Plasma Renin Activity, Reactivity, Concentration and Substrate Following Hypertension During Pregnancy

Effect of Oral Contraceptive Agents

THEODORE A. KOTCHEN, M.D., J. MORLEY KOTCHEN, M.D., GORDON P. GUTHRIE, JR., M.D., AND CAROL M. COTTRILL, M.D.

SUMMARY Plasma renin activity is suppressed in approximately 25% of patients with essential hypertension, and the rate of in vitro angiotensin I production after addition of exogenous renin (renin reactivity) is increased in plasma of hypertensive patients. We have recently observed that blood pressure (116 ± 1.5/68 ± 1.7 mm Hg) of young women who had hypertension during a first pregnancy 3-6 years earlier (n = 63) was higher (p < 0.005) than blood pressure (109 ± 1.4/61 ± 1.7 mm Hg) of women who remained normotensive during pregnancy (n = 52). To determine if alterations of the renin-angiotensin axis observed in patients with established hypertension also occur in young adults with relatively high blood pressure, plasma renin activity (PRA), plasma renin concentration (PRC), plasma renin substrate (PRS) and plasma renin reactivity (PRR) were compared in these two groups of subjects. Overall, PRA and PRC were inversely related to systolic blood pressure (p < 0.02). Excluding women on oral contraceptive agents, the PRA response to standardized treadmill exercise was suppressed (< 1.0 ng/ml/hr) in 19% of women with a history of hypertension during pregnancy and in no women who remained normotensive throughout a previous pregnancy; PRR did not differ (p > 0.8) in the two groups of young mothers (27.1 ng/ml/30 min ± 1.2 SE vs 26.2 ng/ml/30 min ± 0.9 SE). Thus, renin suppression, but not increased PRR, precedes the onset of hypertension. Oral contraceptive usage was associated with higher systolic blood pressures, increased PRS, and low PRC. Highest blood pressures and lowest PRA occurred in women with a history of hypertension during pregnancy who were taking oral contraceptive agents at the time of study. (Hypertension 1: 355-361, 1979)

KEY WORDS 

blood pressure • exercise • hypertension • oral contraceptive agents • pregnancy • renin

W e have recently reported that arterial blood pressure of women who had elevated pressure during the third trimester of their first pregnancy 3-6 years earlier is higher than that of women who did not have hypertension in pregnancy.1 The purpose of the present study is to compare measurements of the renin-angiotensin system in these two groups of young women to determine if alterations observed in patients with established essential hypertension also occur in young adults with relatively high blood pressure but without clinical hypertension. At the time of study, only 14% of women with a history of hypertension during pregnancy had blood pressure measurements repeatedly above 140/90 mm Hg.

Plasma renin activity (PRA) is suppressed in approximately 25% of patients with essential hypertension,2-4 and it is unclear whether renin suppression is related to the pathogenesis of hypertension or is a consequence of elevated arterial pressure. After adding exogenous renin, the in vitro rate of angiotensin I generation in plasma of hypertensive patients is greater than that in plasma of normotensive subjects,5-9 possibly due to a deficiency of a normally occurring renin inhibiting factor.7 What relationship this may have to elevated arterial pressure is also unclear. In the present study, these measurements were compared in groups of normotensive young women with relatively high and relatively low blood pressures. Hypertension induced by oral contraceptive agents has been attributed by some investigators to a renin-angiotsin mechanism.10-13 Fortuitously, approximately half of the young mothers were taking oral contraceptives at the time of the study. Conse-
quently, the effect of oral contraceptives on the activity of the renin-angiotensin axis was also compared in these young women with relatively high and relatively low blood pressures.

