Blunted Sympathetic Response to Cardiopulmonary Receptor Unloading in Hypertensive Patients With Left Ventricular Hypertrophy
A Possible Compensatory Role of Atrial Natriuretic Factor

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To investigate whether or not hypertension with left ventricular hypertrophy (LVH) modifies the mechanisms underlying the vascular adjustments to orthostatic stress, we evaluated the hemodynamic and hormonal effects of graded lower-body negative pressure (LBNP) (−10 and −40 mm Hg) before and after sympathetic blockade in 10 hypertensive patients with LVH and in five age- and sex-matched normotensive subjects. In control conditions, LBNP elicited comparable vasoconstrictor responses in the forearm in the two groups. In normotensive subjects, graded increases in plasma norepinephrine and plasma renin activity (PRA) and reductions in plasma immunoreactive atrial natriuretic factor (irANF) were recorded. In hypertensive patients, a significant increase in plasma norepinephrine and plasma renin activity was obtained only with the higher level of LBNP, whereas irANF plasma levels decreased progressively. In both groups, sympathetic blockade abolished the increase in plasma renin activity and did not modify the changes in plasma irANF induced by both levels of LBNP in control conditions. The vascular response to −10 mm Hg LBNP remained unchanged after sympathetic blockade in both groups. However, after sympathetic blockade, the vasoconstrictor response to −40 mm Hg LBNP in normal subjects was no longer different from that elicited by −10 mm Hg LBNP, whereas in hypertensive patients the vasoconstrictor response was still significantly higher than that induced by −10 mm Hg LBNP. Direct correlations between the percent changes in forearm vascular resistance and those in plasma norepinephrine and plasma renin activity were found only in normal subjects in control conditions but were not observed after sympathetic blockade. On the contrary, the inverse correlation between changes in irANF plasma levels and in forearm vascular resistance found in control conditions in both groups was still observed after sympathetic blockade. In a separate group of hypertensive patients with left ventricular hypertrophy, exogenous infusion of ANF induced an increase in venous irANF plasma levels of the same magnitude of the decrease evoked by LBNP and significantly reduced forearm vascular resistance. These data show that in hypertensive patients with left ventricular hypertrophy, sympathetic activation does not contribute to the vascular response to cardiopulmonary receptor unloading (−10 mm Hg LBNP). They also suggest that in these patients inhibition of ANF secretion may play a role in the response to a low level of LBNP so that the peripheral vasoconstriction induced by cardiopulmonary receptor unloading is comparable to that observed in normal subjects despite the lack of appropriate sympathetic reflex vasoconstriction. (Circulation 1989;80:883–892)

Although rapid adjustments in blood pressure in humans are primarily obtained through reflex changes in sympathetic tone, recent observations suggest that in some pathologic conditions the pivotal role of the adrenergic system in the mediation of these responses is questionable.
In normal subjects, the hemodynamic adjustments elicited by simulated orthostatic stress seem to be mainly mediated through an increase in sympathetic tone. In fact, Grassi et al\(^2\) reported that inhibition of cardiopulmonary receptors during simulated orthostatic stress results in increased plasma norepinephrine and that simultaneous inhibition of arterial baroreceptors causes a further rise in plasma norepinephrine.

The possibility that the sympathetic system plays a major role in mediating the reflex vascular response to orthostatism is strengthened by the observation\(^3\) that in patients with congestive heart failure, in whom selective impairment of baroreflex-mediated vasoconstrictor response to simulated orthostatic stress has been shown,\(^4\) upright tilt is not associated with the expected increase in plasma norepinephrine, which characterizes the normal response.\(^2\)

We recently reported that in hypertensive patients with mild left ventricular hypertrophy, cardiopulmonary baroreceptor unloading induced by −10 mm Hg lower-body negative pressure (LBNP) elicits a vascular response comparable to that of normotensive control subjects but does not increase plasma norepinephrine levels.\(^1\) In these subjects, higher levels of LBNP result in a significant increase in plasma norepinephrine levels and in a potentiation of the vasoconstrictor response.\(^1\) In the same patients, unloading of cardiopulmonary receptors also fails to modify arginine vasopressin release or plasma renin activity.\(^1\) This observation rules out the possibility that an enhanced activity of these hormonal systems balanced the blunted sympathetic response. In this regard, it should be pointed out that plasma levels of norepinephrine only partially reflect sympathetic activity in humans.\(^5\) Therefore, despite the lack of significant changes in plasma norepinephrine, unloading of cardiopulmonary baroreceptors may still induce a reflex increase in adrenergic tone also in patients with left ventricular hypertrophy. Moreover, the participation of other mechanisms should be considered. For instance, remarkable changes in the release of atrial vasoactive and natriuretic peptides take place when atrial pressure changes,\(^6\) thus raising the possibility that atrial natriuretic factor (ANF) is involved in the complex adjustments occurring in response to simulated orthostatic stress.

