Renin-Angiotensin-Aldosterone System in Normal and Hypertensive Pregnancy
Response to Postural Stimuli

Virginia G. Fagundes, Cristiane C. Lamas, and Emilio A. Francischetti

Most studies that have attempted to distinguish pregnancy-induced hypertension from chronic hypertension in pregnancy include arbitrary clinical definitions and morphological reports based on renal biopsy. To evaluate whether these conditions have different responses to stimuli to the renin-angiotensin-aldosterone system, we studied four normal nonpregnant women, eight normal pregnant women, 10 women with pregnancy-induced hypertension, and 14 with chronic hypertension in pregnancy, in the third trimester of pregnancy, after they had sequentially adopted the supine, the left lateral recumbent, and the orthostatic positions for 90 minutes each. Postural maneuvers did not significantly change mean arterial pressure in pregnancy-induced hypertensive or in normal pregnant women, although in chronic hypertensive women, a significant reduction in this parameter was observed in left lateral recumbency. The renin-angiotensin-aldosterone system was significantly less activated with women in the supine position in pregnancy-induced hypertensive and chronic hypertensive women; however, as opposed to pregnancy-induced hypertensive women, those with chronic hypertension resumed their humoral response to upright posture, which was accompanied by a significant reduction in sodium excretion. The parallelism between plasma renin activity and aldosterone levels, absent in normal pregnancy, returned in pregnancy-induced hypertensive and chronic hypertensive women in the erect posture (r=0.73, p<0.01; r=0.68, p<0.01, respectively). These data suggest that the adoption of the left lateral recumbent position in pregnancy reduces mean arterial pressure only in chronic hypertensive women. Moreover, in chronic hypertension, the upright position provoked a significant response of the renin-angiotensin-aldosterone system. This effect was not observed in women with pregnancy-induced hypertension.

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Plasma renin activity (PRA), both active and inactive, and angiotensinogen, angiotensin II (Ang II), and aldosterone levels are all increased in normal pregnancy. In one longitudinal study of 20 primigravid women from 10 weeks gestation, Ang II concentration rose progressively and reached a maximum in midgestation. The renin-angiotensin system is thus among the earliest hormone systems alerted to the state of pregnancy. In normal pregnancy, a marked reduction in pressor responsiveness to Ang II has also been demonstrated. This expressive resistance to the pressor effects of Ang II seems to originate very early in both human and experimental models of gestation.

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creasing rises in PRA proportional to the increasing severity of the disease, although the absolute values of PRA remain lower when compared with normal individuals.\(^{13}\)

The purpose of the present study was to evaluate in hypertensive states of pregnancy (PIH and chronic hypertension in pregnancy [CHP]) the response of the components of the renin-angiotensin-aldosterone system and of natriuresis to postural changes in the last trimester of gestation and to compare these data with those obtained from normal nonpregnant women and normal pregnant women submitted to the same posture maneuvers and in the same gestational age.

**Methods**

**Patients**

Women with PIH and CHP were previously diagnosed and followed at the Hypertension, Metabolism and Nutrition Section of the Department of Internal Medicine, Rio de Janeiro State University. The PIH group was composed of 10 pregnant women, six white and four nonwhite, 14–30 years of age, seven of them primigravid. The remaining three multiparous of this group had been pregnant once before, fulfilling in this pregnancy the criteria for PIH, which included the normalization of blood pressure after being discharged from the hospital. The CHP group had 14 women, four white and 10 nonwhite, 20–41 years old. All pregnant women were in the third trimester of pregnancy. In our research unit, PIH has been defined as the occurrence of a systemic blood pressure of 140/90 mm Hg or more, on at least two separate determinations, renal function studies, and cardiovascular evaluation. Antihypertensive therapy was interrupted 72 hours before blood collection. Informed consent was obtained in keeping with the guidelines of the State University of Rio de Janeiro committee on human investigation.

**Control Subjects**

Control subjects consisted of eight normal pregnant women, 21–33 years old, seven white and one nonwhite, and four normal nonpregnant volunteers from the University Hospital Community, three white and one nonwhite, 21–33 years old. The control pregnant subjects were all primigravid.

