Low Renin in Young Mothers and their Children Following Hypertension in Pregnancy

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SUMMARY Young women who became pregnant as adolescents and developed hypertension during their first pregnancies had higher blood pressures than women who had remained normotensive throughout pregnancy. These young mothers served as subjects for a study to evaluate the relationship between different levels of "normal" blood pressure and renin-aldosterone. Overall, plasma renin activity (PRA), but not plasma aldosterone, was inversely related to systolic blood pressure both before ($r = -0.28; p < 0.003$) and after ($r = -0.24, p < 0.01$) treadmill exercise. Unrelated to blood pressure, PRA was also lower in blacks and in women using oral contraceptive agents ($p < 0.01$). Of women with a history of hypertension in pregnancy, 30% (9 of 30) had low PRA after exercise. Low renin was associated with higher blood pressures. At the time of a second exercise test 3 years later, these women still showed elevated arterial pressure and low renin. PRA was also suppressed in the children of mothers with low renin, and there were significant correlations between maternal and child PRA ($r = +0.55; p < 0.003$) and between maternal and child aldosterone ($r = +0.60; p < 0.001$). In conclusion, low renin may be an appropriate response to higher arterial pressures, and within families may be a marker of "pre-hypertension." (Hypertension 4 (suppl II): II-119-II-124, 1982)

KEY WORDS • pregnancy • renin-aldosterone • adolescence • exercise testing • plasma renin activity • risk factors • gestational hypertension

We have previously reported that women with a history of hypertension during primiparous adolescent pregnancy have higher arterial pressures 3-6 years later than women who had remained normotensive throughout pregnancy. Blood pressures were also higher in the children of women with hypertension during pregnancy. In these women, hypertension during pregnancy was generally mild; none had seizures or more than 1+ proteinuria. Thus, these women had "gestational" hypertension rather than pre-eclampsia, and it has recently been suggested that gestational hypertension is a sign of latent hypertension, unmasked by pregnancy. Plasma renin activity (PRA) is suppressed in approximately 25% of patients with essential hypertension, although aldosterone secretion is either normal or low. The mechanism for renin suppression in the majority of patients with low-renin essential hypertension has not been convincingly identified. The population of young mothers provided the opportunity to determine if PRA is also suppressed in a defined group of young adults with "normal" but relatively higher arterial pressures.

Clinically, renin suppression is generally defined by measuring PRA in response to a provocative maneuver. Exercise is a potent stimulus to renin release, and the increase of PRA is proportional to the intensity of exercise. In the present study, PRA and plasma aldosterone were measured before and after treadmill exercise in this population of young mothers. Treadmill exercise was selected as the stimulus for renin release because it is a relatively simple, noninvasive procedure that is acceptable to young adults. To determine if renin responses to exercise are stable over time, selected subjects were restudied approximately 3 years after the initial exercise test. The children of these subjects were also exercised to determine if there are familial resemblances of renin and aldosterone.
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 53 women selected from the same population and who did not have hypertension during pregnancy participated in the follow-up study 3 to 6 years after their first pregnancy.

Peripheral venous blood was obtained by separate venipunctures both before and within 30 seconds after standardized treadmill exercise for measurement of PRA and plasma aldosterone concentration. Plasma renin substrate (PRS) was also measured before exercise. Subjects were supine at least 15 minutes before the pre-exercise blood sample was obtained. We used a previously described modification of the Balke exercise protocol. Briefly, subjects walked at 3.5 miles per hour for a maximum of 15 minutes. The treadmill was progressively elevated 2°/min, and blood pressure was measured every 3 minutes. Exercise was monitored with a 15-second Lead 5 ECG strip every minute and was discontinued for either cardiac abnormalities, the subject’s request, or a heart rate greater than 200. Overall mean exercise time was 11.4 min ± 0.3 s. On the day before the exercise, a timed overnight urine was collected for measurement of sodium, potassium, and creatinine excretion.

