Cardiopulmonary Reflex Before and After Regression of Left Ventricular Hypertrophy in Essential Hypertension

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SUMMARY Studies that have examined the cardiopulmonary receptor control of circulation in hypertension have produced conflicting results. In 10 normotensive subjects and in age-matched essential hypertensive subjects without ($n = 10$) or with left ventricular hypertrophy ($n = 12$), as well as in seven subjects of the latter group restudied after 1 year of treatment that induced regression of cardiac hypertrophy, we examined the cardiopulmonary reflex by increasing central venous pressure and stimulating cardiopulmonary receptors through passive leg raising and by reducing central venous pressure and deactivating cardiopulmonary receptors through nonhypotensive lower body negative pressure. Reflex responses were measured as changes in forearm vascular resistance (mean blood pressure divided by plethysmographically measured blood flow), plasma norepinephrine concentration, and plasma renin activity. In hypertensive subjects without left ventricular hypertrophy, stimulation and deactivation of cardiopulmonary receptors caused changes in forearm vascular resistance, norepinephrine concentration, and plasma renin activity that were modestly reduced as compared with those in normotensive subjects. However, all these changes were markedly reduced in hypertensive subjects with left ventricular hypertrophy. Following regression of left ventricular hypertrophy, the changes in vascular resistance, plasma norepinephrine, and plasma renin activity induced by cardiopulmonary receptor manipulation all improved markedly. These results demonstrate that cardiopulmonary receptor regulation of peripheral vascular resistance and of neurohumoral variables is impaired in essential hypertension and that the impairment is much more pronounced when this condition is associated with cardiac structural alterations. Therapeutic regression of these alterations, however, leads to a marked improvement of this reflex, with consequent favorable effects on circulatory homeostasis. (Hypertension 12: 227–237, 1988)

S TUDIES performed in animals and humans have shown that reflex control of circulation depends not only on arterial baroreceptors but also, and to an important extent, on receptors located in the cardiopulmonary region. These receptors reduce sympathetic vasoconstrictor tone to skeletal muscle, splanchnic, and other regional circulations.[1-3] Furthermore, they inhibit renin secretion from the kidney[1, 4-7] and, possibly, vasopressin

release,[8] thereby controlling not only blood pressure but also blood volume.

The value of cardiopulmonary receptors in cardiovascular regulation makes it important to know whether this reflex mechanism is altered in hypertension. However, the limited number of studies that have addressed this issue have produced incomplete and conflicting results. Cardiopulmonary receptor influences on sympathetic activity were found to be enhanced in spontaneously hypertensive rats[9] but impaired in rabbits with renovascular hypertension.[10] Likewise, while in borderline hypertensive subjects cardiopulmonary receptor modulation of forearm vascular resistance was found to be increased,[11] a reduction was reported in subjects with more definite blood pressure elevations.[12, 13]

In the present study we compared the cardiopulmonary receptor influence on forearm circulation and renin release in normotensive subjects and in essential hypertensive subjects with and without left ventricular hypertrophy. The results demonstrate that the cardiopulmonary reflex is impaired in this condition. However, the impairment is modest in mild hypertension and becomes marked when the hypertension is so severe as to be associated with hypertrophic changes of the heart.

Subjects and Methods

Our study was performed with subjects of both sexes (25 men, 7 women), whose ages ranged from 18 to 42 years. Ten subjects (mean age 29.1 ± 3.2 [SE] years) were normotensive and had no history of cardiovascular disease. The remaining 22 subjects had essential hypertension. None of the hypertensive subjects had a history of cerebrovascular complications, myocardial infarction, or heart failure; none had a fundus beyond Grade 1 or 2 (Keith-Wagener classification) or clinical or laboratory evidence of coronary heart disease, peripheral artery disease, or major renal damage.

In 10 hypertensive subjects (mean age, 29.9 ± 2.6 years) an echocardiogram was within normal limits, while in the remaining 12 hypertensive subjects (mean age, 29.1 ± 2.2 years) it showed a left ventricular hypertrophy. None of the hypertensive subjects were under antihypertensive treatment at the time of the study, either because the hypertension had just been discovered or because treatment had been withdrawn 1 to 2 weeks before. Treatment also was withdrawn for 1 to 2 weeks in the subjects who underwent a second study (see Protocol).

All subjects gave their consent to the investigation after being informed of its nature and purpose.

Hemodynamic Measurements

Hemodynamic measurements consisted of arterial blood pressure, heart rate, central venous pressure, forearm blood flow, and forearm vascular resistance. Arterial blood pressure was measured with a mercury sphygmomanometer using the first and the fifth Korotkoff sounds to identify systolic and diastolic blood pressure, respectively. Heart rate was measured beat-to-beat by a cardiotachometer triggered by the R wave of an electrocardiogram. Central venous pressure was measured by a catheter placed in or near the right atrium from an antecubital vein of the arm employed for blood pressure measurements and connected to a Statham transducer (Model P231D, Gould Statham, Hato Rey, Puerto Rico).

Forearm blood flow was measured by venous occlusion plethysmography (Hokanson EC4, Inagua, WA, USA)[14] using a mercury-in-Silastic strain gauge applied around the forearm contralateral to that employed for blood pressure measurements. The strain gauge was placed approximately 4 to 5 cm below the antecubital crease, and the measurements were performed at constant room temperature (23–24 °C) while circulation of the hand was temporarily arrested by application of a suprasystolic pressure in a cuff positioned around the wrist. Forearm vascular resistance was derived from the ratio between mean arterial pressure (diastolic blood pressure plus one third of pulse pressure) and forearm blood flow.