The present study was planned 1) to evaluate the effects of sympathetic blockade on the vascular response to cardiopulmonary baroreceptor unloading in hypertensive patients with left ventricular hypertrophy and 2) to investigate the possible role of the reduction in ANF (99–126) in the reflex response induced by the fall in venous return that occurs during orthostatic stress.

Methods

Patients

The study was performed in 10 patients (six men and four women; mean age, 47±4 years) with established mild or moderate essential hypertension. They were 10 nonconsecutive patients with a normal coronary arteriogram who underwent coronary arteriography to define the cause of their chest pain syndrome. None of these patients had electrocardiographic evidence of myocardial infarction or exercise tests and other tests positive for ischemic heart disease. In these patients, blood pressure readings were above 160 mm Hg systolic and 95 mm Hg diastolic in at least five consecutive readings obtained in the outpatient clinic. None of the patients had received any treatment for at least 3 weeks before the study. Blood pressure was measured with the patient in the sitting position, after a 10-minute rest in a darkened room, by means of a standard sphygmomanometer with a cuff of appropriate size and by following the recommendations of the American Heart Association.\(^9\) Secondary hypertension had been previously ruled out in all patients by laboratory and radiographic studies. Five age-matched normotensive volunteers (three men and two women; mean age, 43±3 years) were also studied as a control group. In all subjects, the existence of major diseases other than hypertension was excluded. All subjects were fully informed about the procedure and the aim of the study, and written consent was obtained in all cases. None of the normotensive subjects showed signs of left ventricular hypertrophy as assessed by echocardiography\(^10,11\) before the study. On the contrary, all the hypertensive patients satisfied the echocardiographic criteria for left ventricular hypertrophy, that is, a left ventricular mass index higher than 134 g/m² for men and 110 g/m² for women.\(^11\)

In the week preceding the study, the patients were hospitalized. During this period, they received a daily diet containing 1,500 ml fluids, 150 meq Na, and 70 meq K. From days 4 to 7, sodium balance was maintained in the steady state as verified on the basis of body weight, sodium intake, and urinary sodium output. Both two-dimensional and M-mode echocardiography were performed and processed as previously reported from this laboratory.\(^12\) Two days before the invasive study session, the subjects were familiarized with the LBNP device. Subjects were requested to refrain from cigarette smoking and coffee drinking in the 12 hours immediately before the study session.

Procedures

The study was performed on day 7 of hospitalization after an overnight fast in a quiet room with the temperature kept between 22° and 24° C. No premedication was administered. On arrival at the laboratory, forearm volume was measured by water displacement. Then, the subjects assumed the supine position with the right arm supported at the midthoracic level, relaxed and with hands opened in the control environment, and electrocardiographic leads were attached for electrocardiographic monitoring. An LBNP chamber, similar to that described by
Mark et al. was placed over the lower portion of each subject's body, from the iliac crest down, so that graded levels of LBNP could be applied to progressively unload cardiac and arterial baroreceptors. Under local anesthesia with 2% lidocaine, a heparinized arterial catheter was introduced percutaneously into the left brachial artery to directly measure systemic blood pressure. Mean arterial pressure was determined by integration of the pulsatile trace throughout 5-second periods. In hypertensive patients, a triple lumen thermodilution Swan-Ganz catheter was introduced through an antecubital vein and was positioned with the distal tip in the pulmonary artery, and cardiac output was assessed in triplicate by thermodilution with a 9520-A Edwards cardiac output computer (Edwards Laboratories, Santa Ana, California). Right atrial and pulmonary capillary wedge pressures were also recorded. In the control group, according to the suggestions of the ethical committee of our institute, only right atrial pressure was obtained through a polyethylene catheter introduced percutaneously in an antecubital vein and positioned under fluoroscopy in the right atrium. Heart rate was taken from an electrocardiographic lead monitored continuously during the study, and the patients were asked to breathe regularly. Systemic arterial and right atrial pressures were continuously measured with a Statham P23Db pressure transducer (Cleveland, Ohio) and recorded simultaneously with the electrocardiogram on a multichannel polygraph at a paper speed of 100 mm/sec.

