Cardiopulmonary Receptor Modulation of Plasma Renin Activity in Normotensive and Hypertensive Subjects

GUIDO GRASSI, CRISTINA GIANNATTASIO, ANTONIO SAINO, ETTORE SABADINI, ANGELA CAPOZI, LORENA SAMPIERI, CESARE CUSPIDI, AND GIUSEPPE MANCIA

SUMMARY Cardiopulmonary receptors modulate renin release in several animal species. However, their involvement in reflex control of this humoral substance in humans is controversial. Furthermore, no information is available on the alteration of this control in hypertension. We studied the modulation of plasma renin activity (radioimmunoassay) in 12 normotensive subjects and in 12 age-matched subjects with untreated hypertension of mild or moderate degree. Cardiopulmonary receptors were stimulated by increasing central venous pressure (right atrial catheter) and cardiac volume (echocardiographic measurement) through passive leg raising and deactivated by reducing central venous pressure and cardiac volume through lower body negative pressure. The stimuli were maintained for 20 to 30 minutes, and their degree was set to avoid changes in blood pressure (indirect or direct measurements) and heart rate, thus avoiding involvement of arterial baroreceptors. In normotensive subjects, deactivation of cardiopulmonary receptors induced a progressive rise in plasma renin activity and stimulation of cardiopulmonary receptors induced a progressive fall. The reflex gain (ratio between plasma renin activity and central venous pressure or cardiac volume changes) was similar for deactivation and stimulation. During cardiopulmonary receptor deactivation, the gain corresponded to that obtained by dividing the increase in plasma renin by the reduction in central venous pressure induced by tilting. Cardiopulmonary receptor deactivation and stimulation also induced clear-cut changes in plasma renin activity in hypertensive subjects, but the percent magnitude of the reflex plasma renin activity excursion was less than that in normotensive subjects. These observations indicate that cardiopulmonary receptors modulate plasma renin activity in humans. This modulation is presumably responsible for the rise in plasma renin activity occurring during changes in posture. The cardiopulmonary receptor modulation of renin remains operative, although with a reduced effectiveness, in mild or moderate essential hypertension.

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KEY WORDS • cardiopulmonary receptors • renin-angiotensin system • hypertension • tilting • baroreceptor reflexes • peripheral circulation

ALTHOUGH well established in several animal species, 1-5 the ability of cardiopulmonary volume receptors to modulate renin release in humans is controversial. This modulation has been advocated by Julius and colleagues, 6-7 who have observed that the reduction in venous return induced by compression of the lower limbs in normotensive subjects is followed by a neurogenic rise in plasma renin activity (PRA). However, Mark et al. 8 have reported that a reduction in venous return induced by application of negative pressure to the lower body in normotensive subjects causes a neurogenic rise in PRA only when associated with a blood pressure fall. They concluded that cardiopulmonary receptors can modulate renin release only if arterial baroreceptors are concomitantly involved. This conclusion has not been dismissed by the recent finding that PRA is reduced when venous return is increased by head-down tilting, 9 because under this condition carotid transmural pressure...
and carotid baroreceptor activity are increased by displacement of the carotid sinuses below the heart.

The present study was undertaken with three aims in mind: 1) to reexamine the ability of cardiopulmonary receptors to increase and reduce PRA by more stringently verifying, through indirect or direct monitoring, the absence of any concomitant blood pressure alteration; 2) to compare the cardiopulmonary receptor modulation of renin in normotensive and essential hypertensive patients; and 3) to determine whether this modulation plays an important role in the marked rise in PRA that occurs during assumption of the upright posture.10, 11

**Subjects and Methods**

Our study was performed on 24 subjects of both sexes (18 male, 6 female subjects) whose age ranged from 16 to 39 years (mean age, 26.0 ± 1.2 [SEM] years). Twelve subjects were normotensive (mean age, 24.9 ± 1.6 years) and had no medical history of cardiovascular disease, while the remaining 12 subjects (mean age, 27.0 ± 1.7 years) had essential hypertension of a mild or moderate degree; their diastolic blood pressure was above 95 mm Hg and below 105 mm Hg at two office cuff measurements made at an interval of 30 days. The hypertensive subjects had no evidence of major target-organ damage based on history and clinical examination performed before the study (electrocardiogram, chest roentgenogram, funduscoppy, plasma creatinine level, creatinine clearance, urinalysis). Echocardiographic study showed modest left ventricular hypertrophy (septal thickness, 14 mm; posterior wall thickness, 11 mm) in only one subject.