In each subject septal and left posterior cardiac wall thickness was measured in diastole by monodimensional echocardiography after bidimensional echocardiographic control (ATL 300 ultrasonograph, Seattle, WA, USA). Left ventricular mass index was calculated according to the formula of the Penn convention.[15] All measurements were made by a single investigator who was unaware of the subjects' blood pressure values and of the data on the cardiopulmonary reflex. Two echocardiographic measurements obtained on the same subject at a 1-day interval agreed by ±8%, indicating a good within-subject reproducibility of the data.

Humoral Measurements

Humoral measurements consisted of plasma renin activity and plasma norepinephrine concentration in blood samples (13 ml) withdrawn from the right atrium. Plasma renin activity was measured by radioimmunoassay,[16] and plasma norepinephrine concentration was measured by high performance liquid chromatography.[17] Blood for plasma renin activity assay was collected in EDTA-treated tubes, and blood for plasma norepinephrine measurements was collected in EDTA glutathione–treated tubes. All samples were collected in prechilled tubes and processed at 4 °C, and the plasma was kept at −70 °C until assayed.

Maneuvers for Deactivating and Stimulating Cardiopulmonary Receptors

Deactivation of cardiopulmonary receptors was obtained by reducing central venous pressure through application of negative pressure to the lower body.[3] To this aim, the subjects were put supine and their legs and lower abdomen were enclosed in a Plexiglas box that was sealed at the level of the anterosuperior iliac crests. The pressure within the box was reduced to levels approximating −7, −15, −25, and −40 mm Hg by a commercial vacuum cleaner. The former two stimuli did not affect blood pressure and heart rate and therefore selectively deactivated cardiopulmonary receptors,[3] while the latter two stimuli reduced blood pressure and involved arterial baroreceptors in the reflex responses. The −7 and −25 mm Hg stimuli were maintained for 5 minutes, while the −15 and −40 mm Hg stimuli were maintained for 20 minutes to allow evaluation of the more slowly developing renin response.[7, 18]

Stimulation of cardiopulmonary receptors was obtained by increasing central venous pressure through passive elevation of the legs and the lower

pelvis of the supine subjects to 60 degrees.[3, 19] This stimulus was also maintained for 20 minutes to allow evaluation of the renin as well as the hemodynamic responses.

Cold Pressor Test and Furosemide Injection

In each subject the blood pressure, heart rate, and forearm vascular responses to a cold pressor test were evaluated by immersion of one hand in ice water (4 °C) for 60 seconds.

The renin response to furosemide (Lasix, Wellcome) was evaluated by measuring plasma renin activity in samples taken from the right atrium before and 1 hour after the intravenous injection of 40 mg of the drug. This test was done to assess cardiovascular and renin responsiveness to stimuli different from those originating in the cardiopulmonary region.[20, 21]

Protocol

Following a 1-day hospitalization during which the subjects were familiarized with the procedure, the study was conducted as follows: 1) half of the subjects were put in the supine position and fitted with the lower body negative pressure device; 2) the catheter was positioned in the right atrium, and the blood pressure and blood flow measurement techniques were set ready; 3) 30 minutes later the lower body negative pressures were applied in a random order, at intervals of 15 minutes; 4) the lower body negative pressure device was removed, and 30 minutes later the leg-raising maneuver was performed; 5) after a further 20 minutes the cold pressor test was performed, followed 20 minutes later by the furosemide injection. In the other half of the subjects the protocol was the same except that the leg raising preceded the lower body negative pressure maneuvers.

Blood pressure, heart rate, central venous pressure, forearm blood flow, and forearm vascular resistance were measured before and at the 5th and 20th minutes of leg raising and lower body negative pressures. Forearm blood flow measurements were derived from the average of three consecutive values. Two sequential blood flow averages agreed by ±6%, indicating a good within-subject reproducibility of the data. Blood samples for plasma renin and norepinephrine measurements were withdrawn before and at the 20th minute of leg raising and lower body negative pressure. The withdrawal time was approximately 30 seconds.

In seven subjects with hypertension and left ventricular hypertrophy, evaluation of the cardiopulmonary reflex was repeated after 1 year of antihypertensive treatment (atenolol, 100 mg q.d., 2 subjects; atenolol, 100 mg q.d., plus slow-release nifedipine, 20 mg b.i.d., 5 subjects). In all these subjects echocardiograms performed after 6 and 12 months of treatment indicated regression of left ventricular hypertrophy (see Results). Treatment was withdrawn 1 to 2 weeks before the second

study to avoid interference of the drug(s) with cardiovascular control. No follow-up could be performed in the remaining five subjects with hypertension and left ventricular hypertrophy.

Data Analysis

All results are presented as means ± SE. The statistical significance of the difference in the means was assessed by one-way analysis of variance. The *t* test for unpaired observations was used to locate the differences among the various groups. A *p* value below 0.05 was taken as the minimal level of statistical significance.

