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Baroreflex sensitivity and cardiopulmonary blood volume in normotensive and hypertensive patients

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Baroreflex sensitivity and cardiopulmonary blood volume were determined in 95 men, including normotensive and hypertensive subjects with normal renal function and balanced sodium intake and urinary output. Baroreflex sensitivity was estimated by determining the slope of the regression line relating the increase of systolic pressure to the cardiac slowing after transient rises of arterial pressure. A technique of gradual atropinisation was used to evaluate the parasympathetic mediated component of the reflex. With this method, it was possible to calculate the exact atropine dose abolishing the reflex sensitivity. This index was not dependent on age. It was negatively correlated to the diastolic pressure in normotensive patients but not in hypertensive patients. The ratio between the cardiopulmonary and the total blood volume was considered as an index of sympathetic venous tone. This ratio was positively correlated to the diastolic pressure in normotensive patients, but not in hypertensive patients. This study strongly suggests that a precise sympathetic-parasympathetic balance existed in the normotensive patients. This balance was disrupted in the hypertensive patients pointing to abnormalities in the autonomic nervous system of permanently hypertensive patients.

Increasing evidence suggests that essential hypertension is associated with a pronounced disturbance of the autonomic nervous system. Profound changes in the metabolism and the activity of the autonomic nerves have been shown in various models of experimental hypertension (Chalmers, 1975; Haeusler, 1975; Reid *et al.*, 1975). No comparable information has been obtained in man, because of the difficulty in assessing the sympathetic and parasympathetic status.

Although the sympathetic system in essential hypertension has been extensively studied, few quantitative estimations are available. Nevertheless, the evidence for an overactive sympathetic activity remains controversial (Louis *et al.*, 1974; Berglund *et al.*, 1976). Among the haemodynamic values, heart rate, response to tilt, and basal cardiopulmonary blood volume have been proposed as indices of sympathetic activity (Frohlich *et al.*, 1967; DeQuattro and Miura, 1973; Ellis and Julius, 1973; Safar *et al.*, 1975). Information concerning the parasympathetic system is more difficult to obtain, because of the lack of adequate indices. However, a possible approach for assessment of parasympathetic function results from the evaluation of baroreceptor responsiveness to rising arterial pressure. Recent studies have shown that baroreflex bradycardia is mediated predominantly by the parasympathetic (Eckberg *et al.*, 1971; Pickering *et al.*, 1972).

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In order to help elucidate the role of the parasympathetic system in hypertension, we have studied, in 95 normal and essential hypertensive subjects, the baroreflex cardiac slowing consecutive to a transient rise of arterial pressure. A special method is suggested to enable a quantitative evaluation of the baroreflex parasympathetic component to be made. In some patients, sympathetic activity was also estimated by the measurement of the basal cardiopulmonary blood volume.

Subjects and methods

SUBJECTS

Ninety-five subjects [mean age: 36 $\pm$4 years ($\pm$1 standard error of the mean)] were included in this study. The diastolic pressure recordings of outpatients ranged between 60 and 140 mmHg, corresponding to normal subjects or patients referred to the hospital because of high blood pressure.

The subjects were untreated or had discontinued their therapy at least four weeks before the study. They were admitted to hospital for 6 days and

placed on a sodium diet of 100 mmol per day.

All the patients referred because of suspected hypertension were submitted to extensive investigations including blood and urinary electrolytes, catecholamine determinations, endogenous creatinine clearance, timed intravenous urography, and/or renal arteriography. All of these patients were listed as essential hypertensives. None had neurological or cardiac involvement; mild to moderate left ventricular hypertrophy was observed in 41 patients. Mean creatinine clearance was 86 ± 12 ml/min per m^2.

Consent for investigations was obtained after detailed description of the procedure, and the procedure was approved by INSERM (Institut National de la Santé et de la Recherche Médicale).

ESTIMATION OF BAROREFLEX SENSITIVITY

Seventy-two patients were studied in the supine position without premedication, on the third day in hospital. Under local procaine anaesthesia, a polyethylene catheter was introduced into the right brachial artery for continuous measurement of the intra-arterial blood pressure. Arterial pressure, respiratory movements obtained by a pneumograph, and electrocardiogram were recorded simultaneously on a multichannel oscillograph (Siemens). A second cannula was inserted in a median antecubital vein and allowed the multiple bolus injections necessary for the baroreflex sensitivity estimation.