**Study Protocol**

The patients and control individuals fasted overnight, and at 8 AM an antecubital vein of the left or right arm was catheterized for blood sampling. The study protocol lasted 270 minutes, divided into three intervals of 90 minutes during which the patients adopted, sequentially, the supine (SUP), left lateral recumbent (LLR), and upright (orthostatic) (ORT) positions. At the end of each 90-minute period, 20 ml of blood was drawn in a plastic syringe. This volume was immediately processed to obtain plasma and serum, which were frozen at -30°C for subsequent assay. Urine samples represented the volumes of the three different 90-minute intervals. Blood pressure levels were the mean of three consecutive measurements obtained in the adopted position before blood sampling.

Systemic blood pressure was measured with an aneroid sphygmomanometer and according to the disappearance of Korotkoff phase V sound. The parameter was expressed as mean arterial pressure (MAP) calculated by the formula: MAP equals diastolic blood pressure plus one third of the difference between systolic and diastolic blood pressures.

**Laboratory Techniques**

Sodium concentration was determined by flame photometry (model 400, Corning Glass Inc., Corning, N.Y.). PRA was measured by radioimmunoassay as described by Haber et al\(^ {19}\) and modified by Sealey and Laragh\(^ {20}\), with the results expressed in nanograms of angiotensin I generated per milliliter of plasma per hour (ng/ml/hr). Serum aldosterone concentration was determined by radioimmunoassay according to the method of Varsano-Ahanon and Ulick\(^ {21}\) modified by Manlimos and Abraham\(^ {22}\), and the results are expressed as picograms per milliliter of plasma (pg/ml).

**Statistics**

Results are expressed as mean±SEM. Student's t-test determined the significance of differences between normotensive controls and hypertensive patients. Correlations were performed by linear least-squares regression analysis. A value of \(p<0.05\) was accepted as significant.

**Results**

**Blood Pressure**

In the PIH and CHP groups, MAP was significantly higher than in normal pregnant and normal nonpregnant women (\(p<0.01\)) in any of the adopted positions (Table 1). Postural maneuvers such as the SUP, LLR, and ORT positions did not significantly change MAP in normal women, in the PIH group, and in normal nonpregnant women. However, in the CHP group, a significant reduction of MAP was observed in the LLR as compared with the SUP position (102.9±3 versus 109.1±3 mm Hg, respectively, \(p<0.05\)) and as compared with the ORT position (110.7±2 mm Hg, \(p<0.05\)).
TABLE 1. Physiological Responses to Different Postural Stimuli in Study Groups

<table>
<thead>
<tr>
<th>Variables and groups</th>
<th>Supine</th>
<th>Left lateral recumbent</th>
<th>Orthostatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNP</td>
<td>83.8±2.9</td>
<td>83.8±2.9</td>
<td>79.0±5.0</td>
</tr>
<tr>
<td>NP</td>
<td>84.1±3.1</td>
<td>82.6±2.7</td>
<td>79.4±3.5</td>
</tr>
<tr>
<td>PIH</td>
<td>110.8±5.0</td>
<td>106.0±5.2</td>
<td>106.1±4.6</td>
</tr>
<tr>
<td>CHP</td>
<td>109.1±3.3</td>
<td>102.9±3.0*</td>
<td>110.7±2.1</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNP</td>
<td>1.0±0.4</td>
<td>0.5±0.1</td>
<td>3.4±1.0</td>
</tr>
<tr>
<td>NP</td>
<td>21.6±6.4†</td>
<td>14.7±4.5*</td>
<td>20.7±6.7</td>
</tr>
<tr>
<td>PIH</td>
<td>6.9±1.1</td>
<td>6.1±0.8</td>
<td>8.8±2.2</td>
</tr>
<tr>
<td>CHP</td>
<td>6.8±1.0</td>
<td>7.0±1.2</td>
<td>11.0±2.2‡</td>
</tr>
<tr>
<td>Aldosterone level (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNP</td>
<td>84.3±18.5</td>
<td>84.0±12.4</td>
<td>106.8±12.6</td>
</tr>
<tr>
<td>NP</td>
<td>303.6±52.4</td>
<td>206.4±29.0*</td>
<td>401.0±59.4</td>
</tr>
<tr>
<td>PIH</td>
<td>211.3±34.4</td>
<td>160.5±19.6</td>
<td>202.1±35.1</td>
</tr>
<tr>
<td>CHP</td>
<td>231.7±40.4</td>
<td>173.7±23.9</td>
<td>343.7±60.0</td>
</tr>
<tr>
<td>Urinary sodium excretion (μmol/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNP</td>
<td>400.8±58.6‡</td>
<td>421.2±97.5</td>
<td>117.4±32.5</td>
</tr>
<tr>
<td>NP</td>
<td>100.7±12.7</td>
<td>290.7±37.7*</td>
<td>145.4±24.3</td>
</tr>
<tr>
<td>PIH</td>
<td>118.6±33.1</td>
<td>206.1±41.3*</td>
<td>81.1±16.9</td>
</tr>
<tr>
<td>CHP</td>
<td>141.1±29.0</td>
<td>184.0±25.8</td>
<td>62.0±10.9‡</td>
</tr>
</tbody>
</table>