The internal diameter of the brachial artery was determined by means of transcutaneous pulsed Doppler velocimetry (Echovar Doppler Pulsed, Alvar Electronic, Montreuil, France). The Doppler velocimeter was operated at a frequency of 8 MHz, was pulsed at 15 kHz, and was equipped with two original features as previously described. The probe position was adjusted over the brachial artery and was fixed throughout the study by means of a stereotaxic device placed around the arm. Flow through the brachial artery was measured as previously described. The random variability between repeated measurements with this method was 7±2%. In humans, arterial flow of superficial arteries deduced from concomitant pulsed Doppler measurements of diameter and blood velocity was found to be strongly correlated for the brachial artery to the forearm arterial flow measured by strain-gauge plethysmography. Forearm vascular resistance (FVR), expressed in millimeters of mercury per milliliter per second, was calculated by dividing mean arterial pressure, in millimeters of mercury, by brachial artery blood flow in milliliters per second.

Blood losses and fluid administration did not exceed 250 ml. A polyethylene catheter was inserted into an antecubital vein for drug and fluid administration. To minimize blood losses, baseline measurements of immunoreactive (ir) ANF plasma levels were not repeated before each stimulus. However, in preliminary experiments performed in three normotensive subjects we found that after -40 mm Hg LBNP, plasma irANF returns to baseline within 20 minutes (control, 68±12 pg/ml; -40 mm Hg LBNP, 29±3 pg/ml; 20 minutes after LBNP, 63±6 pg/ml; NS vs. control).

Protocol

A first group of experiments involved hypertensive patients with left ventricular hypertrophy.

Hemodynamics measured at baseline included systemic arterial pressure, pulmonary capillary wedge pressure, right atrial pressure, heart rate, cardiac output, and forearm blood flow.

Twenty minutes after catheter placement, baseline hemodynamics were measured. Blood samples for determining plasma irANF levels were obtained simultaneously from the catheter placed in the pulmonary artery (PA-irANF) and from that inserted in an antecubital vein (V-irANF). Blood samples for determining plasma renin activity (PRA) and noradrenaline concentration were obtained from an antecubital vein. LBNP (-10 mm Hg) was then applied for 15 minutes. Blood samples and hemodynamic measurements were obtained during the last 3 minutes of LBNP. After 30 minutes, -40 mm Hg LBNP was applied for 15 minutes, and the hemodynamics were measured during the last 3 minutes. Interventions were performed in random order. The forearm vascular response to cold pressor test was also recorded in control conditions and after the combined intravenous administration of propranolol and phentolamine to test the effectiveness of the sympathetic blockade. Response to cold pressor test was evaluated by immersion of the subject's left hand in ice water for 90 seconds. Then, the subjects were given propranolol (0.1 mg/kg i.v. during a 10-minute period), and after a 20-minute recovery period, phentolamine was administered (repeated bolus injections of 0.1 mg/kg at 20-minute intervals). Finally, hormonal and hemodynamic parameters were measured again before and during LBNP.

In a second group of experiments, hemodynamic and hormonal responses elicited by graded LBNP were assessed in normotensive volunteers. In these experiments, we measured right atrial pressure, arterial blood pressure, heart rate, brachial blood flow, V-irANF levels, plasma norepinephrine levels, and PRA. The protocol of this group of experiments was the same as that used in the first group. In three normotensive subjects and in three hypertensive patients, all responses were tested also before and after the intravenous administration of the same vehicle rather than propranolol and phentolamine.

In three hypertensive patients and in three normotensive subjects, V-irANF was measured at 30-minute intervals for 3 hours in the absence of any intervention to rule out the possibility that time-
dependent changes in irANF might have occurred during the study.

