total' Autonomic Block Periods

		Resting	Cardiac block	'Total' block
BP (mm Hg)	N	102.0 \pm 1.7*	106.0 \pm 1.7	78.0 \pm 2.8
	H	138.0 \pm 2.7*	144.0 \pm 2.7	98.0 \pm 2.9
	Δ	36.0 \pm 3.2†	38.0 \pm 3.2	20.0 \pm 4.0
CI (liters/min. m ²)	N	3.37 \pm 0.2	3.91 \pm 0.25	3.32 \pm 0.20
	H	3.58 \pm 0.12	3.67 \pm 0.11	3.14 \pm 0.11
	Δ	0.21 \pm 0.23	-0.24 \pm 0.27	-0.18 \pm 0.23
TPRI (units/m ²)	N	29.8 \pm 1.5	27.2 \pm 1.5	23.4 \pm 1.2
	H	38.8 \pm 1.3	39.4 \pm 1.4	30.8 \pm 1.2
	Δ	9.0 \pm 2.0	12.2 \pm 2.1	7.4 \pm 1.7

Abbreviations: \overline{BP} = mean blood pressure; CI = cardiac index; $TPRI$ = total peripheral resistance index; N = normotensive subjects; H = hypertensive subjects; Δ = hypertensive - normotensive value.

*In each subject resting results based on 10 measurements, cardiac and 'total' autonomic block each on 5; standard error calculated between subjects.

†Standard error is standard error of difference between the groups.

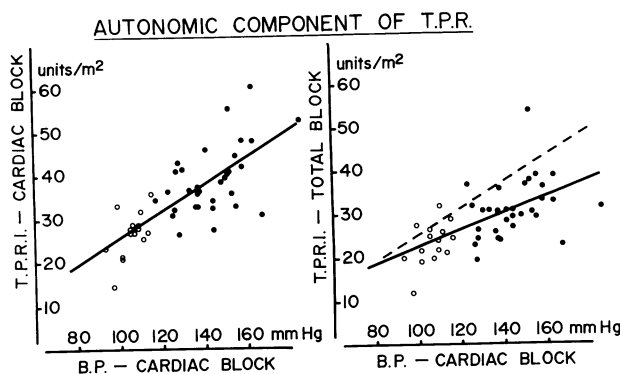


Figure 2

(Left) Relationship between mean \overline{BP} during cardiac block, and TPRI during cardiac block derived from all the normotensive (open circles) and hypertensive subjects (closed circles) showing the calculated regression line. (Right) Relationship between mean arterial pressure during cardiac block, with total peripheral resistance value (TPRI) obtained in each subject during subsequent 'total' autonomic block. The heavy line is the calculated regression line, whilst the dashed line is the regression line from the graph on the left.

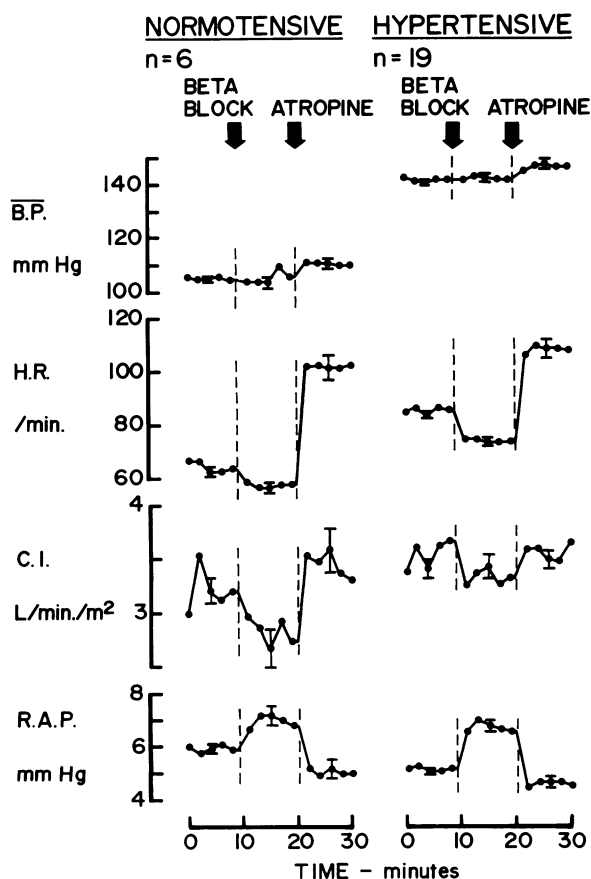


Figure 3

Circulatory effects in six normotensives and 19 hypertensives of giving first a beta-adrenergic blocking drug, and then atropine. Notation as in figure 1.