Results

Baseline Values

As shown in Table 1, septal wall thickness and left ventricular mass index were similar in normotensive subjects and in subjects defined as hypertensive without left ventricular hypertrophy but markedly increased in subjects defined as hypertensive with left ventricular hypertrophy. Compared with normotensive subjects, hypertensive subjects without left ventricular hypertrophy had greater blood pressure, heart rate, and forearm vascular resistance values, whereas central venous pressure, plasma renin activity, and plasma norepinephrine were not significantly different in the two groups. Blood pressure and heart rate were not further increased in hypertensive subjects with left ventric-

TABLE 1. *Baseline Values of Normotensive Subjects and Hypertensive Subjects Without and With Left Ventricular Hypertrophy*

Variable	Normo-tensive ($n = 10$)	Hyper-tensive ($n = 10$)	Hyper-tensive with LVH ($n = 12$)
Mean arterial pressure (mm Hg)	95.5±2.5	112.9±2.5*	118.1±3.1*
Heart rate (beats/min)	64.4±1.0	76.8±1.8†	71.6±2.0
Central venous pressure (mm Hg)	1.1±0.3	1.4±0.2	2.0±0.2†
Forearm vascular resistance (units)	22.6±2.4	37.0±1.8*	42.9±2.0*
Plasma norepinephrine (pg/ml)	194±25	202±23	256±24*·‡
Plasma renin activity (ng Ang I/ml/hr)	1.2±0.2	1.2±0.1	1.6±0.2†·‡
Septal wall thickness (mm)	9.2±0.4	9.3±0.3	12.4±0.6*·§
Posterior wall thickness (mm)	8.1±0.2	8.4±0.4	11.8±0.4*·§
Left ventricular mass index (g/m²)	90±4.3	98±5.1†	149±10.0*·§

Data are shown as means ± SE. LVH = left ventricular hypertrophy; Ang I = angiotensin I.

*$p < 0.01$, †$p < 0.05$, compared with values in normotensive subjects.

‡$p < 0.05$, §$p < 0.01$, compared with values in hypertensive subjects without LVH.

ular hypertrophy; however, this group did exhibit a significant rise in central venous pressure, plasma renin activity, and plasma norepinephrine. Forearm vascular resistance showed a further rise in these subjects with respect to the already elevated value in hypertensive subjects without left ventricular hypertrophy.

Leg Raising and Lower Body Negative Pressure

Figures 1 and 2 show that in the three groups of subjects the increase in central venous pressure induced by raising the legs for 5 minutes was accompanied by a rise in forearm blood flow and a fall in forearm vascular resistance. Conversely, the progressive fall in central venous pressure induced by applying a lower body negative pressure for 5 minutes was accompanied by a progressive fall in forearm blood flow and rise in forearm vascular resistance. The changes in vascular resistance were only slightly reduced in hypertensive subjects without left ventricular hypertrophy as compared with normotensive subjects. However, a pronounced reduction was observed in hypertensive subjects with left ventricular hypertrophy. This reduction occurred when the stimuli were associated with no significant changes in blood pressure and heart rate (leg raising and the two milder degrees of lower body negative pressure) i.e., when they selectively involved the cardiopulmonary receptors. It also occurred when they were associated with hypotension and tachycardia (the two more pronounced degrees of lower body negative pressure) i.e., when they involved the arterial baroreceptors as well. The hypotension was greater and the tachycardia smaller in hypertensive subjects with left ventricular hypertrophy than in the other two groups. The responses at the 20th minute of lower body negative

pressure and leg raising were superimposable on those obtained at the 5th minute of either maneuver (data not shown).

Similar results were obtained for plasma norepinephrine and plasma renin activity (Figure 3). Leg raising was associated with a fall in both variables, which showed a progressive rise during a non-hypotensive and a hypotensive lower body negative pressure. The changes in plasma norepinephrine were maximal in normotensive subjects, unchanged or modestly reduced in hypertensive subjects without left ventricular hypertrophy, and markedly reduced in hypertensive subjects with left ventricular hypertrophy (see Figure 3, left panel). This was also the case for plasma renin activity, except for the hypotensive lower body negative pressure, which caused a rise in this variable that was not significantly different among the three groups (see Figure 3, right panel).

In Figure 4 the percent changes in forearm vascular resistance, plasma norepinephrine, and plasma renin activity induced by leg raising and a nonhypotensive lower body negative pressure (-15 mm Hg) were added to show the overall responses to selective alterations in cardiopulmonary receptor activity from above to below their baseline activity. Compared with normotensive subjects, the overall vascular response was reduced in hypertensive subjects without left ventricular hypertrophy, but a much greater reduction was observed in hypertensive subjects with left ventricular hypertrophy. This was also the case for the overall renin and norepinephrine responses. In all 32 subjects taken together, the magnitude of the vascular and norepinephrine responses was inversely related to left ventricular mass index ($r = 0.45$ and 0.54, respectively, $p < 0.05$).
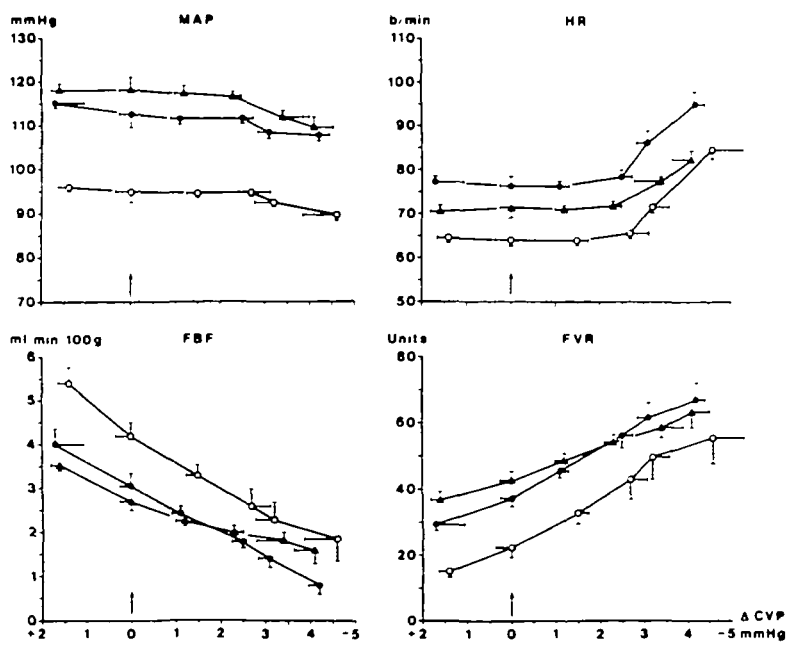

