Impaired Control of Vasopressin Release in Hypertensive Subjects with Cardiac Hypertrophy

BRUNO TRIMARCO, NICOLA DE LUCA, ANTONIO DE SIMONE, MASSIMO VOLPE, BRUNO RICCIARDELLI, GIUSEPPE LEMBO, AND MARIO CONDORELLI

SUMMARY The effects of graded lower body negative pressure (−10 and −40 mm Hg) on vascular resistance and plasma vasopressin, norepinephrine, and renin activity were assessed in seven hypertensive subjects with left ventricular hypertrophy and seven sex-matched and age-matched normotensive subjects. In both groups increasing levels of lower body negative pressure induced a progressive decrease in right atrial pressure and an increase in vascular resistance. In normal subjects plasma vasopressin, norepinephrine, and renin activity were progressively raised, whereas only the higher level of stimulation increased plasma renin activity, norepinephrine, and vasopressin in hypertensive subjects. Propranolol induced a significant increase in plasma vasopressin in normal subjects (from 1.3 ± 0.1 to 2.0 ± 0.1 pg/ml; p<0.05) but not in hypertensive subjects. In this latter condition −10 mm Hg lower body negative pressure failed to increase plasma vasopressin, norepinephrine, and renin activity in normal subjects. Propranolol abolished the change in plasma renin activity in both groups, reduced the increase in vascular resistance induced by −40 mm Hg lower body negative pressure in normotensive subjects, but did not modify the rise in vasopressin elicited by this stimulus in normal subjects or the humoral and hemodynamic reflex responses evoked in hypertensive subjects. These results suggest that cardiopulmonary receptors are involved in the control of vasopressin release in normal subjects, whereas in hypertensive subjects with left ventricular hypertrophy, this control is altered because of an impaired function of cardiopulmonary receptors.

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KEY WORDS • propranolol • lower body negative pressure • norepinephrine

ALTHOUGH the sensitivity of the nonosmotic control of arginine vasopressin (AVP) release in humans seems to be somewhat controversial,14 recent reports5,6 support the hypothesis that factors other than blood osmolality are involved in the regulation of AVP release in humans. In particular, Leimbach et al.5 demonstrated that combined unloading of cardiac and arterial baroreceptors induced by lower body negative pressure (LBNP) increases plasma AVP in subjects with high plasma osmolality. Egan et al.6 reported that the selective unloading of cardiopulmonary receptors, by thigh-cuff inflation, increases plasma AVP levels in humans. These observations raise the possibility that AVP release may be altered in patients with impaired cardiopulmonary or arterial baroreceptor reflex responsiveness.

In patients with established hypertension, we observed that the postural change from the supine to the upright position did not induce the rise in AVP plasma levels observed in normotensive subjects.7 More recently, we reported8 that hypertensive patients with left ventricular hypertrophy (LVH) show a selective impairment of ventricular receptors, which play a major role in the mediation of the hemodynamic response to simulated orthostatic stress.9

In an attempt to evaluate the specific influence of cardiopulmonary and arterial receptors on AVP release, in the present study we compared the effects of two levels of LBNP (i.e., −10 and −40 mm Hg) in hypertensive subjects with LVH and in an age and sex-matched control group of normotensive subjects. In addition, as propranolol has been reported to act on cardiopulmonary receptors by attenuating the firing of ventricular receptors with nonmyelinated vagal afferents10 and by reducing the responsiveness of sympathetic afferents,11 we investigated the effects of the drug on AVP plasma changes induced by simulated orthostatic stress.

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Subjects and Methods

The study was performed in seven subjects (4 men and 3 women; mean age, 34 ± 3 years) with established mild or moderate essential hypertension. In these subjects, blood pressure readings were above 160 mm Hg systolic and 95 mm Hg diastolic for at least five consecutive measurements obtained in the outpatient clinic. None of these subjects had received any treatment for at least 3 weeks before the study. Blood pressure was measured with the subject 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 following the recommendations of the American Heart Association.16 Secondary hypertension had been previously ruled out in all hypertensive subjects by laboratory and roentgenographic studies.