In five separate hypertensive patients with left ventricular hypertrophy (four men and one woman; mean age, 45 ± 5 years; mean body weight, 76 ± 4 kg; blood pressure, 162 ± 6/109 ± 5 mm Hg; and left ventricular mass index, 143 ± 3 g/m²), we also assessed the effects of ANF infusion on forearm hemodynamics and plasma norepinephrine level. These patients were asked to follow the same guidelines pertaining to diet, personal habits, and drug intake. Two baseline measurements separated by a 20-minute interval were obtained 30 minutes after catheterization procedures had been completed. In particular, we measured systolic and diastolic arterial and right atrial pressures, heart rate, and forearm blood flow; also, blood samples were obtained for ANF and norepinephrine assay. Then, ANF (α-human-1-28-ANF, Bissendorf peptide GmbH) was infused intravenously at a dosage of 2.5 ng/kg/min for 20 minutes with a Harvard infusion pump (South Natick, Massachusetts). All measurements were repeated in the same order at 15–20-minute intervals from the beginning of the infusion. The dosage of ANF was chosen on the basis of the results of pilot experiments to achieve an increase in plasma ANF levels of about 50 pg/ml, which is the same magnitude of the decrease in venous ANF levels caused by LBNP. Subsequently, ANF was infused at a dosage of 5 ng/kg/min for 20 minutes, and measurements were repeated.

Hormonal Measurements

PRA was measured by radioimmunoassay according to the method described by Menard and Catt (sensitivity, 50 pg/tube angiotensin I; intra-assay and interassay variability coefficients 6% and 10%, respectively). Plasma norepinephrine assay was performed with cation-exchange high-performance liquid chromatography with electrochemical detection. The samples were previously extracted and concentrated by adsorption onto activated alumina, and the catecholamines were eluted with perchloric acid 0.1 M. Analytical recovery, with dihydroxybenzylamine (Aldrich Chemical, Milwaukee, Wisconsin) used as internal standard, ranged from 63% to 75%. The chromatograms were obtained with a 20 cm×4 mm-column of strong cation-exchange material (Nucleosil 5 SA, Macherey-Nagel, Duren, FRG) and the Model 5100A (Environmental Sciences Associates, Bedford, Massachusetts) as electrochemical detector. The mobile phase, delivered by ConstaMetric III pump (LDC/Milton Roy, Riviera Beach, Florida) equipped with an extra pulse dampener, was a phosphate-citrate buffer (pH 4.2). The detection limit of the assay was 10 pg. Intra-assay and interassay variation coefficients for norepinephrine were 6.3% and 12.1%, respectively. Plasma irANF levels were determined by radioimmunoassay as previously described, with rabbit antiserum (RAS 8798, Peninsula Lab Europe), iodinated human ANF-(99-126) (2,000 Ci/mmol, Amersham), and human ANF-(99-126) (Bissendorf) as a standard. ANF was extracted from plasma with SEP-PAK C₁₈ cartridges (Waters Associates, Milford, Massachusetts). The recoveries, determined on each plasma sample by adding to it a minimal amount of radio labeled ANF, ranged from 71% to 90%. The peptide retained on the column was eluted with 80% acetonitrile in 0.1% trifluoroacetic acid. The eluates were dried overnight in a Savant Speed-Vac evaporator and reconstituted in radioimmunoassay buffer (phosphate buffer, 0.1 M, pH 7.4, containing 0.3% bovine serum albumin, 0.1% Triton X-100, and 0.1% sodium azide). The assay was a sequential radioimmunoassay with delayed addition of tracer. Bound to free separation was carried out with ice-cold dextran-coated charcoal 1.5% in radioimmunoassay buffer. Results were calculated from standard curves plotted from bound to free peptide counts per minute and log ANF standard and were corrected for internal recovery. Intra-assay and interassay variation coefficients were 6.6% and 10.5%, respectively. The radioimmunoassay sensitivity was 1 fmol/tube.

Data Analysis

Data are presented as mean±SEM. The individual values of each parameter obtained in basal conditions and in response to the two levels of LBNP before and after sympathetic blockade were compared by analysis of variance and Duncan’s multiple range test. Responses to the cold pressor test were compared by paired t test. Baseline values of the two study groups were compared by unpaired t test. Comparison of regression lines was performed according to standard methods.

Results

Population Characteristics

Systolic and diastolic arterial pressures and FVR were significantly higher in hypertensive patients than in normotensive control subjects (Table 1). The two groups also had different echocardiographic determinations of left ventricular wall thickness (septum plus posterior wall thickness) and left ventricular mass index. However, mean values of left ventricular internal dimensions, measured at both end systole and end diastole, in hypertensive patients were comparable with those of normotensive control subjects (Table 1).