FIGURE 1. Hemodynamic changes accompanying a 5-minute increase in central venous pressure (CVP) induced by leg raising and a progressive reduction in CVP in 5-minute steps induced by progressively greater lower body negative pressures. Changes in CVP are shown as alterations from the control value, which is indicated as 0. The hemodynamic values at control CVP (0) are indicated by the arrow. Values are means ± SE from 10 normotensive subjects (O), 10 hypertensive subjects without left ventricular hypertrophy (●), and 12 hypertensive subjects with left ventricular hypertrophy (▲). MAP = mean arterial pressure; HR = heart rate; FBF = forearm blood flow; FVR = forearm vascular resistance.
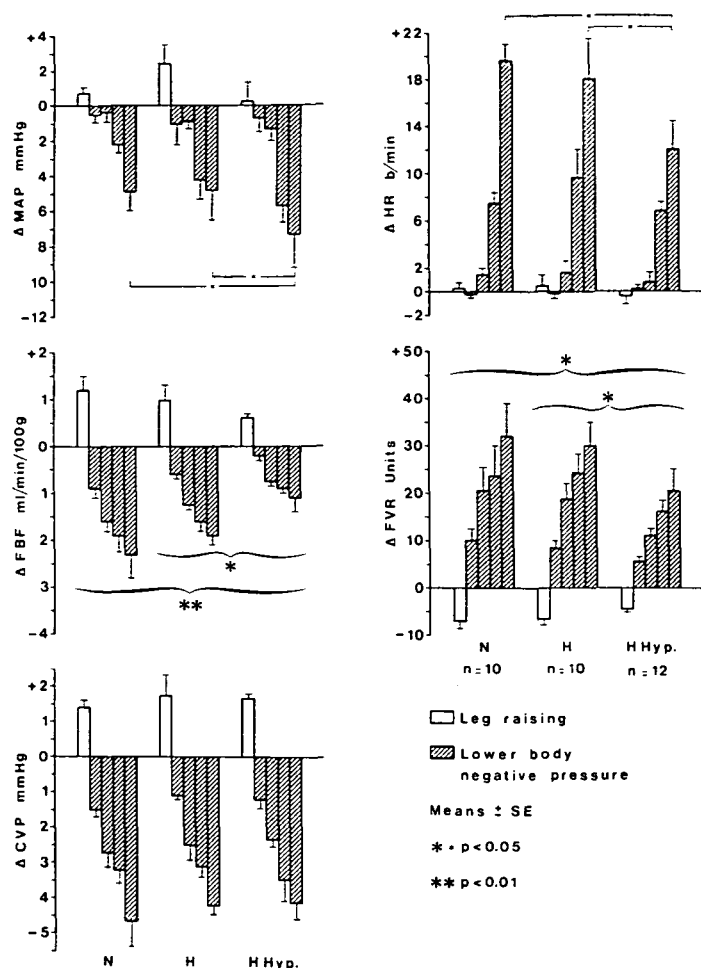
FIGURE 2. *Hemodynamic responses to the increase and the progressive reductions in central venous pressure (CVP) referred to in Figure 1 as changes from control values. Values are means ± SE from the same three groups shown in Figure 1. Small asterisks and lines refer to statistical significance of the difference in response to a single change in CVP. Large asterisks and brackets refer to statistical significance of the difference in all responses combined. N = normotensive; H = hypertensive; H Hyp = hypertensive with left ventricular hypertrophy. See Figure 1 for key to other abbreviations.*

Cold Pressor Test and Furosemide Injection

As shown in Table 2, immersion of one hand in ice water caused increases in blood pressure, heart rate, and forearm vascular resistance that were not significantly different in normotensive subjects and hypertensive subjects with or without left ventricular hypertrophy. The increase in plasma renin activity induced by furosemide was also similar in the three groups. In hypertensive subjects with left ventricular hypertrophy all responses were somewhat attenuated when expressed in percentages but the differences with the other two groups were not statistically significant.

Regression of Left Ventricular Hypertrophy

Table 3 shows that in the seven hypertensive subjects with left ventricular hypertrophy who were restudied after 1 year of antihypertensive treatment, septal wall thickness, posterior wall thickness, and left ventricular mass index were markedly reduced with respect to the values measured before treatment. This reduction was accompanied by a reduction in central venous pressure, forearm vascular resistance, plasma norepinephrine, and plasma renin activity. Blood pressure and heart rate were not significantly different in the two conditions,

presumably as a result of interruption of treatment 1 to 2 weeks before the second study.