Seven age and sex-matched normotensive subjects (4 men and 3 women; mean age, 33 ± 3 years) were also studied as a control group. They were seven non-consecutive patients with a normal coronary arteriogram who underwent coronary arteriography to define the cause of their chest pain syndrome. None of them had electrocardiographic (ECG) evidence of myocardial infarction or exercise stress test results positive for ischemic heart disease. 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 all provided written consent. None of the normotensive subjects showed signs of LVH as assessed by echocardiography13 measured before the invasive study, whereas all the hypertensive subjects satisfied the echocardiographic criteria for LVH.

In the week preceding the study, the subjects were hospitalized. During this period, they received a daily diet containing 1500 ml of fluids, 150 mEq of sodium, and 70 mEq of potassium. From Day 4 to 7, it was verified on the basis of body weight, sodium intake, and urinary sodium output that sodium balance was maintained in the steady state. Two-dimensional and M-mode echocardiograms were obtained and processed as previously reported from this laboratory.14 Two days before the invasive study session, the subjects were made familiar with the LBNP device and the neck chamber. Subjects were requested to refrain from cigarette smoking and coffee drinking during the 12 hours immediately prior to 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. Upon arrival at the laboratory, subjects assumed the supine position and had ECG leads attached for ECG monitoring. A LBNP chamber, similar to that described by Mark and Kerber,15 was placed over the lower portion of each subject's body, from the iliac crest down, to apply graded levels of LBNP to progressively unload cardiac and arterial baroreceptors. With the subjects under local anesthesia with 2% lidocaine, a heparinized arterial catheter was introduced percutaneously into the right brachial artery and positioned under fluoroscopy in the ascending aorta for direct measurement of systemic blood pressure. Mean arterial pressure was obtained by the integration of the pulsatile trace over periods of 5 seconds. A triple-lumen Swan-Ganz catheter was introduced through an antecubital vein and positioned 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, CA, USA). Right atrial, pulmonary artery, and pulmonary capillary wedge pressures were also recorded. Heart rate was taken from an ECG lead monitored continuously during the study, and the subjects were asked to breathe regularly. Systemic and pulmonary arterial pressure and right atrial pressure were continuously measured with a Statham P23Db pressure transducer (Oxnard, CA, USA) and recorded simultaneously with the ECG lead on an EP 12 multichannel polygraph (OTF Biomedica, Florence, Italy). All tracings were recorded at a paper speed of 100 mm/sec. Blood samples for the determination of biohumoral parameters were obtained from the right atrial catheter. Blood losses and fluid administration did not exceed 250 ml. A polyethylene catheter was inserted into a contralateral antecubital vein for drug and fluid administration.

Baseline hemodynamic measurements included systemic and pulmonary arterial pressure, right ventricular pressure, heart rate, and cardiac output. Systemic vascular resistance (dyn · sec · cm⁻²) was calculated as (mean arterial pressure − right atrial pressure)/(cardiac output) × 80.

To test the selectivity of propranolol effects on cardiopulmonary receptors, we also evaluated arterial baroreceptor responsiveness before and after propranolol administration by assessing 1) the slope of the relationship obtained by plotting systolic blood pressure against RR interval after the intravenous injection of phenylephrine (2 μg/kg), as previously reported from this laboratory,16 and 2) carotid baroreceptor unloading evoked by increasing neck pressure by means of a neck chamber, as previously described.16 Neck pressure was applied at + 60 mm Hg for 2 minutes to decrease transmural carotid pressure and thereby to unload the carotid baroreceptors. The hemodynamic effects induced by the changes in neck tissue pressure were analyzed according to the technique of Mancia et al.17 by dividing arterial pressure and heart interval values into 1) the control value (the average value during the 30 seconds preceding the change in neck tissue pressure), 2) the early response (the average value in the 10-second period from the 5th to the 15th second following the change in neck tissue pressure), and 3) the steady state response (the average value during the last 30 seconds of the neck tissue pressure change).