Hemodynamic parameters were comparable in the two groups of subjects, although initial irANF levels tended to be higher in hypertensive patients (Figure 1).

Effects of Lower-Body Negative Pressure During Control Conditions

Hemodynamics. In both groups, graded LBNP induced a progressive fall in right atrial pressure, but no significant change in mean arterial pressure occurred in forearm blood flow, whereas pulse pressure was significantly reduced, and heart rate
TABLE 1. Systemic and Forearm Hemodynamics and Echocardiographic Left Ventricular Anatomy in the Two Study Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control subjects (n=5)</th>
<th>Hypertensive patients (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>120±4</td>
<td>169±6**</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>70±2</td>
<td>123±5**</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>70±2</td>
<td>68±1</td>
</tr>
<tr>
<td>Forearm vascular resistance (mm Hg/ml/sec)</td>
<td>81±9</td>
<td>126±10**</td>
</tr>
<tr>
<td>Interventricular septum thickness+ posterior wall thickness (cm)</td>
<td>1.64±0.04</td>
<td>2.37±0.1**</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>96±5</td>
<td>163±9**</td>
</tr>
<tr>
<td>LV diastolic diameter (cm)</td>
<td>5±1</td>
<td>5.5±0.1</td>
</tr>
<tr>
<td>LV systolic diameter (cm)</td>
<td>3.1±0.08</td>
<td>3.7±0.1</td>
</tr>
</tbody>
</table>

Data are mean±SEM. **p<0.01 vs. control subjects.

Increased only at −40 mm Hg LBNP (Table 2). Both levels of LBNP induced a significant increase in FVR (Figure 1), which was comparable in the two groups. A strong inverse correlation was determinable between the changes in right atrial pressure and in FVR elicited by LBNP in normal subjects (r=−0.898, n=10, p<0.01) and in hypertensive patients with left ventricular hypertrophy (r=−0.822, n=20, p<0.01).

Hormonal Parameters

In normal subjects, plasma norepinephrine concentrations and PRA were significantly increased at −10 mm Hg LBNP, whereas irANF levels fell. These responses were enhanced by the higher level of LBNP (Figure 1). In hypertensive patients, −10 mm Hg LBNP failed to raise plasma norepinephrine concentrations and PRA, but it still caused a fall in both PA-irANF (from 263±30 to 164±18 pg/ml, p<0.01) and V-irANF levels (Figure 1). Because the difference between PA-irANF and V-irANF levels can be taken as an index of ANF release and because cardiac output can be assumed to be the volume of distribution of ANF, we estimated ANF release by the formula arteriovenous volume multiplied by cardiac output. ANF release showed a significant reduction during −10 mm Hg LBNP (from 1151±129 to 659±66 ng/min, p<0.001), and it further fell at −40 mm Hg LBNP (348±80 ng/min, p<0.001). In these patients, the higher level of LBNP induced significant increases in plasma norepinephrine concentrations and in PRA (Figure 1), which were comparable to those observed in normal subjects.

Relations Between Hemodynamic and Hormonal Parameters

In normotensive subjects, the changes in right atrial pressure were inversely correlated with those in plasma norepinephrine (r=−0.930, n=10, p<0.01). In these subjects, there were also significant, direct correlations between the changes in plasma norepinephrine levels or in PRA and the corresponding changes in FVR (r=0.812 and r=0.762, respectively, n=10, both p<0.01). Finally, an inverse correlation between the changes in V-irANF plasma levels and those in FVR (r=−0.706, n=10, p<0.05) was found.

In hypertensive patients with left ventricular hypertrophy, there was an inverse correlation between reductions in right atrial pressure or in left ventricular filling pressure, as assessed by pulmonary capillary wedge pressure (baseline, 19±1 mm Hg; −10 mm Hg; LBNP, 17±1 mm Hg, p<0.05; −40 mm Hg LBNP, 12±1 mm Hg, p<0.01) and increases in FVR. Reductions in right atrial pressure or left ventricular filling pressure were also directly correlated with reductions in PA- and V-irANF levels and in irANF release evoked by the two levels of LBNP (all p<0.01). Because in hypertensive subjects with left ventricular hypertrophy, plasma norepinephrine levels