Circulation, Volume XLVIII, July 1973

groups beta-blockade elicited a fall in heart rate and a rise in atrial pressure while a fall in CI was more striking in the non-atropinized group. In the latter the fall in heart rate was significantly greater in hypertensives ($12 \pm 0.7/\text{min}$) than in normotensives ($7 \pm 1.1/\text{min}$; P diff 0.001). In atropinized subjects the reduction in heart rate after beta-blockade was greater than in the resting subjects, and the response of the hypertensives ($25 \pm 1.6/\text{min}$) was only slightly greater than that of normotensives ($22 \pm 1.4/\text{min}$; P diff 0.2). We have taken that the best estimate of 'true' cardiac sympathetic effects is the mean of the estimates obtained from resting and previously atropinized subjects (see Discussion). In the hypertensives this was $(12 + 25)/2 = 18.5 \pm 1.7/\text{min}$, while in normotensives it was $(7 + 22)/2 = 14.5 \pm 1.7/\text{min}$.

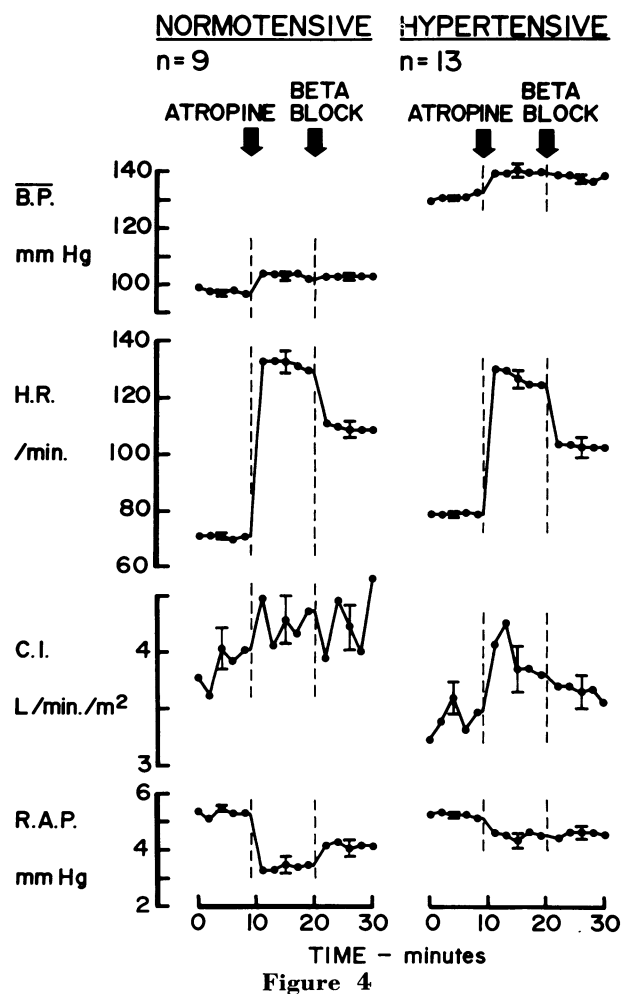


Figure 4

Circulatory effects in nine normotensives and 13 hypertensives of giving first atropine, and then a beta-adrenergic blocking drug (propranolol, oxprenolol, prindolol). Notation as in figure 1.

($P = 0.1$). The findings suggest that cardiac sympathetic effects on heart rate were only marginally increased in hypertensives if at all.

Vagal effects were assessed from the heart rate changes produced by atropine in a group of resting subjects (fig. 4), and in another group of previously beta-blocked subjects (fig. 3). In both these groups atropinization evoked marked tachycardia, some rise in CI and arterial pressure, and reduction in right atrial pressure. In both the resting and previously beta-blocked subjects the increase in heart rate after atropine was smaller in hypertensives ($49 \pm 1.2/\text{min}$; $34 \pm 1.5/\text{min}$) than in the corresponding group of normotensives ($61 \pm 1.7/\text{min}$; $44 \pm 2.2/\text{min}$). We have again taken the mean of each estimate as the best assessment of the 'true' resting vagal effect on heart rate. This gave a rise in rate of $41.5 \pm 2.1/\text{min}$ in hypertensives, and $52.5 \pm 2.7/\text{min}$ in normotensives ($P \text{ diff} < 0.01$). The vagal effects on heart rate were thus significantly smaller in hypertensives.