As shown in Figure 5, the increase in central venous pressure induced by leg raising caused a greater reduction in forearm vascular resistance after than before regression of left ventricular hypertrophy. Likewise, the reductions in central venous pressure induced by lower body negative pressure caused greater increases in forearm vascular resistance after than before regression of left ventricular hypertrophy regardless of whether the responses were accompanied by no alteration in blood pressure and heart rate or by hypotension and tachycardia. The hypotension was less pronounced when left ventricular hypertrophy had regressed.

The reductions and increases in plasma norepinephrine and plasma renin activity induced by the central venous pressure changes were also greater after than before regression of left ventricular hypertrophy, although the differences in the plasma renin activity in response to reduction in central venous pressure did not reach statistical significance (Figure 6). When expressed as changes induced by the increase plus the nonhypotensive reduction in central venous pressure, the vascular responses before and after regression of left ventricular hypertrophy
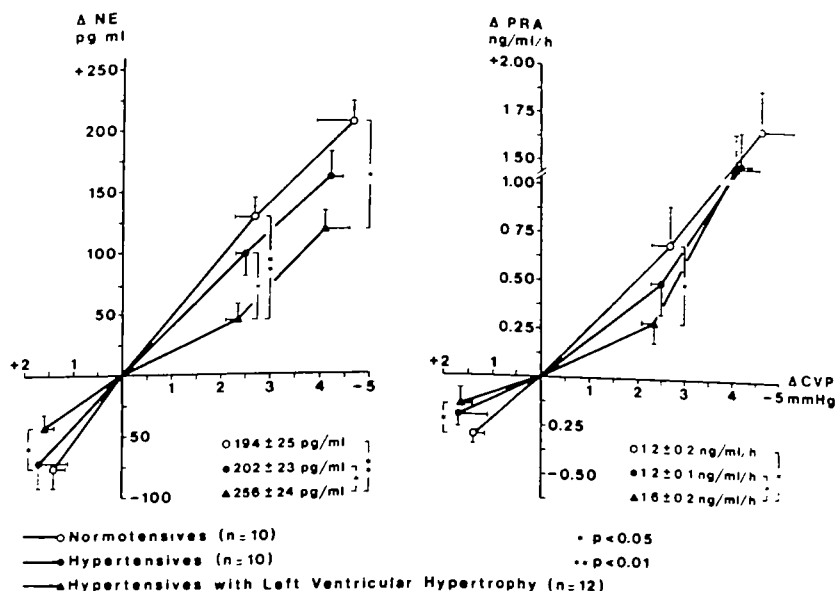
FIGURE 3. *Plasma norepinephrine (NE) and plasma renin activity (PRA) responses to the rise in central venous pressure (CVP) induced by leg raising and two progressive falls in CVP respectively induced by a lower body negative pressure (−15 mm Hg) that caused little or no change in blood pressure and a lower body negative pressure (−37.5 mm Hg) that caused a reduction in mean arterial pressure. Values are means ± SE from the three groups of subjects shown in Figure 1. Data refer to 20th-minute changes in all variables. For other explanations see Figure 1. Asterisks refer to the difference among the three groups.*

were 31.9 ± 4.2 and 101.9 ± 11.3%, the norepinephrine responses were 40.1 ± 6.6 and 81.0 ± 12.3%, and the plasma renin activity responses were 38.7 ± 8.9 and 63.4 ± 8.5%, respectively. All these differences were statistically significant ($p < 0.01$ for forearm vascular resistance and plasma norepinephrine; $p < 0.05$ for plasma renin activity).

Arterial Baroreceptor Reflex Before and After Regression of Left Ventricular Hypertrophy

Previous studies have shown that the tachycardia accompanying the fall in blood pressure induced by a marked degree of lower body negative pressure originates exclusively from deactivation of arterial baroreceptors.[22] This allowed us to express the sensitivity of the baroreceptor control of heart rate as the ratio between the increase in this variable and the concomitant reduction in mean arterial pressure induced by a 5-minute application of lower body negative pressure at −40 mm Hg. As shown in Figure 7, left panel, the sensitivity of the baroreceptor–heart rate control was not significantly different in normotensive and mildly or moderately essential hypertensive subjects, but it was markedly reduced in hypertensive subjects with left ventricular hypertrophy. This reduced value, however, significantly and markedly improved following regression of left ventricular hypertrophy (see Figure 7, right panel).

Discussion

We believe that our study offers the first detailed information about the alterations in the cardiopulmonary receptor control of vascular resistance and plasma renin activity in essential hypertension of different severity. Furthermore, it shows the relationship between these alterations and left ventricular hypertrophy and documents the consequences of reversal of this structural abnormality on this reflex. Finally, it provides under the same circumstances data on the baroreceptor–heart rate reflex. These various points, as well as their pathophysiological implications, will be discussed separately.