Values are mean±SEM. NNP, normal nonpregnant; NP, normal pregnant; PIH, pregnancy-induced hypertension; CHP, chronic hypertensive pregnant.

*/?<0.05 compared with supine and orthostatic.
†/p<0.01 compared with PIH and CHP.
‡p<0.05 compared with supine and left lateral recumbent.
§p<0.05 compared with NP, PIH, and CHP.

Plasma Renin Activity

In normal pregnancy and in the PIH and CHP groups, PRA values were significantly higher as compared with normal nonpregnant women (p<0.05), except for the PIH group in the ORT position (Table 1). However, in normal pregnancy, PRA values were higher than in the PIH and CHP groups, although this was statistically significant only in the SUP position (p<0.01). Concerning postural changes, the PIH group showed no significant differences in PRA between the SUP, LLR, and ORT positions. In normal pregnancy, PRA levels in the LLR position were significantly lower than in the SUP and ORT positions (p<0.05). Different from the PIH group, patients with CHP reassumed their response to postural stimuli (11.0±2 versus 6.8±1 ng/ml/hr and versus 7.0±1 ng/ml/hr, ORT versus SUP and ORT versus LLR, respectively, p<0.05).

Serum Aldosterone Concentration

In the PIH group, serum aldosterone levels in the SUP and LLR positions were lower than in normal pregnant women, although the difference was statistically significant only in the ORT position (202.1±35.1 versus 401.0±59.4 pg/ml, PIH versus normal pregnant, p<0.05). In normal pregnancy, the LLR position elicited the lowest circulating levels of aldosterone, as compared with the SUP and ORT positions (206.4±29 versus 303.6±52.4 and versus 401.0±59.4 pg/ml, respectively, p<0.05). In the CHP group, there was a marked increase in aldosterone levels in the ORT position, but similar to normal nonpregnant volunteers, this difference was not significant.

Urinary Sodium Excretion

In all pregnant women, urinary sodium excretion (UNV) was significantly reduced in the SUP position when compared with normal nonpregnant women (p<0.01). In normal pregnancy and in the PIH group, UNV was higher in the LLR position in comparison to the SUP and ORT positions (p<0.01). In the CHP group, UNV in the LLR and SUP positions was significantly higher than that obtained in the ORT position (184.0±25.8 and 141.1±29 versus 62.0±10.9 μmol/min, respectively, p<0.01). The mean total UNV in the 270-minute interval was 939.3 μmol/min in normal nonpregnant women, 536.8 μmol/min in normal pregnant women, 405.8 μmol/min in the PIH group, and 387.1 μmol/min in the CHP group.