The basal sensitivity of the baroreflex was determined by using the technique of Smyth *et al.* (1969). Several bolus intravenous injections of 50 to 200 μg phenylephrine were given to induce a transient rise of the arterial pressure by 20 to 40 mmHg. The systolic blood pressure of each beat was plotted against the second interval RR (in ms) following it. Plotting was started 10 beats after the end of injection until just after the peak systolic pressure; RR intervals during inspiration were not included in order to reduce the effects of sinus arrhythmia. Linear relations between RR intervals and systolic blood pressure were observed and the RR systolic pressure correlations with a P value of less than 0·02 were discounted. The reflex sensitivity was expressed as the slope of the regression line (milliseconds increase in RR interval per mmHg rise in systolic blood pressure). The mean value of two or three slopes was used as estimation of the basal sensitivity and called 'basal slope'.

The baroreflex sensitivity tested by means of phenylephrine was also determined after propranolol and after propranolol plus atropine by intravenous injection.

Beta adrenergic blockade by propranolol was induced before atropinisation. The dose of propranolol (0·2 mg/kg body weight) was known to produce effective beta-adrenergic blockade (Jose and Taylor, 1969). The baroreflex slope was calculated 10 minutes after the intravenous injection of propranolol and was called 'slope after propranolol'.

Parasympathetic blockade by atropine was induced after propranolol blockade. As well established in the literature, total parasympathetic blockade can be obtained by the intravenous injection of 0·04 mg/kg atropine sulphate (Jose and Taylor, 1969; Eckberg *et al.*, 1971; Pickering *et al.*, 1972). However, the corresponding baroreflex response is almost abolished and does not, therefore, allow determination of the precise level of parasympathetic blockade. In the present study, progressive parasympathetic blockade was used by dividing the total dose of atropine of 0·04 mg/kg into 6 successive and cumulative doses; individual doses were injected intravenously every 10 minutes. The baroreflex slope was repeatedly determined during this gradual atropinisation as follows: each partial dose of atropine was followed 5 minutes later by the determination of the slope; each slope determination was followed by 5 minutes of rest in order to eliminate any remaining effect of the phenylephrine. This procedure was repeated 6 times. Through all this period, no significant change in blood pressure was observed. The slopes so calculated declined as progressive parasympatoetic blockade occurred. The slope was plotted semilogarithmically against the immediate preceding dose of atropine expressed per kilogram of body weight. A significant negative linear correlation was found between the slope and the log atropine dose (Fig. 1). By means of this log dose slope curve, the dose of atropine corresponding to a zero slope was calculated. This dose was called 'atropine blocking dose' and was used as a quantitative evaluation of the parasympathetic blockade level (Fig. 1).

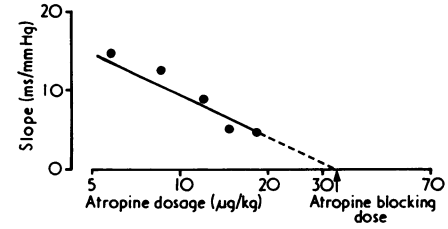

Fig. 1 *Dose response curve between the atropine dose and the slope of the baroreflex (semilogarithmic scale). The arrow corresponds to the so-called 'atropine blocking dose' (see text).*

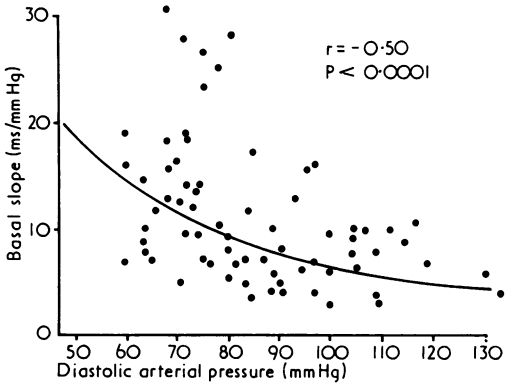

Fig. 2 *Relation between the basal slope and the diastolic arterial pressure in the overall population. The hyperbolic model existed even with the semilogarithmic scale.*

CARDIOPULMONARY BLOOD VOLUME ESTIMATION

Cardiopulmonary blood volume (CPBV) was measured on the third day in hospital in 95 patients, as previously described (Safar *et al.*, 1975). Two polyethylene catheters were introduced, the first into the right brachial artery and the other into a median antecubital vein. They were respectively advanced under fluoroscopic control into the aortic arch and the main pulmonary artery. Cardiopulmonary blood volume was expressed as the volume between the main pulmonary artery and the aortic root immediately distal to the aortic valves. It was calculated by the Stewart-Hamilton method (Hamilton *et al.*, 1932) as following: CPBV (ml/kg) = CI (ml/min/kg) × Tm (s) (PA-Ar); Tm(PA-Ar) equals mean transit time in seconds from the pulmonary artery (PA) to the tip of the arterial catheter (Ar).