Humoral Measurements

Urinary and serum electrolytes were measured with a flame photometer. Plasma osmolality was determined by freezing point depression using an automated
osmometer. Serum electrolytes and plasma osmolality were measured on the study day. Plasma renin activity (PRA) and plasma aldosterone (PA) concentration were measured by radioimmunoassay using Sorin-Biomedica kits (Saluggia, Vercelli, Italy). PRA was assessed by measuring the amount of angiotensin I generated after a 120-minute incubation period at a pH of 6 (sensitivity, 0.18 + 0.04 ng/ml; intra-assay and interassay variability coefficients, 6 and 10%, respectively). The sensitivity of the PA assay was 10.5 ± 2 pg/ml, and the intra-assay and interassay variability coefficients were 8 and 13%, respectively. Norepinephrine (NE) was measured by a specific radioenzymatic method. Plasma AVP was measured by radioimmunoassay technique as described by Robertson. Briefly, the samples were collected in prechilled heparinized tubes, immediately placed on ice, and then centrifuged according to the suggestions of Preibisz et al. to obtain a platelet-free plasma. The platelet-free plasma was divided in two aliquots and stored at −70°C, usually for less than 2 weeks.

Plasma Extraction

For the plasma extraction, 1000 cpm of [125I]AVP in 25 μl of phosphate buffer (pH 7.6) was added to 4.0 ml of platelet-free plasma to serve as a tracer during extraction. Proteins were precipitated by the addition of 8 ml of cold acetone and removed by centrifugation. Then, petroleum ether (20 ml) was added to the supernatant, the top phase was discarded after centrifugation, and the remainder was evaporated. Dried extracts were then reconstituted in 1 ml of phosphate buffer and counted in a Packard counter (efficiency, 75%; Packard Instruments, Downers Grove, IL, USA) to calculate the percentage of AVP recovered, which was about 60%. In addition, 1000 cpm [125I]AVP was added to 24 tubes containing 4.0 ml of bovine serum albumin assay buffer. These tubes underwent acetone/petroleum ether extraction and then were resuspended in the assay buffer and counted for AVP recovery calculation. They showed a recovery percentage quite similar to that of the unknown samples and served as blanks in the radioimmunoassay.

Radioimmunoassay

Based on the results of previous pilot experiments designed to improve the assay sensitivity, the amount of [125I]AVP added to each assay tube was 3000 cpm. The amount of AVP antiserum added to each tube was chosen to allow 30 to 35% binding. In particular, the standard curve and the unknown samples were prepared in duplicate by mixing AVP antiserum with increasing amounts of synthetic AVP in 400 μl of the recovery blank or 400 μl of the reconstituted dried extracts, respectively. After a 60-hour equilibration period at 4°C, about 3000 cpm of [125I]AVP was added as fresh tracer to all tubes. The tubes were returned to the refrigerator for at least 96 hours. The separation procedure of the antibody-bound, labeled antigen from the free labeled antigen was performed by adding ice-cold dextran-charcoal (carbon decolorizing alkaline; Norit A, Fisher Scientific, Pittsburgh, PA, USA; dextran 10, Pharmacia Fine Chemicals, Uppsala, Sweden) to each tube. After a 10-minute centrifugation at 1500 g, the supernatant of each assay tube was counted. Lyophilized AVP antiserum, [125I]AVP, and synthetic AVP were purchased from the Bühlmann Laboratories, Basel, Switzerland.

To calculate the AVP content of each tube, the log of the ratio of antibody-bound radioactivity of each sample to the antibody-bound radioactivity of the zero dose was placed on the ordinate, while the unlabeled antigen concentration was entered on the logarithmic scale on the abscissa. Correction was made for the extraction losses. For quality control, three samples containing three different concentrations of exogenous AVP (low, 1.25 pg/ml; medium, 2.5 pg/ml; and high, 5 pg/ml; stored in 4-ml aliquots at −70°C) were assayed in duplicate with each set. Assay sensitivity was 0.6 pg/tube. The antisemum used showed the following cross-reactivities: AVP, 100%; lysine vasopressin, 0.007%; oxytocin, less than 0.0001%. The intra-assay and interassay variability coefficients, calculated according to the method of Rodbard, were 6.7 and 7.8% for the low, 5.1 and 7.9% for the medium, and 5.7 and 9.3% for the high AVP concentrations, respectively.

Protocol

After catheter placement, a 20-minute rest period was observed, then baseline measurements were obtained. Thereafter, −10 mm Hg LBNP was applied for 20 minutes in an attempt to unload cardiopulmonary baroreceptors alone. Blood sampling and hemodynamic measurements were performed during the last 3 minutes of LBNP. After a 30-minute rest period, the subjects underwent 20 minutes of −40 mm Hg LBNP, and the variables were remeasured during the last 3 minutes of this level of LBNP. The hemodynamic response to intravenous phenylephrine injection and a 60 mm Hg increase in neck tissue pressure were also recorded. Interventions were performed in random order. Then, the subjects were given propranolol, 0.1 mg/kg i.v., over 10 minutes. After a further 20-minute recovery period, humoral and hemodynamic parameters were measured again before and during the previously mentioned stimuli.