Correlation Study

In normal pregnancy, no significant correlation was observed between PRA and serum aldosterone level in any of the positions studied. However, in the PIH and CHP groups, when patients adopted the ORT position, a positive and highly significant correlation between PRA and serum aldosterone level was observed (r=0.73 and r=0.68, respectively, p<0.01).
These data are in accord with the literature and are the result of the hemodynamic changes possibly other hand, the LLR position provoked a substantial increase of natriuresis in all pregnant women studied. However, different from the PIH group, MAP was significantly reduced when CHP women adopted the LLR position. This observation suggests that postural changes have a greater hemodynamic effect in CHP than in PIH patients and may be clinically useful in distinguishing both conditions.

In normal pregnancy, the renin-angiotensin-aldosterone system was remarkably activated, and the hemodynamic changes induced by postural maneuvers caused quantitative alterations in PRA and aldosteronemia. Different factors, such as enhanced hepatic synthesis of angiotensinogen induced by estrogenic action,23 the secretion of active renin or prorenin by the uteroplacental complex,24,25 and the reduced vascular response to Ang II,2 have been considered as possible explanations for the rise in PRA. Although the factors controlling Ang II sensitivity and receptor affinity are under debate, sodium and calcium concentration in the vessel wall and a greater synthesis of kinins and prostaglandins26–28 may be important factors.

It is well known that in PIH the renin-angiotensin system is less activated than in normal pregnancy.3,12–14 Besides confirming this aspect, our data also demonstrate that the different postural stimuli did not evoke distinct responses in PRA and serum aldosterone levels. The renin-angiotensin-aldosterone system was also less activated in chronic hypertensive pregnant women, confirming previous results.10 However, in the PIH and CHP groups, a significant correlation between PRA and aldosterone levels was observed, which suggests that in normal pregnancy, other factors besides Ang II, such as progesterone and sodium or potassium homeostasis, control the synthesis and secretion of aldosterone.29 The returned parallelism in the hypertensive states of human pregnancy is not explained in light of our present knowledge.

U\textsubscript{Na}V levels were significantly reduced when all pregnant women adopted the SUP position. On the other hand, the LLR position provoked a substantial increase of natriuresis in all pregnant women studied. These data are in accord with the literature and are the result of the hemodynamic changes possibly determined by the different postural maneuvers of the study protocol.30 In normal pregnancy, there is a significant sodium retention on the order of 500–900 meq.31 In pregnancy hypertensive states, sodium retention is even more pronounced.32 Our PIH and CHP women excreted 25% and 28% less sodium, respectively, than normal pregnant women. Sodium retention associated with a hemodynamic state of blood volume contraction and high vascular resistance suggests sodium redistribution to the interstitial space, including the walls of arterioles.33

The contracted plasma volume observed in PIH should physiologically stimulate the renin-angiotensin system and vasopressin secretion. However, this does not happen and is one of the enigmas of PIH.6 Endothelin, the potent peptide released from endothelial cells, may have a central role in this enigma, as it acts as a potent vasoconstrictor locally, interacting with vascular smooth muscle cells, and as a circulating hormone.34–36 Evidence also shows that endothelin stimulates aldosterone biosynthesis,37 inhibits renin release from juxtaglomerular cells,38 and enhances the release of atrial natriuretic factor.39 Atrial natriuretic factor decreases plasma volume, probably by its vasodilator effect on systemic capillary permeability.40 PIH has been characterized as a state of abnormal secretion of atrial natriuretic factor,41 and correlation of endothelin, endothelial cell damage, and toxemia of pregnancy has also been claimed.42 Inadequate interaction of these modulators, which are responsible for the maintenance of vascular tone, could be one of the explanations for the genesis of PIH.

This study demonstrates that postural changes have different effects on the systemic blood pressure of hypertensive states of pregnancy, with the LLR position reducing MAP only in CHP and not in PIH. Postural stimuli did not elicit a response of the components of the renin-angiotensin-aldosterone system in PIH, although orthostatism provoked a significant response of the system in CHP. In addition, a return of the parallelism between circulating renin and serum aldosterone levels was observed in PIH and CHP.

References


KEY WORDS • pregnancy-induced hypertension • chronic hypertension • renin-angiotensin-aldosterone system
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