The subjects received no antihypertensive treatment during the 3 weeks before study. They were placed on a standard diet containing 150 mmol sodium and 60 mmol potassium per day beginning 4 to 5 days before study. All gave their consent to the entire procedure and avoid a reduction in blood pressure and an engagement of arterial baroreceptor reflexes.

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**Cardiovascular and Plasma Renin Measurements**

Cardiovascular measurements consisted of arterial blood pressure, heart rate, central venous pressure, end-diastolic left ventricular diameter, forearm blood flow, and forearm vascular resistance. Arterial blood pressure was measured by a mercury sphygmomanometer applied to the right or the left arm (18 subjects) or by a catheter introduced percutaneously into a radial artery and connected with a transducer (Model P23ID, Gould Statham, Hato Rey, Puerto Rico) positioned at the level of the right atrium (6 subjects). Heart rate was measured beat-to-beat by a cardiometer triggered by the R wave of an electrocardiographic lead. Central venous pressure was measured by a catheter placed in the right atrium from an antecubital vein of the arm employed for blood pressure measurements and connected with a transducer (P23ID, Gould Statham). End-diastolic left ventricular diameter was measured by two-dimensional echocardiography from the septal leading edge to the posterior wall leading edge, at the peak of the R wave of the electrocardiogram. Thus, alterations in the stimulus to cardiopulmonary receptors could be estimated by volume as well as pressure changes in the heart.

Forearm blood flow was measured by venous occlusion plethysmography (Model EC2, Hokanson, Issaquah, WA, USA),12 using a mercury-in-Silastic strain-gauge plethysmograph applied around the forearm contralateral to the arm used for blood pressure measurements. The strain-gauge was placed approximately 4 to 5 cm below the antecubital crease, and the measurement was performed at constant room temperature (23–24°C) while circulation to the hand was arrested by application of suprasystolic pressure to a cuff applied to the wrist. Forearm vascular resistance was calculated from the ratio between mean arterial pressure (diastolic blood pressure plus one-third of pulse pressure) and forearm blood flow. PRA was measured in systemic plasma by radioimmunoassay,13 using blood samples (6 ml) withdrawn either from the right atrial catheter (16 subjects) or from a small cannula placed in an antecubital vein of the arm from which blood pressure was monitored (8 subjects). Blood samples were collected in tubes containing EDTA and processed at room temperature.

**Maneuvers for Deactivating and Stimulating Cardiopulmonary Volume Receptors**

Cardiopulmonary receptors were deactivated by reducing venous return and central venous pressure through application of negative pressure to the lower body.14 The subjects were enclosed in the supine position in a Plexiglas box, which was sealed at the level of the anterosuperior iliac crests. The pressure within the box was reduced below the atmospheric pressure by a commercial vacuum cleaner, and the stimulus was maintained for 20 or 30 minutes. The applied negative pressure was kept around 15 mm Hg (mean, 14.8 ± 1.6 mm Hg) to only moderately affect venous return and avoid a reduction in blood pressure and an engagement of arterial baroreceptor reflexes.

Cardiopulmonary receptors were stimulated by increasing venous return and central venous pressure through passive elevation of the legs and the lower part of the pelvis of the supine subjects to between 55 and 60 degrees.14, 15 This stimulus was maintained for 20 or 30 minutes.