To simplify the experimental procedures and to keep blood losses under 250 ml, we did not examine whether basal levels of AVP were reestablished after each stimulus. However, in preliminary experiments aimed at assessing the time course of the change in plasma AVP concentration following the higher level of LBNP, we found that, following −40 mm Hg LBNP, plasma AVP returned to baseline within 10 minutes (baseline, 1.3 ± 0.2 pg/ml; after −40 mm Hg LBNP, 3.6 ± 0.4 pg/ml; 10 minutes after the end of LBNP stimulus, 1.2 ± 0.2; n = 3). In three hypertensive subjects and three normotensive subjects, all the responses also were tested before and after the intravenous administration of vehicle. Finally, to rule out the possibility that time-dependent changes in AVP may occur during the study, in three hypertensive and in three normotensive subjects plasma AVP levels were mea-
sured every 30 minutes for 5 hours in the absence of any intervention.

Data Analysis

Data are presented as means ± SE. Baseline values of the two study groups in control conditions and after propranolol administration were compared by unpaired t test. Responses to baroreceptor unloading by neck chamber or loading by phenylephrine injection before and after propranolol were compared by paired t test. The individual values of each parameter obtained in control conditions and in response to the two levels of LBNP before and after propranolol were analyzed by analysis of variance and Duncan’s multiple-range test.

Results

Resting Measurements

Hemodynamics

Mean arterial pressure (MAP), pulse pressure, and total peripheral resistance (TPR) were significantly higher in hypertensive subjects than in normotensive controls (Table 1). Right atrial pressure (RAP) and left ventricular filling pressure (LVFP), as estimated by pulmonary capillary wedge pressure, tended to be higher in hypertensive subjects, but the difference did not achieve statistical significance (see Table 1). The two groups also differed in their echocardiographic measurements of left ventricular wall thickness (septum and posterior wall thickness; hypertensive subjects, 2.09 ± 0.04 cm; normal subjects, 1.61 ± 0.04 cm; p < 0.01) and left ventricular mass index (hypertensive subjects, 130 ± 7 g/m²; normal subjects, 89 ± 3 g/m²; p < 0.01), while the mean value of the left ventricular internal dimensions of the two groups, measured at both end systole and end diastole, were comparable (data not shown).

As expected, intravenous propranolol administration (0.1 mg/kg body weight) decreased heart rate and increased TPR in both groups (see Table 1). Furthermore, RAP and LVFP tended to be higher after propranolol administration in both groups, but this increase did not achieve statistical significance (see Table 1).

Biohumoral Parameters

The two groups were quite comparable with regard to the hormonal profile. Although baseline values of AVP tended to be higher in hypertensive subjects as compared with normotensive subjects, the difference was not statistically significant (Table 2).

The intravenous administration of propranolol increased AVP in normal subjects (Figure 1) but not in hypertensive subjects (Figure 2), whereas it failed to modify PRA, PA, and NE as well as plasma osmolality in both groups (see Table 2).