To determine stability of renin status over time, selected groups of mothers were restudied approximately 3 years after the first exercise test, using an identical protocol. At this second study, renin and aldosterone responses to exercise were also measured in the children of the young mothers.

PRA and aldosterone were measured by radioimmunoassay. PRS was measured as previously described. Urine sodium and potassium concentrations were measured by flame photometer, and creatinine was measured by the method of Kennedy et al.

Analysis of variance was used to test the statistical significance of group differences.

Results

At 3- to 6-year follow-up, women with a history of hypertension in pregnancy had higher (p < 0.005) systolic and diastolic blood pressures than women who had remained normotensive throughout pregnancy (Table 1). In both groups, PRA and aldosterone increased in response to exercise (p < 0.001), and, overall, both before and after exercise PRA and plasma aldosterone did not differ significantly in the two groups of women. However, based on a history of blood pressure in pregnancy and current contraceptive usage, both before and after exercise PRA and plasma aldosterone were each significantly lower in women with hypertension during pregnancy and who were using oral contraceptives at the time of study, compared to all other groups (Figs. 1 and 2). Blood pressures were also higher in this group of women.

To relate measurements of renin and aldosterone to current blood pressures, the young mothers were reclassified into those with systolic blood pressure in the upper quartile of the follow-up blood pressure distribution ("high"), the lower quartile ("low"), and the mid 50th percentile ("intermediate"). In each of these three blood pressure groups, PRA and plasma aldosterone again increased (p < 0.001) in response to exercise (Table 2). Both before and after exercise, PRA in the high blood pressure group was less (p < 0.03) than that in the low blood pressure group. Overall, there was a significant inverse correlation between systolic blood pressure and both pre-exercise PRA (r = -0.28; p < 0.003) and postexercise PRA (r = -0.24; p < 0.01). Although PRS did not differ significantly among blood pressure groups, overall there was a significant positive correlation between systolic blood pressure and PRS (r = +0.27; p < 0.006) for all subjects.

Plasma aldosterone was significantly correlated with PRA both before (r = +0.25; p < 0.02) and after (r = +0.43; p < 0.0001) exercise, and in response to exercise there was a significant correlation between the increment of PRA and the increment of aldosterone (r = +0.40; p < 0.0001). However, mean plasma aldosterone concentrations did not differ among blood pressure groups, and unlike PRA, aldosterone was not significantly correlated with blood pressure.

| Table 1. Blood Pressure (BP) of 116 Young Mothers at 3 to 6 Years after Pregnancy |
|---------------------------------|----------|----------|
| Classification                  | No.      | Systolic BP (mm Hg) | Diastolic BP (mm Hg) |
| History of BP in pregnancy:     |          |              |                      |
| Hypertensive                    | 63       | 116 ± 2      | 69 ± 2               |
| Normotensive                    | 53       | 109 ± 1*     | 60 ± 2*              |
| Follow-up BP distribution:      |          |              |                      |
| High                            | 29       | 127 ± 1      | 73 ± 2†              |
| Intermediate                    | 59       | 113 ± 1*     | 64 ± 2               |
| Low                             | 28       | 102 ± 1      | 58 ± 3*              |

*p < 0.05 compared to other group(s).
†p < 0.001 compared to other groups.

High BP distribution is upper quartile of follow-up BP distribution; Intermediate BP is mid 50th percentile; Low BP is lower quartile. Values are means ± SE.
LOW PRA AFTER HYPERTENSION IN PREGNANCY/Cotrill et al.