The ability of cardiopulmonary deactivation and stimulation to evoke reflex responses also was assessed by measurement of vasomotor changes in a major target for the cardiopulmonary receptor influence (i.e., forearm circulation).14, 16

**Head-up Tilting**

Head-up tilting was obtained by means of an electrically operated table that passively moved the subjects from the supine to the upright position (60–65 degrees) in 30 seconds. Tilt was maintained for 20 minutes. A vasovagal reaction occurred in three subjects and prevented us from using their responses to tilt in the data analysis.
Protocol and Data Analysis

Between 1 and 2 days before the study, each subject was brought to the laboratory to be familiarized with the various maneuvers that had to be performed. The study proper was conducted in the morning. In half of the subjects the sequence was as follows: 1) the subjects were put in the supine position and fitted with the lower body suction device; 2) the catheters were inserted, and the echocardiographic, blood pressure, and blood flow measuring devices were set ready; 3) after an interval of 30 minutes, lower body negative pressure was applied; 4) the lower body suction device was removed, and after a further 30-minute interval, the leg-raising maneuver was performed; 5) after another 30 minutes head-up tilting was performed. In the remaining subjects the maneuvers applied were the same, except that head-up tilting and leg raising preceded lower body suction.

Blood pressure, heart rate, central venous pressure, end-diastolic ventricular diameter, forearm blood flow, forearm vascular resistance, and PRA were measured before and at the 5th, 10th, 20th, and 30th minute of the various maneuvers employed in the study. The forearm blood flow measurements were derived from the average of three consecutive values. The blood samples for the PRA measurements were withdrawn within 30 seconds after the hemodynamic measurements had been completed.

The results from all subjects are expressed as means ± SEM. The statistical significance of the differences in the means was assessed by two-way analysis of variance. A "p" value below 0.05 was considered statistically significant.

Results

Effects of Lower Body Negative Pressure and Passive Leg Raising

As shown in Figure 1, the 20-minute application of negative pressure to the lower body caused no alteration in systolic blood pressure, diastolic blood pressure, and heart rate, even when blood pressure was measured intra-arterially (Figure 2; see Table 1). During this maneuver there were sustained reductions in central venous pressure and left ventricular diastolic diameter and an early, marked and sustained reduction in forearm blood flow and increase in forearm vascular resistance. These changes were accompanied by a rise in PRA that became progressively larger from the 5th to the 20th minute.

The effects of 20 minutes of passive leg raising in the same 24 subjects are illustrated in Figure 3. This
maneuver caused no change in systolic blood pressure, diastolic blood pressure, and heart rate (see Figure 1 and Table 1), a sustained increase in central venous pressure and left ventricular diastolic diameter, and an early, marked and sustained increase in forearm blood flow and reduction in forearm vascular resistance. There was a slight but significant fall in PRA throughout the stimulus application that also had a tendency to increase in magnitude from the 5th to the 20th minute.

In 12 subjects lower body negative pressure and passive leg raising were prolonged beyond 20 minutes because of the time-related progression of the changes in PRA. As shown in Table 2, prolongation of lower body negative pressure caused an increase in central venous pressure, left ventricular end-diastolic diameter, systolic and diastolic blood pressure, heart rate, forearm blood flow, and a reduction in forearm vascular resistance.

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Table 2. Hemodynamic and PRA Changes Induced by 30 Minutes of Lower Body Negative Pressure and Passive Leg Raising in Twelve Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lower body negative pressure</th>
<th>Passive leg raising</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20th min</td>
<td>30th min</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>-2.3 ± 0.3</td>
<td>-2.3 ± 0.4</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>-1.8 ± 2.1</td>
<td>-3.1 ± 2.1</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>+0.1 ± 1.1</td>
<td>-1.4 ± 1.5</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>+1.2 ± 1.0</td>
<td>+3.2 ± 1.2</td>
</tr>
<tr>
<td>FBF (ml/min/100 g)</td>
<td>-1.9 ± 0.3</td>
<td>-1.8 ± 0.3</td>
</tr>
<tr>
<td>FVR (units)</td>
<td>+11.2 ± 1.7</td>
<td>+10.2 ± 2.0</td>
</tr>
<tr>
<td>PRA (ng Ang I/ml/hr)</td>
<td>+0.6 ± 0.1</td>
<td>+0.7 ± 0.1</td>
</tr>
</tbody>
</table>

Data are mean (± SE) changes from control values at the 20th and 30th minute of either maneuver. The changes were not statistically significant.