Effectiveness of Block

The different types of autonomic blockade considerably modified the normal arterial pressure and heart rate responses during and after Valsalva maneuver in both groups of subjects (fig. 5). Before blockade the pulse pressure was markedly reduced and the heart rate increased during the period of raised intrathoracic pressure, while the mean arterial pressure had become completely restored at the end of that period. After the maneuver, the characteristic systolic and diastolic pressure overshoots and cardiac slowing were observed.²³ Cardiac block with atropine and beta-blocking drugs had relatively little effect on the pressure responses during block, but the overshoot was attenuated, and the heart rate response virtually abolished. After 'total' autonomic block the mean arterial pressure and pulse pressures both declined while the intrathoracic pressure was raised, the mean arterial pressure falling by 40-50 mm Hg (mean change from control 48 ± 4.5 (SD) mm Hg) in this time. At the end of the maneuver the arterial pressure recovered only gradually without any overshoot.

We also examined the response to posture in seven hypertensive subjects. Before block assumption of the upright sitting posture resulted in a rise in heart rate ($P < 0.025$), a slight increase in TPRI ($+6.1 \pm 3.3 \text{ units/m}^2$; $0.1 > P > 0.05$), and little change in arterial pressure and CI. After 'total' autonomic block there was no change in heart rate,

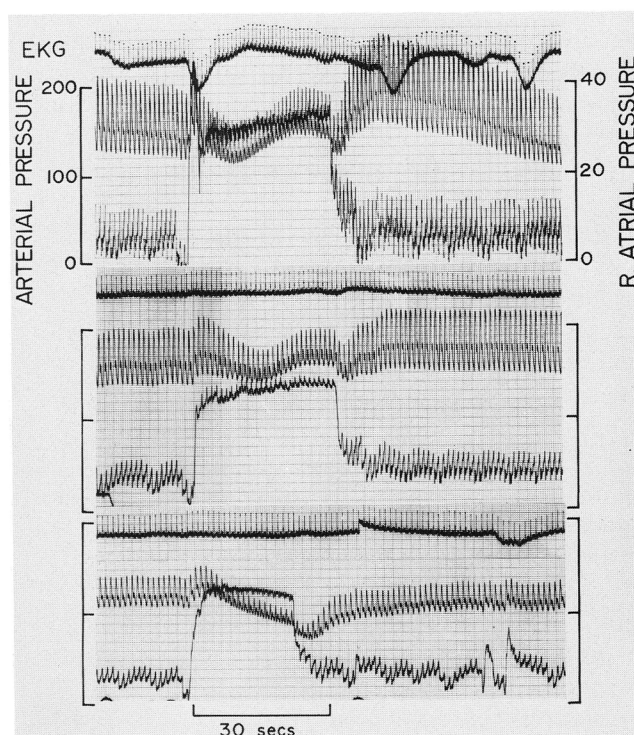


Figure 5

Responses to Valsalva maneuver in one subject obtained before any block (top), after complete cardiac block with atropine + propranolol (middle), and after 'total' autonomic block with atropine + propranolol + guanethidine + phentolamine (bottom). Each record shows from top electrocardiogram (EKG), arterial pressure and right atrial pressure.

TPRI fell by an average of $5.1 \pm 1.8 \text{ units/m}^2$ ($P < 0.05$), and arterial pressure and CI fell by $46 \pm 4.3 \text{ mm Hg}$ and $0.98 \pm 0.15 \text{ liters/min per m}^2$ respectively. The hypotension was rapidly reversed on returning to the supine posture.

Discussion

Degree of Autonomic Block

The adequacy of 'total' autonomic block in the present study is important in interpreting the differences in magnitude of non-autonomic effects on TPRI between hypertensives and normotensives. Although the dose of each autonomic blocking drug used in the present study is as great as any previously used in man, it is smaller than the dose necessary to block the appropriate effectors during maximal physiological stimuli in animal experiments.^{19, 24, 25} The results with cardiac block are substantially in agreement with previous findings of Jose and Taylor,¹⁸ and of Julius, Pascual and London.¹⁰ After 'total' autonomic block the rapid reduction in mean arterial pressure during the period of raised intrathoracic pressure in the

Valsalva maneuver suggests minimal neural control of blood pressure. The reduction in TPRI on standing after 'total' block is consistent with the autoregulatory Bayliss effect resulting from the hypotension,²⁶ rather than with a reflex phenomenon. In addition, the reduction in arterial pressure from the mean resting value in our normotensive and hypertensive subjects, and the absolute levels reached after 'total' block, are identical with the figures observed by Doyle and Smirk,⁴ who determined the lowest blood pressure levels obtainable by large intravenous doses of hexamethonium.