Cardiopulmonary Reflex in Essential Hypertension With and Without Left Ventricular Hypertrophy

Our data show that changes in forearm vascular resistance induced by increasing and reducing central venous pressure without altering blood pressure and heart rate are less in subjects with mild or moderate essential hypertension than in normotensive subjects, but that a further marked reduction of these vasomotor responses occurs in subjects in whom hypertension is accompanied by left ventricular hypertrophy. Furthermore, they show that the plasma norepinephrine and plasma renin activity responses to nonhypotensive and nontachycardic alterations in central venous pressure are characterized by a similar pattern, that is, they are largest in normotensive subjects, slightly reduced in mildly or
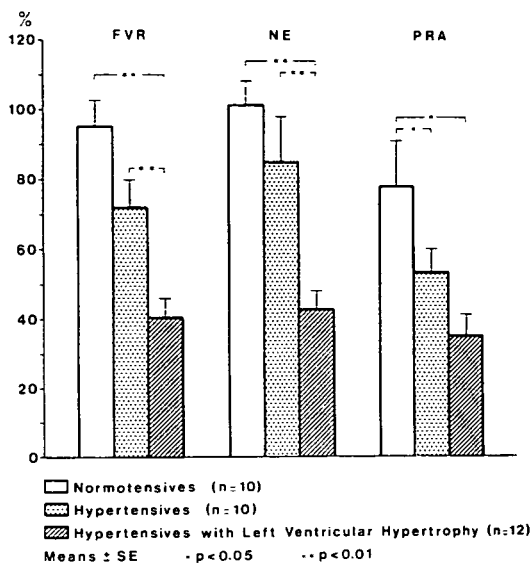
cardiopulmonary receptor ability to modulate plasma renin activity and, presumably, plasma angiotensin and aldosterone levels should make blood volume homeostasis less effective in subjects with hypertension and a hypertrophic heart. Furthermore, the impaired cardiopulmonary receptor modulation of norepinephrine secretion and peripheral vasomotor tone should have similar adverse consequences on blood pressure homeostasis. This was indeed the case in our hypertensive subjects with left ventricular hypertrophy, in whom a pronounced reduction in central venous pressure obtained by increasing the degree of applied lower body negative pressure was accompanied not only by reduced vasoconstrictor and norepinephrine responses but also by a greater blood pressure fall than in the other two groups.

Finally, a marked impairment of the cardiopulmonary reflex means less tonic restraint on neural and humoral influences tending to elevate blood pressure. This phenomenon was reflected in the higher vascular resistance, plasma norepinephrine, and plasma renin activity basally displayed by hypertensive subjects with left ventricular hypertrophy, although the higher central venous pressure observed in these subjects should have induced a decrease in all of these. This alteration could contribute to the maintenance of the high blood pressure state and may represent a factor leading to its further aggravation.

Mechanisms of the Impairment of the Cardiopulmonary Reflex in Hypertension with Left Ventricular Hypertrophy

In hypertensive subjects without or with left ventricular hypertrophy, the increase in forearm vascular resistance induced by the cold pressor test was similar to that observed in normotensive subjects, indicating no reduction in the ability to alter peripheral vasomotor tone in response to alterations in neural drive. Likewise, plasma renin activity responses to injection of furosemide or to hypoten-

FIGURE 4. *Percent changes in forearm vascular resistance (FVR), norepinephrine (NE), and plasma renin activity (PRA) induced by increasing central venous pressure (CVP) by leg raising and reducing CVP by a nonhypotensive lower body negative pressure. Changes induced by reduction and increase in CVP were added to evaluate the overall responses. Values are means ± SE from the same three groups shown in Figure 1.*

moderately hypertensive subjects, and more markedly reduced in hypertensive subjects with left ventricular hypertrophy. This allows us to conclude that, with the possible exception of a very early blood pressure elevation,[11] the neurovascular and humoral modulation exerted by a selective increase and reduction in cardiopulmonary receptor activity is impaired in essential hypertension and that the impairment is particularly pronounced when this condition is severe enough to cause cardiac structural alterations.

This phenomenon has pathophysiological implications. For example, the marked impairment of the

TABLE 2. *Hemodynamic and Humoral Changes Induced by Cold Pressor Test and Furosemide Injection in Normotensive Subjects and Hypertensive Subjects Without and With Left Ventricular Hypertrophy*

	Cold pressor test									Furosemide i.v.		
	Mean arterial pressure (mm Hg)			Heart rate (beats/min)			Forearm vascular resistance (units)			Plasma renin activity (ng Ang I/ml/hr)		
Subjects	Control	Change	%	Control	Change	%	Control	Change	%	Control	Change	%
Normotensive	96.1	17.2	18.1	65.1	14.6	22.4	34.1	61.1	159.0	0.8	1.3	183.1
(n = 10)	±1.8	±2.3	±2.6	±3.0	±3.5	±4.2	±8.1	±16.0	±41.5	±0.1	±0.2	±43.3
Hypertensive without LVH	116.2	20.2	18.6	69.1	14.5	19.6	40.2	77.2	174.1	0.9	1.1	118.3
(n = 10)	±3.8*	±2.4	±2.4	±3.6	±2.5	±3.6	±7.1	±10.6	±43.0	±0.1	±0.3	±40.5
Hypertensive with LVH	120.3	22.2	17.2	68.1	14.1	19.1	43.7	62.3	115.8	1.2	1.3	147.8
(n = 12)	±5.8*	±4.5	±3.9	±4.9	±1.7	±3.3	±5.6*	±8.1	±29.9	±0.3*·†	±0.4	±69.8

Data are shown as means ± SE. Ang I = angiotensin I; LVH = left ventricular hypertrophy.
*p < 0.01, compared with respective value in normotensive subjects.
†p < 0.01, compared with respective value in hypertensive subjects without LVH.