Arterial Baroreceptor Responsiveness

In control conditions, hypertensive subjects showed a significant reduction in arterial baroreceptor respon-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>−10 mm Hg</th>
<th>−40 mm Hg</th>
<th>Baseline</th>
<th>−10 mm Hg</th>
<th>−40 mm Hg</th>
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<tbody>
<tr>
<td>MAP (mm Hg)</td>
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<td></td>
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<tr>
<td>Pretreatment</td>
<td>88 ± 2</td>
<td>87 ± 2</td>
<td>86 ± 2</td>
<td>120 ± 2</td>
<td>120 ± 1</td>
<td>118 ± 8</td>
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<tr>
<td>Posttreatment</td>
<td>87 ± 3</td>
<td>85 ± 2</td>
<td>82 ± 3</td>
<td>120 ± 2</td>
<td>124 ± 2</td>
<td>122 ± 3</td>
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<td>PP (mm Hg)</td>
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<tr>
<td>Pretreatment</td>
<td>52 ± 4</td>
<td>52 ± 6</td>
<td>41 ± 4</td>
<td>66 ± 3</td>
<td>63 ± 2</td>
<td>58 ± 3</td>
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<td>Posttreatment</td>
<td>51 ± 4</td>
<td>48 ± 4</td>
<td>41 ± 3</td>
<td>68 ± 4</td>
<td>66 ± 3</td>
<td>58 ± 4</td>
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<td>HR (beats/min)</td>
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<td>Pretreatment</td>
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<td>74 ± 2</td>
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<td>70 ± 4</td>
<td>73 ± 5</td>
<td>82 ± 6</td>
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<td>Posttreatment</td>
<td>66 ± 2</td>
<td>68 ± 2</td>
<td>76 ± 4</td>
<td>61 ± 2</td>
<td>63 ± 2</td>
<td>72 ± 3</td>
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<td>CVP (mm Hg)</td>
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<tr>
<td>Pretreatment</td>
<td>5.6 ± 0.4</td>
<td>3.1 ± 0.6</td>
<td>1.2 ± 1</td>
<td>6.8 ± 0.7</td>
<td>5.4 ± 0.8</td>
<td>2.9 ± 1</td>
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<td>Posttreatment</td>
<td>6.6 ± 0.8</td>
<td>4.2 ± 1.2</td>
<td>1.3 ± 0.9</td>
<td>7.7 ± 1.2</td>
<td>5.7 ± 0.9</td>
<td>2.7 ± 1</td>
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<td>PCWP (mm Hg)</td>
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<tr>
<td>Pretreatment</td>
<td>9.2 ± 0.5</td>
<td>6.9 ± 0.5</td>
<td>4.2 ± 0.5</td>
<td>11.8 ± 1.3</td>
<td>7.8 ± 1.3</td>
<td>5.1 ± 1.6</td>
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<td>Posttreatment</td>
<td>11.3 ± 0.3</td>
<td>8.8 ± 0.6</td>
<td>5.6 ± 0.7</td>
<td>13.2 ± 1.3</td>
<td>10.1 ± 1.2</td>
<td>7.4 ± 1.4</td>
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<td>CO (L/min)</td>
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<td></td>
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<tr>
<td>Pretreatment</td>
<td>7.75 ± 0.3</td>
<td>6.75 ± 0.3</td>
<td>5.38 ± 0.4</td>
<td>7.09 ± 0.2</td>
<td>6.51 ± 0.3</td>
<td>5.65 ± 0.3</td>
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<td>Posttreatment</td>
<td>6.23 ± 0.39</td>
<td>5.51 ± 0.39</td>
<td>4.93 ± 0.27</td>
<td>6.08 ± 0.28</td>
<td>5.73 ± 0.27</td>
<td>5.01 ± 0.28</td>
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<td>TPR (dyn-sec-cm⁻²)</td>
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<tr>
<td>Pretreatment</td>
<td>910 ± 26</td>
<td>1040 ± 58</td>
<td>1289 ± 91</td>
<td>1360 ± 57</td>
<td>1491 ± 68</td>
<td>1703 ± 89</td>
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<td>Posttreatment</td>
<td>1137 ± 66</td>
<td>1246 ± 68</td>
<td>1350 ± 87</td>
<td>1606 ± 85</td>
<td>1750 ± 92</td>
<td>1976 ± 89</td>
</tr>
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</table>

Values are means ± SE of seven subjects. PP = pulse pressure; HR = heart rate; CVP = central venous pressure; PCWP = pulmonary capillary wedge pressure; CO = cardiac output; TPR = total peripheral resistance.