![Figure 1. Bar graphs of effects of graded lower-body negative pressure before sympathetic blockade (control conditions) on forearm vascular resistance (FVR), plasma norepinephrine concentration (NE), plasma renin activity (PRA), and plasma level of atrial natriuretic factor (V-irANF) in the blood withdrawn from an antecubital vein, in 10 hypertensive patients (cross-hatched columns) and in five normotensive subjects (open columns). Each bar represents mean±SEM. *p<0.05 and **p<0.01 vs. baseline.]
and PRA did not change at −10 mm Hg LBNP, only the changes in these parameters induced by −40 mm Hg LBNP and the simultaneous increases in FVR were plotted and found significant (all \( p<0.01 \)). In contrast, there was an inverse correlation between the changes in PA- and V-irANF levels and in irANF release evoked by both levels of LBNP and the simultaneous changes in FVR (\( r=-0.874, -0.655, \) and \(-0.830, \) respectively, all \( p<0.01 \)).

**Effects of Lower-Body Negative Pressure After Sympathetic Blockade**

The effectiveness of the sympathetic blockade induced by the combined administration of propranolol and phentolamine was shown by the suppression of the FVR increase induced by cold pressor test in control conditions. FVR during the cold pressor test in control conditions rose from 76±8 to 100±9 in normal subjects and from 127±8 to 173±12 mm Hg/ml/sec in hypertensive patients, both \( p<0.01 \), and remained unchanged after sympathetic blockade (normal subjects: 76±7 vs. 79±6; hypertensive subjects: 100±6 vs. 102±7 mm Hg/ml/sec, both NS).

**Hemodynamics**

Sympathetic blockade in both groups reduced baseline values, left ventricular filling pressure,
right atrial pressure, mean arterial pressure, and FVR (Table 2 and Figure 2). LBNP-induced changes in right atrial pressure and in LVPF (baseline, 15±1 mm Hg; -10 mm Hg LBNP; 12±1 mm Hg, p<0.05; -40 mm Hg LBNP, 8±1 mm Hg, p<0.01) were comparable to those recorded in control conditions (Table 2). Also, the changes in forearm blood flow or FVR induced by -10 mm Hg LBNP remained unchanged after the complete sympathetic blockade in normal subjects and in hypertensive patients. On the contrary, the combined administration of propranolol and phenolamine significantly modified the hemodynamic changes induced by -40 mm Hg LBNP in both groups, the reductions in mean arterial pressure and forearm blood flow being greater (Table 2). In normal subjects, the increase in FVR induced by -40 mm Hg LBNP was similar to that elicited by -10 mm Hg LBNP. In hypertensive patients, during -40 mm Hg LBNP, after adrenergic blockade, there was a significant reduction in pulse pressure and a significant increase in FVR compared with baseline and -10 mm Hg LBNP. However, even in these patients, the increase in FVR induced by -40 mm Hg LBNP after sympathetic blockade was significantly smaller than that obtained in control conditions (FVR during control conditions, 65±6; after sympathetic blockade, 34±2 mm Hg/ml/sec, p<0.01). Heart rate rose significantly only during -40 mm Hg LBNP (Table 2).

**Hormonal Parameters**

Sympathetic blockade resulted in an increase in norepinephrine plasma levels, no change in PRA, and a significant fall in baseline V-irANF levels in both groups (Figure 2). In hypertensive patients PA-irANF levels also decreased (from 263±30 to 126±18 pg/ml, p<0.001), and irANF release decreased (from 1151±129 to 412±61 ng/min, p<0.01) after sympathetic blockade.

In normal subjects, after sympathetic blockade, -10 mm Hg LBNP failed to modify plasma norepinephrine levels (392±43 vs. 424±55 pg/ml, NS) and PRA, whereas V-irANF levels fell significantly (Figure 2). When -10 mm Hg LBNP was applied in hypertensive patients after propranolol plus phenolamine administration, PRA and plasma norepinephrine levels (Figure 2) did not change, whereas PA- and V-irANF levels and estimated irANF release decreased. The reductions in irANF were comparable in magnitude with those recorded during -10 mm Hg LBNP under control conditions in normal subjects (Δ%V-irANF, -34±8 vs. 38±4, NS) and in hypertensive patients (Δ%PA-irANF, -28±6 vs. -37±3; V-irANF, -28±7 vs. -41±5; Δ%irANF release, -38±5 vs. -41±4; all NS). During sympathetic blockade in both groups, -40 mm Hg LBNP raised plasma norepinephrine levels (Figure 2) and reduced irANF levels as much as in control conditions (normal subjects: Δ%V-irANF, -59±6 vs. 55±3; hypertensive patients: Δ%PA-irANF, -64±6 vs. -68±5; Δ%V-irANF, -68±8 vs. -74±6; Δ%irANF release, -69±4 vs. -69±6, all NS), whereas PRA did not change (Figure 2).