CVP = central venous pressure; FBF = forearm blood flow; FVR = forearm vascular resistance. See Table 1 for key to other abbreviations.

Comparison of Lower Body Negative Pressure and Passive Leg Raising in Normotensive and Hypertensive Subjects

Baseline systolic blood pressure, diastolic blood pressure, forearm vascular resistance, and PRA were higher in the hypertensive than in the normotensive subjects (Table 3). The 20-minute reduction and increase in central venous pressure and left diastolic diameter induced by lower body negative pressure and passive leg raising (Figure 4), and the resulting alterations in forearm vascular resistance and PRA, were not significantly different in the hypertensive as compared with the normotensive subjects, although there was a tendency for most changes in the hypertensive group to be smaller. This effect is also shown in Figure 5, which refers to the overall excursions of these four variables obtained by the algebraic summation of the

Table 3. Baseline Values of the Normotensive and Hypertensive Subjects Included in the Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive subjects</th>
<th>Hypertensive subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVP (mm Hg)</td>
<td>1.5 ± 0.8</td>
<td>0.7 ± 0.7</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>48.8 ± 1.6</td>
<td>52.3 ± 1.4</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>123.1 ± 2.3</td>
<td>139.1 ± 1.9*</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>78.5 ± 1.9</td>
<td>93.6 ± 1.6*</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>76.0 ± 3.0</td>
<td>74.8 ± 3.1</td>
</tr>
<tr>
<td>FBF (ml/min/100 g)</td>
<td>6.2 ± 0.5</td>
<td>5.3 ± 0.5</td>
</tr>
<tr>
<td>FVR (units)</td>
<td>17.0 ± 1.0</td>
<td>25.0 ± 2.4*</td>
</tr>
<tr>
<td>PRA (ng Ang I/ml/hr)</td>
<td>1.7 ± 0.2</td>
<td>1.9 ± 0.2*</td>
</tr>
</tbody>
</table>

Data are means ± SE from 12 normotensive and 12 hypertensive (n = 8 and 8 for CVP and LVEDD) subjects and represent the average of the values before lower body negative pressure and passive leg raising. LVEDD = left ventricular end-diastolic diameter. See Tables 1 and 2 for key to other abbreviations.

*p < 0.001, compared with normotensive values.
peak changes induced by the two maneuvers. Because of the differences in the baseline values (see Table 3), the normalized excursions of forearm vascular resistance and PRA were significantly less in the hypertensive than in the normotensive subjects.

Head-up Tilting

Head-up tilting caused small changes in systolic and diastolic blood pressure, a marked tachycardia, and a sustained reduction in central venous pressure and left ventricular diastolic diameter. These effects were associated with a significant increase in PRA that progressed in size from the 5th to the 20th minute (Figure 6). The increase was not significantly different in normotensive (n = 11) and hypertensive (n = 10) subjects (increase in PRA at the 20th minute, 0.87 ± 0.2 and 1.11 ± 0.3 ng angiotensin I/ml/hr, respectively).

The alterations in central venous pressure, left ventricular diastolic diameter, and PRA induced by tilting are compared with those induced by lower body negative pressure in Figure 7. Tilting reduced central venous pressure to an extent similar to that observed with lower body negative pressure; it reduced left ventricular diastolic diameter to a greater extent than did lower body negative pressure; and it increased PRA to an extent similar to that observed with lower body negative pressure. The ratio between the increase in PRA and the reduction in central venous pressure was not significantly different in the two conditions (−0.33 ± 0.05 and −0.29 ± 0.08 ng angiotensin I/ml/hr/mm Hg). This was also the case for the increase in PRA over the reduction in left ventricular diameter (−0.37 ± 0.05 and −0.31 ± 0.07 ng angiotensin I/ml/hr/mm).