* p < 0.01, compared with values in normotensive subjects.
† p < 0.05, || p < 0.01, compared with respective pretreatment values.
‡ p < 0.05, $ p < 0.01, compared with respective baseline values.
TABLE 2. Biohumoral Changes Induced by −10 and −40 mm Hg Lower Body Negative Pressure Before and After Propranolol Administration

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive</th>
<th>Hypertensive</th>
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<tbody>
<tr>
<td>AVP (pg/ml)</td>
<td></td>
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<tr>
<td>Pretreatment</td>
<td>1.3±0.1</td>
<td>1.8±0.2*</td>
</tr>
<tr>
<td>Posttreatment</td>
<td>2.0±0.2</td>
<td>1.9±0.3*</td>
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<tr>
<td>PRA (ng Ang I/ml/hr)</td>
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<tr>
<td>Pretreatment</td>
<td>1.2±0.1</td>
<td>1.8±0.4</td>
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<tr>
<td>Posttreatment</td>
<td>1.1±0.3</td>
<td>1.1±0.3</td>
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<tr>
<td>PA (pg/ml)</td>
<td></td>
<td></td>
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<tr>
<td>Pretreatment</td>
<td>193±25</td>
<td>182±21</td>
</tr>
<tr>
<td>Posttreatment</td>
<td>209±32</td>
<td>145±9</td>
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<tr>
<td>NE (pg/ml)</td>
<td></td>
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<tr>
<td>Pretreatment</td>
<td>245±50</td>
<td>239±39</td>
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<tr>
<td>Posttreatment</td>
<td>234±21</td>
<td>181±23</td>
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<tr>
<td>Osm (mosm/l)</td>
<td></td>
<td></td>
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<tr>
<td>Pretreatment</td>
<td>289±4</td>
<td>291±4</td>
</tr>
<tr>
<td>Posttreatment</td>
<td>287±4</td>
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</tr>
</tbody>
</table>

Values are means ± SE of seven subjects. AVP = arginine vasopressin; PA = plasma aldosterone; NE = plasma norepinephrine; Osm = osmolality.

*p<0.05, †p<0.01, compared with respective baseline values.

Responsiveness as compared with normal subjects (Table 3). After intravenous propranolol administration, no significant change in arterial baroreceptor response to selective unloading of the carotid baroreceptors by neck chamber or generalized baroreceptor stimulation by phenylephrine injection was observed in either group as compared with control conditions (see Table 3).

Responses to Lower Body Negative Pressure

Hemodynamics

In both groups −10 and −40 mm Hg LBNP decreased RAP and LVFP to a comparable extent (see Table 1). This response to LBNP was accompanied by a reduction in cardiac output and an increase in TPR without any significant change in MAP (see Table 1). Heart rate rose significantly only at −40 mm Hg LBNP (see Table 1). The higher level of LBNP also caused a significant reduction in pulse pressure (see Table 1). A significant relationship was found between the changes in RAP and TPR induced by LBNP (normotensive subjects, r = 0.844; hypertensive subjects, r = 0.868; all p<0.01). Similarly, during LBNP the changes in LVFP were significantly correlated with those in TPR (normotensive subjects, r = 0.849; hypertensive subjects, r = 0.878; all p<0.01).

After propranolol treatment, the two levels of LBNP induced changes in RAP and LVFP comparable to those recorded in control conditions (see Table 1). However, a significant reduction of the TPR response to −40 mm Hg LBNP was observed only in normotensive subjects (control conditions, 378 ± 84 dyn·sec·cm⁻³ after propranolol, 214 ± 39 dyn·sec·cm⁻³, p<0.01, as assessed by paired t test).

Biohumoral Parameters

In normal subjects, −10 mm Hg LBNP induced a slight, but significant increase in plasma AVP levels (see Figure 1 and Table 2). In contrast, in hypertensive subjects this level of LBNP failed to modify plasma AVP levels (see Figure 2 and Table 2). The higher
level of LBNP induced a significant increase in AVP in normal subjects and in hypertensive subjects (see Figures 1 and 2 and Table 2).

In normotensive subjects, but not in hypertensive subjects, NE and PRA values were significantly raised during −10 mm Hg LBNP as compared with the values obtained in control conditions (see Table 2). The higher level of LBNP was able to significantly increase PRA and NE in both groups of subjects (see Table 2). Finally, no change in PA was observed with both levels of LBNP in either group (see Table 2).

Propranolol administration was able to prevent the effects of LBNP on PRA in both groups (see Table 2). Furthermore, in normal subjects this pharmacological treatment abolished the increase in AVP (see Figure 1 and Table 2) and NE (see Table 2) elicited by −10 mm Hg LBNP, induced a nonsignificant reduction of the increase in NE evoked by −40 mm Hg LBNP, but did not modify the reflex response of AVP to the higher level of LBNP (see Figure 1 and Table 2). In contrast, no change in the reflex response of either of these hormones to −40 mm Hg LBNP could be detected in hypertensive subjects (see Figure 2 and Table 2).