Total blood volume (TBV) was simultaneously measured by radio-iodinated albumin, as previously described (Safar *et al.*, 1975). The CPBV/TBV ratio was calculated. This ratio represented the fraction of total blood volume in the heart and lungs and was independent of normalisation.

Table *Relation between diastolic arterial pressure and baroreflex slope, before and after propranolol: a hyperbolic model ($Y = a/X + b$) was presented*

Y	*X*	*r value*	*P value (n = 72)*	*Regression coefficient (± 1 standard error of the slope)*	*Intercept*
Slope basal value (ms/mmHg)	Diastolic pressure (mmHg)	−0·50	< 0·0001	51·4 ± 7·2	0·34
Slope after propranolol (ms/mmHg)	Diastolic pressure (mmHg)	−0·41	< 0·0001	46·2 ± 9·3	0·51

HAEMODYNAMIC CLASSIFICATION OF PATIENTS

The criterion for the classification of the patients was the diastolic intra-arterial pressure recorded during cardiac output determination. All blood pressure determinations were made with the subject in the resting position after a period of familiarisation. Any patient with adverse reactions was eliminated; in no instance was the basal blood pressure value significantly different on repeat measurements.

The intra-arterial diastolic pressure ranged from 60 to 135 mmHg and presented a continuous series (Pickering, 1968) which was arbitrarily divided into 2 groups. The patients were considered as normotensive when the blood pressure recording showed a diastolic pressure of 90 mmHg or less. The patients were considered as hypertensive when the diastolic pressure was above this value. Statistical analysis using classical methods (Croxton and Cowden, 1939) (difference of means, correlations and regression) was performed in the 2 groups of patients.

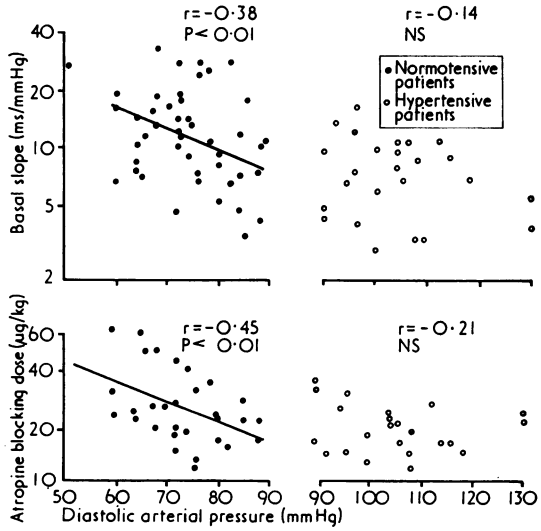

Fig. 3 *Correlations: (i) between the basal slope and the diastolic arterial pressure, and (ii) between the atropine blocking dose and the diastolic arterial pressure, in normotensive and hypertensive patients (semilogarithmic scale).*

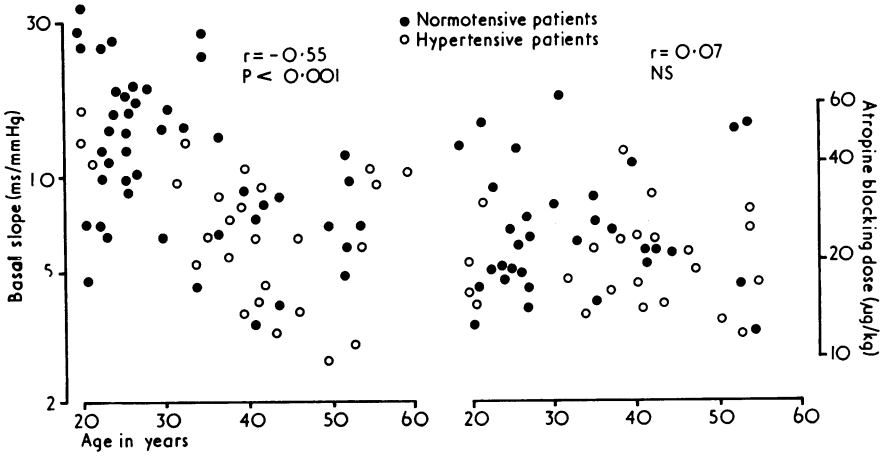

Fig. 4 *Correlations: (i) between the basal slope and age, and (ii) between the atropine blocking dose and age, in the overall population (semilogarithmic scale). Note that the basal slope was negatively correlated to the age both in normotensive and hypertensive patients, while the atropine blocking dose was not.*