TABLE 3. *Baseline Values of Seven Hypertensive Subjects with Left Ventricular Hypertrophy Before and After 1-Year Antihypertensive Treatment*

Variable	Pre-treatment	Post-treatment
Mean arterial pressure (mm Hg)	116.0 ± 1.6	112.2 ± 1.3
Heart rate (beats/min)	72.5 ± 1.9	68.1 ± 1.9
Central venous pressure (mm Hg)	2.1 ± 0.1	1.4 ± 0.2*
Forearm vascular resistance (units)	42.9 ± 2.7	33.5 ± 3.2*
Plasma norepinephrine (pg/ml)	237 ± 26	174 ± 38†
Plasma renin activity (ng Ang I/ml/hr)	1.5 ± 0.2	1.1 ± 0.7†
Septal wall thickness (mm)	13.0 ± 0.8	10.7 ± 0.3†
Posterior wall thickness (mm)	12.1 ± 0.5	9.7 ± 0.3†
Left ventricular mass index (g/m)	145 ± 12.5	112 ± 3.5*

Data are shown as means ± SE. Treatment was interrupted 1 to 2 weeks before the second study. Ang I = angiotensin I.
$*p < 0.01$, $†p < 0.05$, compared with pretreatment values.

sion and reduced renal perfusion pressure induced by a marked lower body negative pressure were not significantly different in the three groups, excluding that the responsiveness of juxtaglomerular cells to physiological stimuli (macula densa stimuli, local baroreceptor stimuli, neural stimuli)[23, 24] was

depressed in hypertensive subjects. Therefore, the depressed neurovascular and humoral responses to cardiopulmonary receptor manipulation observed in these subjects cannot be ascribed to an anomaly of the efferent portion, but rather of the central or afferent portion (or both) of this reflex arch. A central anomaly has been proposed by Thames[10] in a study in which the cardiopulmonary reflex was found to be impaired in rabbits with renovascular hypertension. However, electrophysiological studies have shown that cardiac receptors are reset in cardiac hypertrophy and that the thickening and loss of compliance of the cardiac walls typical of this condition make them somewhat less sensitive to physiological stimuli.[25] It is therefore possible that in hypertensive subjects with hypertrophic hearts, the marked cardiopulmonary reflex derangement has an "afferent" origin (i.e., it originates from the inability of cardiac receptors to properly sense hemodynamic changes taking place in the heart). This possibility is compatible with recent observations that reflex effects of lower body negative pressure are drastically reduced in cardiac transplantation patients, demonstrating their main dependence on receptors located in the heart.[26, 27] It is also compatible with previous observations that these effects are reduced in cardiac hypertrophies of a nonhypertensive nature[28] and with the present observation that the magnitude of the vascular and humoral responses to nonhypotensive and nontachycardic changes in central venous pressure was inversely related to left ventricular mass index.
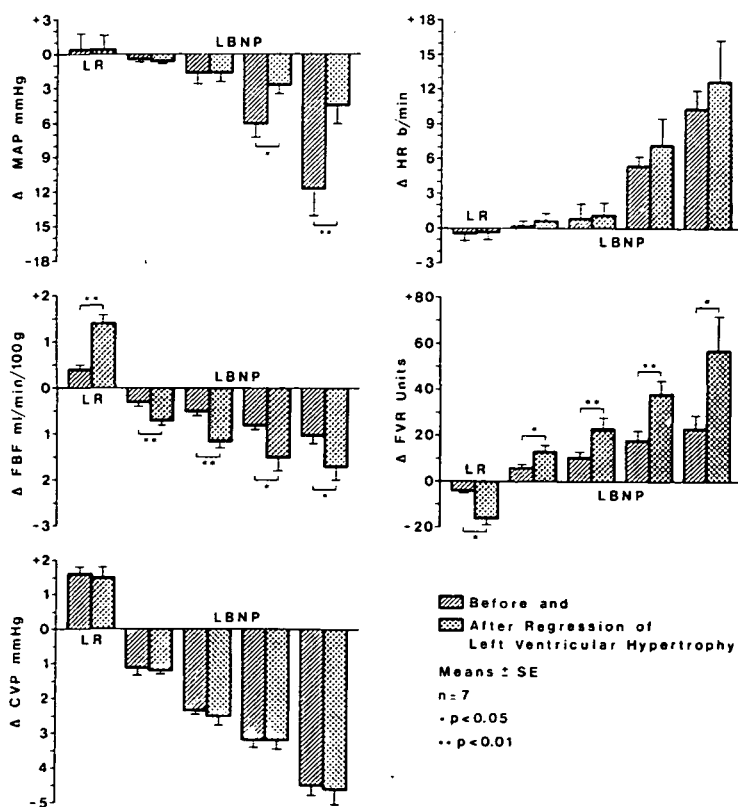