Finally, in the experiments in which the stimuli were performed before and after administration of vehicle, no change in the effects of LBNP on all the considered parameters was recorded in either normal or hypertensive subjects. In particular, plasma AVP for normotensive subjects was 1.3 ± 0.2 pg/ml at baseline, 1.9 ± 0.3 pg/ml during −10 mm Hg LBNP, 3.3 ± 0.4 pg/ml during −40 mm Hg LBNP; and after the injection of 10 ml of saline, 1.3 ± 0.2 pg/ml at baseline, 2 ± 0.3 pg/ml during −10 mm Hg LBNP, and 3.5 ± 0.3 pg/ml during −40 mm Hg LBNP. Plasma AVP in hypertensive subjects was 2.2 ± 0.4 pg/ml at baseline, 2.3 ± 0.4 pg/ml during −10 mm Hg LBNP, 3.7 ± 0.6 pg/ml during −40 mm Hg LBNP; and after the injection of 10 ml of saline, 2.2 ± 0.3 pg/ml at baseline, 2.2 ± 0.4 pg/ml during −10 mm Hg LBNP, and 3.9 ± 0.3 pg/ml during −40 mm Hg LBNP. Also, the experiments aimed at assessing the effect of time on AVP release failed to demonstrate any change in plasma AVP concentration throughout the experiment (normotensive subjects: mean, 1.1 pg/ml; coefficient of variability, 9%; hypertensive subjects: mean, 1.9 pg/ml; coefficient of variability, 5%).

Discussion

Our study was mainly aimed at investigating the effects of changes in cardiac hemodynamics on plasma AVP levels in subjects with impaired left ventricular sensory receptor function. To simplify the study procedures, we evaluated the reflex vascular response to LBNP by measuring the changes in TPR induced by LBNP. This approach might appear to conflict with the data of Oberg and Thoren,24 who reported that cardiopulmonary receptors subserved by vagal afferents exert a tonic inhibitory influence on the vasomotor neurons controlling the efferent sympathetic discharge to muscle and renal resistance vessels. However, Mancia and Donald25 demonstrated in dogs with constant flow extracorporeal circulation, in which changes in aortic pressure reflect changes in TPR, that inhibition of the cardiopulmonary receptors induces changes in arterial pressure. In keeping with this latter observation are the findings of a previous study from our laboratory4 showing that the results obtained by evaluating the effects of LBNP on the forearm vascular resistance are comparable with those obtained by assessing the changes in TPR. Furthermore, Grassi et al.26 reported that the cardiopulmonary receptor reflex can produce a marked and sustained change in plasma NE. Therefore, we also measured this parameter to further characterize the baroreceptor reflex responses.

The hemodynamic results obtained in normal subjects in control conditions are consistent with those reported by other authors who used the LBNP technique. The reflex vascular response to the two levels of LBNP observed in our experiment is comparable to that described by Leimbach et al., Ferguson et al.,9 and Mark et al.15 Furthermore, in accordance with the reports of Egan et al.6 and Grassi et al.,26 we noted a significant rise in plasma NE concentration with the lower level of LBNP and a further increase with the higher level of LBNP. Mark13 suggested that the reflex response induced by LBNP results largely from a reduction in the tonic inhibitory influence of cardiopulmonary and arterial baroreceptors on vasomotor centers. In particular, low levels of LBNP decrease central venous pressure and LVFP, but have no significant effect on MAP, whereas higher levels of LBNP also decrease arterial pressure. Thus, we believe that the lower levels of LBNP induce a selective unloading of