Methods

The original study population consisted of 409 pregnant primiparous adolescent women. Mean age during pregnancy was 16.9 years ± 1.3 SD; 46% of the women were white and 54% were black. Overall 74 women (18%) were diagnosed as having hypertension during pregnancy on the basis of any one of the following criteria: systolic blood pressure >140 mm Hg; diastolic blood pressure >90 mm Hg; >30 mm Hg increase of systolic blood pressure during pregnancy; >15 mm Hg increase of diastolic blood pressure. Sixty-three of these 74 women and an additional 52 women selected from the same population and who did not have hypertension during pregnancy, participated in the current follow-up study 3 to 6 years after their first pregnancy. Thirty-four of the 63 women (54%) with a history of hypertension during pregnancy and 41 of the 52 women (79%) in the normotensive control group were black. Subjects found to have hypertension at the time of follow-up examination were not excluded from study.

Blood pressure was measured in the sitting position according to a previously described standardized protocol. Peripheral venous blood was obtained by separate venepunctures both before and within 30 seconds after standardized treadmill exercise to measure PRA. Subjects were supine at least 15 minutes before the pre-exercise blood was obtained, and supine blood pressure was measured before venepuncture. The exercise protocol used was a previously described modification of the Balke protocol. Briefly, subjects walk at 3.5 miles per hour for a maximum of 15 minutes. The treadmill is progressively elevated 2°/min. Blood pressure is measured every 3 minutes, and exercise is monitored with a 15-second lead five ECG strip every minute. Exercise is discontinued for cardiac abnormalities, at the subject's request, or heart rate greater than 200. Only 28 of the 115 subjects were able to complete the 15-minute protocol; overall mean exercise time was 11.4 min ± 0.3 SE.

Plasma renin activity (active renin) was assayed in quadruplicate by radioimmunoassay for angiotensin I as described by Haber et al. and validated in our laboratory by bioassay. To maintain a constant pH, during the 3-hour incubation before assay, tris buffer (pH 7.4) was added to plasma (100 μl/ml). Total plasma renin concentration (active plus inactive renin), plasma renin substrate (PRS), and plasma renin reactivity (PRR) were also measured in plasma obtained before exercise. For measurement of plasma renin concentration (PRC), plasma was dialyzed against a glycine buffer to pH 3.3, incubated at 32°C for 60 minutes and then dialyzed back to pH 7.4 against a phosphate buffer, according to the method of Skinner. Endogenous renin substrate was totally denatured by acidification, and a constant concentration (1000 ng/ml) of exogenous homologous renin substrate, prepared by the method of Rosenthal et al. from plasma of women taking oral contraceptives, was then added to dialyzed plasma. The concentration of angiotensin I produced after a 60-minute incubation at 37°C was measured by radioimmunoassay. Plasma renin substrate was measured by adding high concentrations of human renin, (1.6 X 10⁻⁸ GU/ml) extracted from kidneys by the method of Haas, and measuring the concentrations of angiotensin I produced after the reaction between exogenous renin and endogenous substrate had proceeded to completion; the concentration of angiotensin I generated after 3- and 6-hour incubations did not differ.

Plasma renin reactivity is the capacity of a lower concentration of exogenous renin to generate angiotensin I after its addition to plasma. This measurement may be affected by endogenous renin substrate concentration as well as by normally occurring circulating inhibitors of the renin-renin substrate reaction. The concentration of angiotensin I produced during a 30-minute incubation after addition of renin (1.1 X 10⁻⁸ GU/ml) was measured. At this enzyme concentration and incubation time, the rate of angiotensin generation was linear with time, thus providing the opportunity to evaluate the kinetics of the enzymatic activity of added renin. For the computation of PRR, the relatively small concentrations of angiotensin generated in aliquots of plasma without added enzyme (1-4% of total angiotensin generated with added enzyme) were subtracted from the concentrations of angiotensin produced after adding renin to plasma.