**Relations Between Hemodynamic and Hormonal Parameters**

Also, during sympathetic blockade, a significant inverse relation between the changes in cardiac pressures and those in FVR was found in both groups (all p<0.01). Similarly, the inverse correlation between changes in plasma irANF levels and irANF release elicited by graded LBNP and the simultaneous changes in FVR persisted after sympathetic blockade in normal subjects and in hypertensive patients (p<0.01 in all cases), but the slope was significantly reduced by the pharmacologic treatment (normal subjects: slope Δ%V-irANF/Δ%FVR, -0.159 vs. -0.573; hypertensive patients: slope Δ%V-irANF/Δ%FVR, -0.213 vs. -0.637; Δ%PA-irANF/Δ%FVR, -0.357 vs. -1.171; Δ%ANF release/Δ%FVR, -0.444 vs. -1.073, all p<0.01). On the contrary, no significant direct correlation between the changes in plasma norepinephrine levels, PRA, and in FVR during LBNP was found after sympathetic blockade.

Finally, administration of vehicle alone did not alter the effects of LBNP. In particular, V-irANF levels in normal subjects and hypertensive patients were: baseline, 70±4 and 126±24 pg/ml; -10 mm Hg LBNP, 46±4 and 92±17 pg/ml; -40 mm Hg LBNP, 28±3 and 41±13 pg/ml, respectively. After the injection of 10 ml saline, V-irANF levels were: baseline, 68±10 and 122±37 pg/ml; -10 mm Hg LBNP, 47±4 and 79±27 pg/ml; -40 mm Hg LBNP, 30±2 and 31±14 pg/ml, respectively.

The time-course experiments showed no change in plasma V-irANF concentrations throughout the experiment (normotensive subjects, mean 65 pg/ml, coefficient of variability 6.8%; hypertensive patients, mean 111 pg/ml, coefficient of variability 7.3%).

**Study With Atrial Natriuretic Factor Infusion**

When ANF was infused in hypertensive patients with left ventricular hypertrophy at the dosage of 2.5 ng/kg/min (V-irANF plasma level, 172±22 vs. 123±18 pg/ml, p<0.01), steady-state right atrial pressure and mean arterial pressure only tended to decrease from baseline values (Figure 3). Simultaneously, plasma norepinephrine levels and heart rate remained unchanged, whereas FVR showed a significant decrease (Figure 3). The higher dosage of ANF infusion (5 ng/kg/min), which raised V-irANF plasma levels to 324±57 pg/ml (p<0.001), induced only a slight reduction in mean blood pressure and a significant reduction in right atrial pressure (Figure 3). Heart rate and plasma norepinephrine levels increased significantly, whereas FVR remained unchanged (Figure 3).

**Discussion**

To verify our previous observation1 in hypertensive patients with left ventricular hypertrophy that
cardiopulmonary receptor unloading does not increase plasma norepinephrine levels as in normotensive subjects, norepinephrine levels were measured in the venous effluent from the forearm, where the changes in sympathetic discharge elicited by low-pressure receptors are more evident. Because it has been reported that changes in plasma catecholamine concentration only partially reflect changes in sympathetic tone, we also assessed the influence of short-term adrenergic blockade on the reflex hemodynamic response induced by unloading of cardiopulmonary receptors.

In hypertensive patients with left ventricular hypertrophy, graded LBNP induced an increase in FVR comparable to that in normotensive subjects, a finding that is consistent with our previous observations. The slopes of the regression lines obtained by plotting the changes in right atrial pressure against the simultaneous changes in vascular resistance, which represent the gain of the reflex, were comparable in the two groups. However, during -10 mm Hg LBNP, increases in plasma norepinephrine levels and PRA did not occur in hypertensive patients as in normal subjects in the present as well as in previous studies. This finding suggests that in patients with left ventricular hypertrophy, sympathetic and renin-angiotensin systems are not responsible for the peripheral vasoconstric-

tive response to cardiopulmonary receptor unloading. Such an interpretation is confirmed by the observation that a comparable reflex vasoconstriction was observed during -10 mm Hg LBNP after sympathetic blockade.