**Figure 1.** Individual arginine vasopressin (AVP) plasma levels during control conditions (CC) and during −10 and −40 mm Hg lower body negative pressure before (A) and after (B) propranolol administration in normotensive subjects.
cardiopulmonary baroreceptors, whereas higher levels of LBNP inhibit arterial and cardiopulmonary baroreceptors. Therefore, the significant increase in plasma AVP levels observed during -10 mm Hg LBNP suggests that low pressure receptors exert a tonic inhibition of AVP release and that their selective unloading induces a reflex increase in AVP plasma levels in normotensive subjects. This finding, which confirms the observation by Egan et al., appears to contrast that of other reports by Goldsmith et al. and Leimbach et al., who failed to observe any significant change in AVP concentration after selective inhibition of cardiac baroreceptors. Our data do not allow any conclusive explanation for this discrepancy. However, the small change in the mean value of plasma AVP level induced by the selective inhibition of cardiopulmonary receptors in our normotensive subjects was comparable to the absolute change in AVP induced by -15 mm Hg in the study by Leimbach et al. In our subjects the individual variation was markedly smaller than that reported by those authors, thus accounting for the different results. In this regard, Preibisz et al. suggested that part of the variability in plasma AVP concentration may be due to the routine methods of centrifugation, which do not completely separate platelets. This possibility also seems to be supported by the observations of Goldsmith et al. and Leimbach et al., who found mean AVP plasma concentrations higher than those reported by Preibisz et al. and those found in the present study. In addition, the mean value of AVP plasma levels found in our hypertensive subjects was comparable to those reported by Preibisz et al.

The finding that in hypertensive subjects -10 mm Hg LBNP, despite a reduction in RAP and LVFP and a reflex vascular response comparable to that evoked in normotensive subjects, failed to induce the changes in AVP, PRA, and NE plasma concentration observed in normal subjects suggests that hypertension-induced LVH impairs the inhibitory influence of cardiopulmonary receptors on sympathetic activity and AVP release. In fact, the inhibition of these baroreceptors caused by -10 mm Hg LBNP failed to induce any rise in PRA, NE, and AVP. On the contrary, arterial baroreceptor control of these functions seems to be better preserved in hypertensive subjects, since the higher level of LBNP induced an increase in AVP, NE, and PRA both in normotensive subjects and in hypertensive subjects with LVH.

The results obtained with propranolol administration seem to lend further support to this hypothesis. In fact, our data show that propranolol does not modify the reflex response to phenylephrine or to an increase in neck tissue pressure and thus seem to rule out the possibility that propranolol blunts the response to LBNP through a reduction of arterial baroreceptor responsiveness. In addition, pretreatment with this drug reduces the firing of ventricular C-fiber vagal afferents in cats and blunts the responsiveness of sympathetic cardiovascular afferents. However, these latter afferents mediate mainly excitatory influences and thereby promote an inhibitory response rather than the excitatory response observed in our subjects during LBNP. Previous reports in humans seem to corroborate the hypothesis that propranolol administration reduces the reflex vascular response to LBNP by reducing the sensitivity of cardiopulmonary receptors with vagal afferents. In these latter studies the reduced vascular response to LBNP after propranolol could not be ascribed to a direct effect of the drug on the vascular wall or to any action on the central nervous system. The effects of propranolol on the NE response to LBNP observed in the present study also corroborate this hypothesis. In fact, the reduction in TPR response to LBNP induced by propranolol pretreatment in normal subjects may be due to the reduction in the reflex increase in plasma NE induced by LBNP. Therefore, the finding that normal subjects exhibited a significant increase in plasma AVP concentration after propranolol administration seems to be due to the propranolol-induced removal of the inhibitory influence on AVP release mediated through the firing of cardiopulmonary receptors. The observation that the increase in plasma AVP levels induced by the inhibition of cardiopulmonary receptors in normotensive subjects does not occur after propranolol administration confirms this hypothesis.
We conclude from these data that in humans cardiopulmonary receptors contribute to the regulation of AVP release. In fact, in normotensive subjects the inhibition of these receptors induces an increase in TPR, PRA, and NE and a small but significant rise in plasma AVP. After propranolol administration, the impairment of these receptors, suggested by the lack of change in NE after a 10 mm Hg LBNP, is accompanied by the abolition of the rise in AVP induced by the lower level of LBNP. Furthermore, our results confirm that cardiopulmonary receptor function is impaired in hypertensive subjects with LVH. In these subjects the vascular response induced by the selective unloading of cardiopulmonary receptors seems to be independent of the changes in the release of PRA and NE, although we cannot rule out the possibility that measurement of venous plasma NE may not be sensitive enough to reflect a low degree of sympathetic neural activation. Thus, the observation that the selective unloading of cardiopulmonary receptors fails to increase plasma AVP in hypertensive subjects with LVH lends further support to the conclusion that these receptors participate in reflex control of AVP release.

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