To determine if changes in PRR reflect differences of endogenous renin substrate, PRR was also measured in plasma in which substrate was denatured by acidification according to the Skinner PRC procedure; before addition of enzyme, homologous substrate was added to these samples (1000 ng/ml). However, acidification of plasma may denature circulating renin inhibiting factors as well as renin substrate. In a separate experiment, substrate but not circulating inhibitors was "selectively" removed by passing plasma over Sephadex G-50-40. Pharmacia K15 (900 X 15 mm) columns were used. Between 3.5 to 4.0 g of Sephadex was swollen overnight and columns were packed by gravity. Five ml of plasma was then placed on the column, and protein separation was monitored by reading the absorbance of the eluate at 280 μm. With this procedure >98% of protein including renin substrate is separated from plasma. The plasma eluate without protein contains renin inhibitory activity, but no measureable renin activity or renin substrate, i.e., no detectable angiotensin I was produced after incubation of the eluate separately with either renin or renin substrate. The rate of angiotensin production was measured after addition of this eluate to renin (8 X 10⁻⁴ GU/ml)-renin substrate (1000 ng/ml).

To provide an estimate of dietary sodium intake, urine sodium-creatinine ratios were determined in a timed overnight urine collection. Sodium and
plasma renin following hypertension of pregnancy/kotchen et al.

Table 1. Systolic and Diastolic Blood Pressure, PRA, PRC, PRS, PRR, and Serum Creatinine in Women with a History of Hypertension During Pregnancy and Women who Remained Normotensive During Pregnancy, Compared with Oral Contraceptive (OC) Usage

<table>
<thead>
<tr>
<th></th>
<th>OC+ (n = 27)</th>
<th>OC- (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting BP (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OC+</td>
<td>120 ± 2.1</td>
<td>113 ± 2.0</td>
</tr>
<tr>
<td>OC-</td>
<td>69 ± 2.9</td>
<td>67 ± 2.1</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-exercise</td>
<td>0.7 ± 0.1</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>Post-exercise</td>
<td>1.5 ± 0.3</td>
<td>3.1 ± 0.4</td>
</tr>
<tr>
<td>PRC (units/ml)</td>
<td>4.3 ± 0.2</td>
<td>5.7 ± 0.4</td>
</tr>
<tr>
<td>PRS (ng/ml)</td>
<td>238 ± 144</td>
<td>151 ± 93</td>
</tr>
<tr>
<td>PRR (ng/ml/30 min)</td>
<td>44.9 ± 2.5</td>
<td>27.1 ± 1.2</td>
</tr>
<tr>
<td>Serum creatine (mg/dl)</td>
<td>1.1 ± 0.1</td>
<td>1.0 ± 0.1</td>
</tr>
</tbody>
</table>

*All values are mean ± SE.

potassium concentration were measured with a flame photometer (Instrumentation Laboratory, Morris Plains, NJ). Serum and urine creatinine concentrations were measured by the method of Kennedy et al.

Since many variables were not normally distributed, except where noted, it was necessary to utilize non-parametric procedures to test statistical significance. Kendall's Tau was used to determine if variables were significantly associated, and the Kurskal-Wallis test was used to determine if there were significant differences among groups.

Results

Based on analysis of variance, at the time of follow-up, in both the supine and sitting positions systolic and diastolic blood pressures of women with a history of hypertension during pregnancy were higher (p < 0.005) than blood pressures of women who had remained normotensive throughout pregnancy, and these differences were maintained after adjusting for an effect of body size on blood pressure (table 1). Blood pressure was not related to race, and blood pressures of blacks and whites did not differ. Systolic blood pressure of women using oral contraceptives was higher (p < 0.004) than respective values of women not using these agents. Excluding women on contraceptives, systolic (p < 0.01) and diastolic (p < 0.05) blood pressures were again higher in women with a history of hypertension during pregnancy.

Fourteen percent of women with hypertension during pregnancy had sustained blood pressure elevations (>140/90 mm Hg) at follow-up study, and all of these women were using oral contraceptive agents. Hypertension was not present in any women who had been normotensive throughout pregnancy.

Overall, both basal and exercise-stimulated PRA were inversely related to pre-exercise supine and sitting systolic blood pressures (table 2, fig. 1).

Separating subjects into those who were using contraceptives and those who were not, the association between PRA and systolic blood pressure was less consistent (table 2). Diastolic blood pressure did not correlate with PRA.