A higher level of LBNP enhanced the forearm vasoconstriction and was accompanied by a significant rise in plasma norepinephrine levels and PRA in normal subjects and in hypertensive patients with left ventricular hypertrophy. Because -40 mm Hg LBNP has been reported to deactivate arterial baroreceptors as well as cardiopulmonary receptors, it is likely that the peripheral vasoconstrictor response to unloading of carotid and sinoaortic baroreceptors is secondary to an increased sympathetic discharge even in hypertensive patients with left ventricular hypertrophy. This is supported by the finding that in these patients the sympathetic blockade blunts the increase in forearm vascular resistance induced by -40 mm Hg LBNP.

The close correlation between the changes in plasma norepinephrine levels and PRA and those in FVR in normal subjects suggests that these hormonal systems play a major role in the mediation of the vascular response to orthostatic stress in these subjects. The lack of significant correlations in hypertensive patients with left ventricular hypertrophy supports the hypothesis that the sympathetic system does not participate in the mediation of the vascular response to cardiopulmonary receptor unloading (-10 mm Hg) in these patients. On the other hand, persistence of comparable forearm vasoconstrictive response to cardiopulmonary receptor unloading in patients with left ventricular hypertrophy in control conditions and in both groups after sympathetic blockade suggests that other mechanisms are involved in the hemodynamic response to this stimulus.

We cannot assess how much of the increase in forearm vascular resistance is due to a decrease in flow, a phenomenon that has recently been indicated as a major factor in the mediation of the response of large arteries to LBNP. However, the mediation of this phenomenon and the contribution of cardiac atria in the maintenance of blood pressure homeostasis seem to be largely related to the intervention of hormonal factors. In fact, Fujita and coworkers reported that in normal subjects ANF has a direct vasorelaxant effect in the forearm vascular bed. These investigators have also shown that intra-arterial administration of ANF, at doses that do not alter heart rate or systemic blood pressure, is able to reduce forearm vascular resistance. In addition, a number of studies have shown that ANF release is closely related to the level of atrial pressure. For this reason, it might be speculated that LBNP reduces plasma ANF levels by reducing atrial pressure. The reduction of the vasodilatory influence of ANF on peripheral vessels may influence the impaired sympathetic response to cardiopulmonary receptor unloading in hyperten-
sive patients with left ventricular hypertrophy, thus permitting a vasoconstrictor response comparable in magnitude to that observed in normal subjects. The results of the present study support such a hypothesis. In both groups of subjects, graded LBNP induced a progressive decrease in right and left atrial pressure that was paralleled by a fall in plasma irANF. A correlation between changes in plasma irANF and in FVR during LBNP was found both in normal subjects and in hypertensive patients, although in the first group the correlation coefficient was significantly smaller than that obtained in hypertensive patients. This latter observation may suggest that ANF participates in the mediation of the reflex response evoked by LBNP also in the normal state, although its possible effect is masked by the activation of sympathetic and renin-angiotensin systems. When the sympathetic response to cardiopulmonary receptor unloading is blunted, as in hypertensive patients with a nondilated hypertrophic left ventricle or in normotensive subjects after sympathetic blockade, a fall in plasma ANF may contribute to maintaining the vasoconstrictive response to –10 mm Hg LBNP.

The mechanisms by which ANF induces hemodynamic responses are still unclear. The changes in ANF plasma levels, comparable in magnitude with those evoked by –10 mm Hg LBNP, induced forearm vasodilatation in patients with left ventricular hypertrophy. This observation suggests that the fall in atrial pressure elicited by LBNP through a venous pooling inhibits ANF release and removes a putative tonic vasodilator mechanism, thus resulting in forearm and systemic vasoconstriction. Therefore, the observation in hypertensive patients with left ventricular hypertrophy, but not in normal subjects, after sympathetic blockade that there was a further increase in FVR with the higher level of LBNP may be explained by the higher baseline plasma ANF levels measured in these patients. In fact, in a previous study, we reported that an increase in irANF plasma levels induced by infusion of exogenous ANF is associated with an enhanced forearm vasoconstrictor response to LBNP. Thus, according to our previous hypothesis, the tonic vasodilating activity exerted by ANF in hypertensive patients with left ventricular hypertrophy would be more marked than in normal subjects, and consequently, the gain of the vasoconstrictor mechanism mediated by a reduction in ANF release would be potentiated.

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