Discussion

In our subjects a reduction in central venous pressure and left ventricular diameter, which caused no change in blood pressure and heart rate, was accompanied by an increase in PRA. Conversely, an increase in central venous pressure and left ventricular diameter, which caused no change in blood pressure and heart rate, was accompanied by a reduction in PRA. These observations support the conclusion of Julius and colleagues and our preliminary data7 that cardiopulmonary receptor deactivation in humans can reflexly increase PRA. Our results add to this conclusion, however, the demonstration that an increase in cardiopulmonary receptor activity has an opposite effect; there-

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**Figure 5.** Changes in central venous pressure (CVP), left ventricular end-diastolic diameter (LVEDD), forearm vascular resistance (FVR), and PRA induced by lower body negative pressure and passive leg raising in the normotensive and hypertensive subjects shown in Figure 4. Data are shown as the algebraic sum of the peak changes induced by the two maneuvers.

**Figure 6.** Effects of 20 minutes of head-up tilting on central venous pressure (CVP), left ventricular end-diastolic diameter (LVEDD), systolic (S) and diastolic (D) blood pressure (BP), heart rate (HR), and PRA. Values are means ± SE from 21 subjects (n = 16 for CVP and LVEDD). C = control.
FIGURE 7. Time course of the changes in central venous pressure (CVP), left ventricular end-diastolic diameter (LVEDD), and PRA induced by lower body negative pressure and head-up tilting. Data are means ± SE.

The second conclusion (i.e., that cardiopulmonary receptor modulation of renin is involved in daily life) is supported by the observations that 1) the increase in renin induced by lower body negative pressure was not significantly less than that observed in the same subjects during tilting and 2) the ratio between this increase and the reduction in central venous pressure or left diastolic ventricular volume was also similar in the two conditions. Because cardiac diastolic volume has been shown to be the major determinant of reflex influences originating from cardiopulmonary receptors, our data suggest that the changes in renin during tilting were due to cardiopulmonary receptor deactivation. Thus, the cardiopulmonary reflex has a primary importance in the neurogenic modification of PRA associated with postural changes. It also suggests that during tilting the baroreceptor deactivation brought about by the displacement of the carotid sinuses above the heart has little additional effect on renin secretion. This is apparently the case also for the vestibular stimulus elicited by tilting.

Finally, we should discuss the alterations of the cardiopulmonary reflex observed in the hypertensive subjects. The PRA responses to cardiopulmonary receptor stimulation and deactivation were slightly less in the hypertensive than in the normotenive subjects when expressed in absolute values, but the difference between the two groups became more evident when normalized values were used instead. This also was the case for the vasomotor responses in the forearm. These observations may be interpreted as an indication that in uncomplicated chronic blood pressure elevations the cardiopulmonary reflex retains a major part of its ability to modulate vascular resistance and renin secretion (and therefore to control blood pressure and volume), but with a somewhat reduced efficiency compared with normotenive persons. In this regard it is interesting that modulation of the forearm circulation by cardiopulmonary receptors has been found to be increased in borderline hypertension and markedly impaired in the presence of cardiac hypertrophy with or without hypertension.

We speculate that the cardiopulmonary reflex may be preserved or even enhanced in the initial stage of hypertension, but that it undergoes progressive impairment as the structural changes of hypertension develop.

Studies in animals have shown that the cardiopulmonary receptor population is characterized by pronounced differences in the threshold of activation, firing rate, and patterns of cardiovascular influence. This raises the problem of the identification of the cardiopulmonary receptors responsible for the modulation of renin. However, no technique presently in use permits us to examine cardiopulmonary receptor heterogeneity in humans, which means that this problem can only be a matter for speculation. In cats and dogs reflex inhibition of renal sympathetic influences depends on nonmyelinated vagal fibers originating in both the heart and lungs. It is therefore possible that receptors widely distributed throughout the cardiopulmonary region are responsible for the modulation of renin secretion in humans.
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