Plasma renin activity increased (p < 0.0001) in response to treadmill exercise; PRA measured after exercise was related to pre-exercise PRA (r = 0.59, p < 0.0001) and duration of exercise (r = 0.21, p < 0.01). Basal and exercise-stimulated PRA were not associated with urinary sodium excretion, estimated by sodium-creatinine ratio in an overnight urine collection. Excluding women on oral contraceptive agents, PRA was lower among blacks than whites.

Table 2. Linear Correlation Coefficients Describing the Association Between Systolic Blood Pressure (SBP) and PRA

<table>
<thead>
<tr>
<th></th>
<th>Supine SBP</th>
<th>Sitting SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-exercise</td>
<td>r = -0.24</td>
<td>r = -0.28</td>
</tr>
<tr>
<td>PRA</td>
<td>p &lt; 0.009</td>
<td>p &lt; 0.003</td>
</tr>
<tr>
<td>Post-exercise</td>
<td>r = -0.23</td>
<td>r = -0.23</td>
</tr>
<tr>
<td>PRA</td>
<td>p &lt; 0.014</td>
<td>p &lt; 0.017</td>
</tr>
</tbody>
</table>

Subjects using oral contraceptives (n = 61)

<table>
<thead>
<tr>
<th></th>
<th>Supine SBP</th>
<th>Sitting SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-exercise</td>
<td>r = -0.18</td>
<td>r = -0.24</td>
</tr>
<tr>
<td>PRA</td>
<td>p &gt; 0.16</td>
<td>p &lt; 0.09</td>
</tr>
<tr>
<td>Post-exercise</td>
<td>r = -0.26</td>
<td>r = -0.33</td>
</tr>
<tr>
<td>PRA</td>
<td>p &lt; 0.06</td>
<td>p &lt; 0.02</td>
</tr>
</tbody>
</table>

Subjects not using oral contraceptives (n = 53)

<table>
<thead>
<tr>
<th></th>
<th>Supine SBP</th>
<th>Sitting SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-exercise</td>
<td>r = -0.27</td>
<td>r = -0.24</td>
</tr>
<tr>
<td>PRA</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.07</td>
</tr>
<tr>
<td>Post-exercise</td>
<td>r = -0.14</td>
<td>r = -0.07</td>
</tr>
<tr>
<td>PRA</td>
<td>p &gt; 0.28</td>
<td>p &gt; 0.60</td>
</tr>
</tbody>
</table>
 whites, both before and after exercise ($p < 0.03$), although blood pressure did not differ. Both before and after exercise, PRA was significantly lower ($p < 0.02$) in women with a history of hypertension during pregnancy and who were presently taking oral contraceptive agents than in any other group (post-exercise PRA remained significantly lower after adjusting for exercise duration); mean systolic blood pressure was also highest in this group ($p < 0.01$).

Among women not using oral contraceptive agents and excluding women who exercised less than 8 minutes, mean post-exercise PRA of women who were normotensive during pregnancy did not differ from the respective value in women with a history of hypertension during pregnancy. The lowest PRA after exercise of women who were normotensive during pregnancy was 1.0 ng/ml/hr, and this value was included within one standard deviation from the mean (fig. 2). Five of 27, or 19% of women who were hypertensive during pregnancy, had a stimulated PRA below this value, and all five values were below one standard deviation from the mean. Mean exercise duration and mean urinary sodium-creatinine and sodium-potassium ratios of these five women did not differ from respective values in either the remainder of this group or

Figure 1. Correlation between systolic blood pressure (SBP) and plasma renin activity (PRA) before exercise. O.C. = oral contraceptives.

Figure 2. Post-exercise plasma renin activity (PRA) in women who were normotensive during pregnancy and in women with a history of hypertension during pregnancy. Subjects on oral contraceptive agents are not included. Shaded area represents 1 standard deviation from the mean.
control women who were normotensive throughout pregnancy. Four of the five women were black, and none of the five was hypertensive.