Results

I—BAROREFLEX SENSITIVITY ESTIMATION

Basal slope in overall population (72 patients)

The basal slope was negatively correlated to the diastolic arterial pressure ($P < 0.001$) (Fig. 2). The correlation existed even for a constant age.

The relation was curvilinear rather than linear. The major model of the curve was hyperbolic (Fig. 2). This model existed even on a semilogarithmic scale. Propranolol did not modify the regression curve (Table).

Comparison between normotensive and hypertensive patients

The basal slope in the normotensive group was negatively correlated to the diastolic pressure ($P < 0.01$) (Fig. 3). No correlation was observed in the hypertensive group (Fig. 3).

Age was negatively correlated to the basal slope, both in normotensive ($P < 0.001$) and hypertensive subjects ($P < 0.001$) (Fig. 4).

The atropine blocking dose was negatively correlated to the diastolic pressure in the normotensive group ($P < 0.001$) (Fig. 3) but not in the hypertensive group (Fig. 3). There was no correlation between age and atropine blocking dose in the overall population or in each subgroup (Fig. 4).

II—CARDIOPULMONARY BLOOD VOLUME ESTIMATION

In normotensive patients, a significant positive correlation was observed between the CPBV/TBV ratio and the diastolic arterial pressure ($P < 0.01$) (Fig. 5). This correlation was not age dependent (partial correlation). In hypertensive subjects no correlation existed between CPBV/TBV ratio and diastolic pressure (Fig. 5). No significant difference existed in the cardiopulmonary blood volumes mean values of normotensive and hypertensive patients.

Discussion

BAROREFLEX SENSITIVITY ESTIMATION

The results of this study indicate that baroreflex sensitivity decreases in parallel with the rise in blood pressure, in agreement with other reports

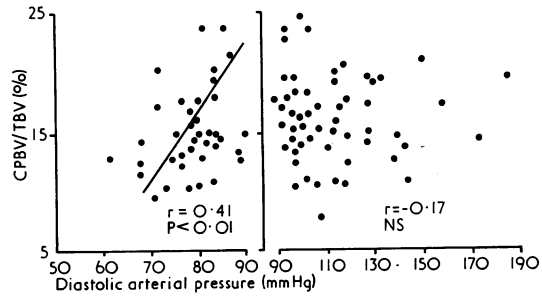

Fig. 5 *Correlation between the CPBV/TBV ratio and the diastolic arterial pressure in normotensive and hypertensive patients. CPBV, cardiopulmonary blood volume; TBV, total blood volume.*

(Bristow *et al.*, 1969; Gribbin *et al.*, 1971; Takeshita *et al.*, 1975). When analysing the overall population, the regression line between the baroreflex sensitivity and the diastolic pressure is of hyperbolic type. This finding is consistent with published studies, in which the plot of baroreflex sensitivity against pressure is curvilinear rather than linear (Bristow *et al.*, 1971; Gribbin *et al.*, 1971). Such a hyperbolic curve points to a defect in the reduction of the slope with increasing pressure in the high blood pressure range. Analysis of the overall population is in agreement with a smooth graduation between normal and high blood pressure as reported in large epidemiological studies (Pickering, 1968). However, in order to help elucidate the mechanisms responsible for the slope decline, the subjects were arbitrarily divided into two groups: normotensive and hypertensive patients.

Two mechanisms are commonly invoked to explain the reduced baroreflex response with increase in blood pressure:

The first is the reduction of the baroreceptors arterial wall compliance resulting from increasing stiffness by medial hypertrophy, arteriosclerosis, or increase in the sodium and water contents or the arterial walls (Bader, 1967). In this study, this hypothesis is supported by the finding that increasing age is associated with the reduction of baroreflex sensitivity. Such a result is observed both in normotensive and hypertensive patients, as previously shown by others (Gribbin *et al.*, 1971).