These findings suggest that peripheral autonomic block to *moderate* physiological stimuli is achieved by the present combination of drugs. The combined intravenous use of guanethidine + phentolamine may have been of advantage, in view of their different sites of action on the peripheral adrenergic neurone.^{20, 27} Phentolamine also has direct vasodilator action which may have contributed to the responses,²⁸ but guanethidine is relatively free of non-autonomic side effects. We have assumed that the side effects are small and affect both groups equally. The block is thus probably adequate in eliminating most of the autonomic tone in both normotensives and hypertensives, and also the reflex changes due to the acute blood pressure drop.

Autonomic and Non-Autonomic TPRI Components

The finding that the elevation in blood pressure in subjects with established essential hypertension is entirely accounted for by a rise in resting TPRI is in agreement with earlier findings.^{9, 29-31} However the present results demonstrate that 60-80% of the difference between hypertensives and normotensives is due to elevation of non-autonomic TPRI component, which rises with increasing severity of hypertension. There is at present no evidence of anatomical differences in length of resistance vessels between hypertensives and normotensives, or differences in blood viscosity.^{7, 32, 33} The high non-autonomic TPRI effect is thus due to progressive reduction in vascular caliber with increasing hypertension. The only peripheral bed so far studied after regional autonomic block in hypertension is the hand circulation, where the non-autonomic resistance component has been found to be elevated.^{34, 35} The present findings suggest that the rise in non-autonomic resistance effect in hypertension probably involves several vascular beds, sufficient to alter TPRI.

The magnitude of the TPRI effect mediated through sympathetic constrictor mechanisms also increases progressively with rise in blood pressure, but this does not necessarily mean that sympathetic neural activity has increased.

From the Laplace relationship tension in the wall of the resistance vessels is a function of transmural pressure and vascular caliber. The tension developed by the muscle is in turn determined by constrictor nerve activity, the muscle's metabolic environment and the length of the muscle fibers, the last being also a function of vessel caliber.³⁶ Hence the equilibrium caliber of the vessel is a complex function of autonomic activity, and arterial pressure. After autonomic block there are greater caliber changes in hypertensives than in normotensives, but there are also greater pressure changes. Hence we cannot conclude that the greater autonomic effect is due to a greater resting sympathetic constrictor nerve activity. It might be a consequence of the elevation of the non-autonomic component of TPRI.

Cardiac Autonomic Effects

In earlier studies assessment of, for example, the cardiac sympathetic effect on heart rate has been made from the changes observed after administration of a beta-blocking agent in subjects not previously given any drug.³⁻⁶ The present method differs in that the estimate is based on the average of the responses to the blocking drug of (1) previously unblocked subjects, and (2) subjects whose other cardiac effector has already been blocked (e.g., by atropine). When estimating the cardiac sympathetic effects from the heart rate response to beta-blockade, the right atrial pressure is above the initial resting value in resting subjects (fig. 3), but below this value in previously atropinized subjects (fig. 4). These changes are likely to be associated with differences in reflex activity.³⁷ The average of the response of the resting and partially blocked groups most closely corresponds to the initial intravascular pressures, and thus provides the best estimate of the 'true' resting autonomic heart rate effects for a given effector mechanism.

The present findings show that the higher resting heart rate in established hypertension is almost entirely due to reduction in vagal effect. Had our estimate of sympathetic effects been based solely on the changes after beta-adrenergic blockade in previously unblocked subjects, we would have inferred that effects had increased in established hypertension, as previously reported in borderline

hypertension.^{8,9} Our findings of reduced parasympathetic effects in established hypertension are similar to those of Julius, Pascual and London¹⁰ in borderline hypertension. Since the 'intrinsic' heart rate¹⁸ after complete cardiac block is the same in both normotensives and hypertensives, the reduced parasympathetic effects in established hypertension will denote reduction in neural vagal activity.

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