Plasma renin concentration (PRC) measured before exercise correlated with PRA \( (r = 0.43, p < 0.0001) \) and was also inversely related to systolic blood pressure \( (r = -0.24, p < 0.02) \). Mean PRC of women taking oral contraceptives was less than that of women not receiving these drugs \( (p < 0.01) \), although PRC was not related to previous blood pressure history. We found no association between PRC and race or sodium excretion. Overall, PRS was inversely related to PRC \( (r = -0.19, p < 0.05) \). Mean PRS was increased in women taking oral contraceptive agents compared to women not on these agents \( (p < 0.01) \). Among women not using oral contraceptives, mean PRS of women with a history of hypertension during pregnancy was greater than that of women who were normotensive during pregnancy \( (p < 0.04) \).

Overall, PRR was directly related to systolic blood pressure \( (r = 0.31, p < 0.001) \) and to PRS \( (r = 0.69, p < 0.0001) \) and inversely related to PRC \( (r = -0.36, p < 0.0001) \). PRR in women with a history of hypertension during pregnancy did not differ from that of women who were normotensive during pregnancy, both unadjusted and adjusted for PRC \( (p > 0.8) \). PRR in plasma of women receiving oral contraceptives was greater than that of women not on contraceptive agents \( (p < 0.01) \), presumably reflecting increased PRS.28

After acidification of plasma and addition of excess exogenous renin substrate, PRR in women on contraceptive agents \( (36.7 \text{ ng/ml/30 min} \pm 1.1 \text{ se}) \) did not differ \( (p > 0.2) \) from that of women not taking contraceptives \( (38.3 \text{ ng/ml/30 min} \pm 0.9 \text{ se}) \). To further determine if increased PRR associated with oral contraceptive usage is related to high endogenous renin substrate and/or the deficiency of a renin inhibiting factor, endogenous renin substrate was "selectively" removed by passing plasma over Sephadex. "Substrate-free" plasma was then added to renin-renin substrate. Compared to the in vitro rate of angiotensin generation after addition of buffer to renin-renin substrate, less angiotensin \( (p < 0.01) \) was generated after addition of Sephadex fractionated plasma (fig. 3). Slightly although not significantly \( (p > 0.1) \) greater inhibition occurred after addition of Sephadex fractionated plasma of women taking oral contraceptive agents than with plasma of women not on these agents. Thus, substrate-free plasma from women taking oral contraceptive agents inhibited the in vitro renin reaction to at least the same extent as plasma from women not using these drugs, suggesting that increased PRR with contraceptive usage reflects increased renin substrate concentration rather than the deficiency of a renin inhibitor.

Discussion

Several investigators have demonstrated that hypertension during pregnancy is associated with an increased incidence of hypertension at a later date.27–30 In the present follow-up study, blood pressure of women with a history of hypertension during nulliparous adolescent pregnancy was significantly higher than the blood pressure of women who were normotensive during pregnancy. Although mean blood pressures of the two groups of women were within the "normal range," recent evidence suggests that small differences of blood pressure in adolescents and young adults may be important predictors of elevated blood pressure and cardiovascular disease at a later age.31–35

The activity of the renin-angiotensin system was compared in these young women with relatively low and relatively high blood pressures. Exercise was selected as a standardized stimulus for renin because it is brief, well tolerated, and requires no drug administration. We have previously observed that the magnitude of the renin response is related to the intensity of exercise.36 Plasma renin concentration, basal PRA, and PRA stimulated by standardized treadmill exercise were inversely related to systolic but not to diastolic blood pressure. Blood pressure was highest and PRA was lowest among women with a history of hypertension during pregnancy who were taking oral contraceptive agents at the time of study. In response to exercise, excluding women on oral contraceptive agents, we found that PRA was suppressed in 19% of women with a history of hypertension during pregnancy, despite a somewhat lower percentage of black subjects in this group. It is well recognized that PRA is suppressed in approximately 25% of patients with essential hypertension, generally measured in response.
to dietary sodium deprivation or to acute furosemide administration.  
Fasciola et al. \textsuperscript{37, 38} reported that patients with essential hypertension and their first degree relatives also have a suppressed renin response to exercise. The current demonstration that renin is suppressed in young women with relatively high, but “normal” blood pressure and normal renal function, suggests that low renin is an appropriate physiologic response to relatively higher arterial pressures. An inverse correlation between blood pressure and unstimulated PRA has previously been observed in normotensive subjects \textsuperscript{39} and between blood pressure and “total renin” in hypertensive patients. \textsuperscript{40}  