FIGURE 5. *Hemodynamic responses to the increase and the progressive reduction in central venous pressure (CVP) before and after regression of left ventricular hypertrophy. Values are means ± SE from seven of the 12 hypertensive subjects with left ventricular hypertrophy who were restudied after 1 year of antihypertensive treatment. Data refer to 5th-minute changes in all variables. LBNP = lower body negative pressure; LR = leg raising. See Figure 1 for key to other abbreviations.*
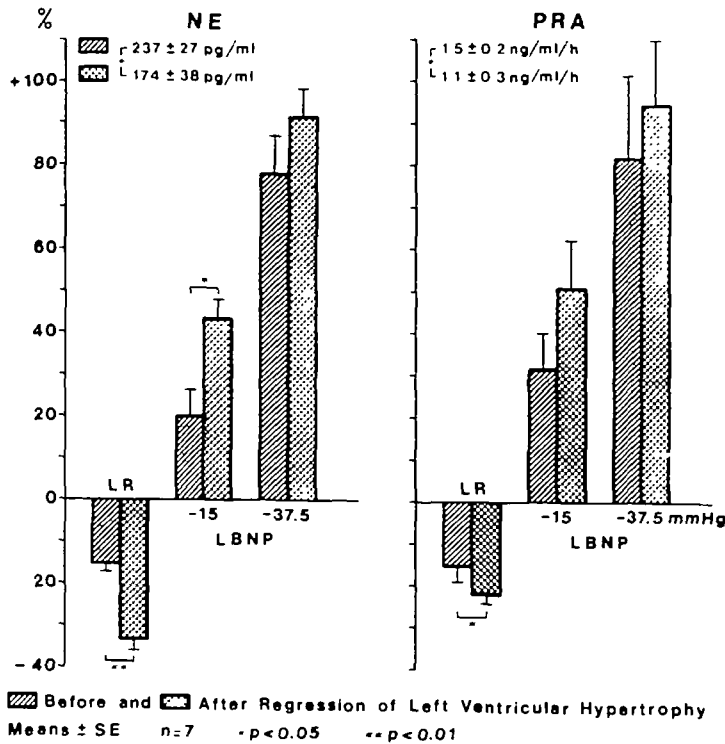
FIGURE 6. *Norephinephrine (NE) and plasma renin activity (PRA) responses to leg raising (LR) and a nonhypotensive (−15 mm Hg) or hypotensive (−37.5 mm Hg) lower body negative pressure (LBNP) in the seven subjects shown in Figure 5. Data refer to 20th-minute changes in all variables. For further explanations, see Figure 5.*

Cardiopulmonary Reflex After Regression of Left Ventricular Hypertrophy

A major result of our study is that, in the seven hypertensive subjects with left ventricular hypertrophy who were restudied after 1 year of antihypertensive treatment, a clear regression of left ventricular hypertrophy was associated with a marked improvement of the ability of the cardiopulmonary receptors to modulate their vascular and humoral targets. This finding could not be compared with data obtained by restudying subjects without left ventricular hypertrophy or in whom this alteration had not regressed. However, previous observations made by our group demonstrate that repeated testing of the cardiopulmonary reflex over a time span incompatible with an anatomical remodeling of the heart does not show alterations in the reflex sensitivity.[29-31] Thus, the improvement of the cardiopulmonary reflex likely was caused by regression of left ventricular hypertrophy. This implies that this regression has a beneficial effect on cardiac function, restoring its normal role in reflex cardiovascular homeostasis. In our patients, this was also demonstrated by the findings that 1) the more pronounced degrees of lower body negative pressures induced much lower falls in blood pressure following return of the heart toward a normal mass and 2) this return was associated with a reduction in the elevated basal vascular resistance, plasma norepinephrine, and plasma renin activity values shown when left ventricular hypertrophy was manifest.

Arterial Baroreceptor Control of Heart Rate Before and After Regression of Left Ventricular Hypertrophy

Data in animals[32-35] and in humans[35, 36] indicate that hypertension does not cause major changes in

arterial baroreceptor control of blood pressure and systemic circulation. On the other hand, baroreceptor control of heart rate is clearly impaired in this condition.[37, 38] In the present study this impairment was shown by the observation that the tachycardia observed when lower body negative pressure caused a blood pressure fall was progressively and steeply reduced on going from normotensive to essential
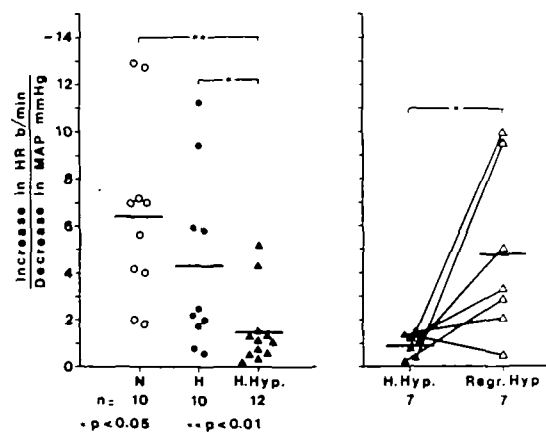

FIGURE 7. *Ratios of increases in heart rate (HR) over decreases in mean arterial pressure (MAP) observed during the 5-minute application of a lower body negative pressure of −37.5 mm Hg. Individual data obtained from normotensive (N) subjects, hypertensive subjects without left ventricular hypertrophy (H), hypertensive subjects with left ventricular hypertrophy (H Hyp; left panel), and hypertensive subjects with left ventricular hypertrophy before and after regression of this condition (Regr Hyp; right panel).*

hypertensive subjects without and with left ventricular hypertrophy. Interestingly, in addition to restoring the cardiopulmonary reflex, regression of this structural alteration improved the baroreceptor–heart rate reflex as well. We can speculate that this improvement is induced by an enhancement of the depressed chronotropic responses observed in the hypertrophic heart.[38-40] It is also possible (and not exclusive of the former explanation) that the regression of vascular hypertrophy[41, 42] and the increase in vascular compliance[43] induced by antihypertensive treatment could make baroreceptors more sensitive to mechanical stimuli and enhance their overall reflex control. This effect may further contribute to restoration of blood pressure homeostasis.

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