The second possibility for the diminished baroreflex response is parasympathetic nerve depression (Bristow *et al.*, 1971; Eckberg *et al.*, 1971; Pickering *et al.*, 1972). In the present report, a special method using gradual atropinisation was used to determine the atropine dose required to block completely the parasympathetic component of the baroreflex. Beta-adrenergic blockade, intended to eliminate any sympathetic interaction, did not modify the baroreflex responsiveness. The finding that the atropine blocking dose decreases with increasing diastolic pressure indicates a parasympathetic tone depression consecutive to the rise in blood pressure. This result is seen in normotensive subjects, but not in hypertensive groups. However, the possibility remains that the parasympathetic nerve depression may reflect a reduction in compliance in the baroreceptor region and hence less baroreflex buffering of sympathetic tone, and reflex increase of parasympathetic tone. This mechanism should affect mainly the older subjects with higher pressures in whom the baroreceptor arterial wall is likely to be stiffer. The lack of correlation of the atropine blocking dose with age excludes this hypothesis. This latter is not in agreement with previous studies (Nalefski and Brown, 1950) suggesting that vagal tone diminishes progressively with age. However, the decreased vagal tone with age in these reports was only based on the changes in heart rate after atropine administration, whereas the proposed atropine blocking dose is estimated from the overall baroreceptor arc reflex and so provides a more reliable index.

Of the two mechanisms responsible for the slope decline, arterial baroreceptor compliance appears to play a role in both normotensive and hypertensive subjects. In contrast, the parasympathetic depression of the baroreflex with increased pressure exists only in the normotensive patients. The lack of such a phenomenon in hypertensives points to a malfunction of the parasympathetic nervous system in these patients.

CARDIOPULMONARY BLOOD VOLUME ESTIMATION

The cardiopulmonary blood volume, by reflecting the fraction of blood in the lungs and the heart, is mainly determined by the compliance of the capacitance vessels in the peripheral circulatory system. It has been well established that the constriction of capacitance vessels is related to sympathetic venous tone (Yu, 1969). In addition, the cardiopulmonary blood volume has been shown to be strongly correlated to major biological sympathetic indices, such as plasma dopamine-beta-hydroxylase activity and vascular reactivity to norepinephrine in borderline hypertension, which is characterised by sympathetic hyperactivity (Safar *et al.*, 1975; Alexandre *et al.*, 1975). Thus, it can be tentatively concluded that determination of the cardiopulmonary blood volume constitutes an indirect estimation of sympathetic venous tone.

According to the above statement, the finding that the CPBV/TBV ratio increases in parallel with the diastolic pressure suggests the existence of a common sympathetic influence on these two factors. These results are observed in the normotensive, but not in the hypertensive group. Since the hypertensive patients had no evidence of cardiac impairment, it does not seem likely that a change of the compliance of the left ventricle could explain the lack of correlation. Thus, the disappearance in the correlation between diastolic pressure and CPBV/TBV ratio in hypertensive group suggests a disrupted sympathetic mechanism in these patients.

PARASYMPATHETIC AND SYMPATHETIC BALANCE IN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS

Previous studies provide evidence of a parasympathetic-sympathetic balance. Central or peri-

pheral autonomic interactions modulate the baroreflex (Gellhorn, 1964; Glick and Braunwald, 1965; Warner and Russell, 1969; Klevans and Gebber, 1970; DeQuattro and Miura, 1973). The attenuation of the baroreflex sensitivity in states of heightened sympathetic activity such as exercise (Bristow *et al.*, 1971; Pickering *et al.*, 1972) and heart failure (Eckberg *et al.*, 1971) are considered to be the result of central modulation of the reflex arc rather than the direct interaction of sympathetic and parasympathetic activities peripherally. Julius *et al.* (1971) reported a simultaneous increase of sympathetic activity and decrease of parasympathetic tone in patients with borderline hypertension.

The present study is in agreement with these findings. In the normotensive group, the increase in pressure is related both to: (i) a decrease in the atropine blocking dose and, (ii) an increase in the CPBV/TBV ratio, so evoking a precise sympathetic-parasympathetic balance. Such a balance is disrupted in hypertensive patients, indicating an alteration in both sympathetic and parasympathetic controls. This observation is consistent with previous experimental studies (Chalmers, 1975; Reid *et al.*, 1975) which have shown that impairment of the autonomic nervous system, particularly in its central connections, might represent a trigger mechanism for the initiation and the maintenance of hypertension.

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