A number of investigators have reported that the enzymatic activity of added renin is increased in plasma of hypertensive patients. \textsuperscript{5} Increased renin reactivity has been attributed to the deficiency of a renin inhibiting factor \textsuperscript{7} or to the presence of a renin activator. \textsuperscript{9} In the present study, overall, PRR was directly related to systolic blood pressure. However, excluding women on oral contraceptive agents, PRR was not related to blood pressure, suggesting that in the absence of oral contraceptive usage increased PRR is specifically related to the hypertensive state.  

Similar to earlier reports, \textsuperscript{11-13} we observed that PRS was increased and PRC was decreased by oral contraceptive therapy. Because the velocity of the in vitro renin reaction is related to PRR, and because of an apparent negative feedback between PRS and PRC, several investigators have suggested that increased substrate results in maintenance of constant PRA via suppression of PRC. \textsuperscript{11, 12} Failure of this feedback mechanism, resulting in increased PRA, has been proposed as a possible cause of contraceptive induced hypertension; however, Beckerhoff et al. \textsuperscript{14} observed that PRC was lower in hypertensive than normotensive women taking oral contraceptives. Although it may not be appropriate to extrapolate to patients with clinical hypertension, we observed that higher blood pressures related to contraceptive usage were associated with suppressed rather than increased PRA. Confirming earlier reports, we also observed that PRR is increased in women using oral contraceptive agents. \textsuperscript{42-45} Although elevated PRR has generally been attributed to high substrate concentrations, McDonald et al. \textsuperscript{47} have recently reported that alterations of modifiers of the renin reaction by estrogen therapy also contribute to the increased enzymatic activity of added renin. To evaluate the potential contribution of renin activators or inhibitors in the present study, renin substrate was denatured by prior acidification of plasma and the reactivity of added renin was measured after replacing denatured endogenous substrate with a relatively crude preparation of homologous substrate. Under these circumstances, PRR in plasma of women taking contraceptives did not differ from that of women not using these agents, suggesting that elevated PRR accounted for increased PRR in unacidified plasma. However, it is possible that cofactors present in the preparation of added substrate may have masked renin inhibitors or acceleration associated with contraceptive usage. We have recently reported that dialysis of plasma against an acid buffer also denatures a circulating renin inhibitor. \textsuperscript{48} To “selectively” extract substrate, without loss of inhibitory activity, plasma was passed over a Sephadex column. Substrate-free plasma from women using oral contraceptives inhibited the in vitro renin reaction to at least the same extent as plasma from women not on contraceptives. Thus, it is unlikely that increased PRR is related to loss of a renin inhibiting factor.  

In summary, current blood pressures of young women with a history of hypertension during pregnancy were higher than blood pressures of women who remained normotensive throughout pregnancy. Overall, among these women, PRA and PRC were inversely related to blood pressure, and the PRA response to exercise was suppressed in 19% of normotensive subjects with relatively high blood pressure. However, PRR did not differ in women with relatively high and relatively low blood pressures. Thus, renin suppression but not increased PRR appears to precede the hypertensive state. Oral contraceptive usage was associated with higher systolic blood pressures, high PRA and PRR, and low PRC. Highest blood pressures and lowest PRA occurred in those women with a history of hypertension during pregnancy who were taking oral contraceptive agents at the time of study.  

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