PREQ: HBP ORAL CONTRA • HBP CD
5.0 40 3.0 20 1.0
• PRE EX POST EX (n-27) (n-36)

NBP INBP (n=28) (n=25)
• p<0.04 COMPARED TO OTHER GROUPS

In addition to blood pressure, PRA was also related to oral contraceptive use and race. Blood pressure did not differ by race, and systolic blood pressure of contraceptive users (116 mm Hg ± 1 se) was higher (p < 0.004) than that of women not using oral contraceptive agents (110 mm Hg ± 1 se). Excluding women using oral contraceptive agents, PRA before and after exercise was lower (p < 0.01) in blacks than in whites (fig. 3). Among white subjects, both the pre-exercise and post-exercise PRA of contraceptive users were lower (p < 0.01) than respective values of women not using these agents. This difference by contraceptive usage persisted after adjusting for an effect of blood pressure on PRA. PRA was not affected by oral contraceptive usage among blacks, and among women taking oral contraceptive agents, PRA was not affected by race. Overall, after adjusting for effects of race and oral contraceptive usage, significant associations between blood pressure and both pre-exercise PRA (p < 0.001) and postexercise PRA (p < 0.007) persisted.

To determine if low renin is related to a history of hypertension in pregnancy and to determine if low renin status persists over time, selected subjects were restudied. When women using oral contraceptive agents were excluded, the mean postexercise PRA of

| Table 2. Mean Plasma Renin Activity and Aldosterone Responses to Exercise by Blood Pressure Group |
|---------------------------------|-----------------|-----------------|-----------------|
|                                 | High (n = 29)   | Intermediate (n = 59) | Low (n = 28) |
| Plasma renin activity (ng/ml/hr):              |                  |                  |                |
| Pre-ex                                       | 0.8 ± 0.2       | 1.1 ± 0.1       | 1.4 ± 0.2†     |
| Post-ex                                      | 2.1 ± 0.5       | 2.9 ± 0.3       | 3.7 ± 0.5*     |
| Plasma aldosterone (ng/dl):                  |                  |                  |                |
| Pre-ex                                       | 5.8 ± 1.4       | 6.2 ± 0.9       | 7.8 ± 1.6      |
| Post-ex                                      | 15.4 ± 3.0      | 15.9 ± 2.0      | 18.1 ± 3.5     |
| Plasma renin substrate                       |                  |                  |                |
| (ng/ml)                                      | 1950 ± 124      | 1841 ± 83       | 1803 ± 123     |

*p < 0.03 compared to "high" group.
†p < 0.01 compared to "high" group.
Pre-ex = before exercise; Post-ex = after exercise. See table 1 for explanation of High, Intermediate, and Low BP group. Values are means ± se.
women with a history of hypertension in pregnancy did not differ from that in women who had remained normotensive throughout pregnancy (fig. 4). Among women who remained normotensive throughout pregnancy, the lowest postexercise PRA was 1.0 ng/ml/hr. Nine of 30 (30%) women with a history of hypertension in pregnancy had a postexercise PRA below this value, and hence are defined as having low renin. Approximately 3 years after the initial study, repeat exercise testing was carried out in these nine women with low PRA as well as in a group of women with a history of hypertension in pregnancy and normal PRA (n = 10) and a group of women who had remained normotensive throughout pregnancy (n = 10). At the time of both the initial and repeat exercise testing (approximately 4 and 7 years after pregnancy, respectively), the systolic blood pressure of women with low renin was significantly higher than that of the other two groups (table 3). In women with a history of hypertension in pregnancy and low PRA at the time of the first exercise test, pre- and postexercise PRA in the second exercise test were also lower (p < 0.05) than the respective values of the other two groups. There were no group differences of plasma aldosterone, either before or after exercise.

At the time of the mothers' second exercise test, pre- and postexercise PRA were also measured in their children (mean age, 7.8 year ± 0.2 SE). Blood pressure of children of mothers with hypertension in pregnancy and low renin was somewhat higher than that of the other groups, although this difference did not achieve statistical significance (table 3). Before exercise, PRA of children of women with hypertension in pregnancy and low renin was lower (p < 0.05) than the pre-exercise PRA in children of the other two groups of mothers. Among the children, there were no group differences of postexercise PRA or of plasma aldosterone either before or after exercise. Before exercise, there was a significant correlation between maternal and child PRA (r = +0.55; p < 0.003) and between maternal and child aldosterone (r = +0.60; p < 0.001). Among both mothers and children, there were no group differences in urine sodium-creatinine or sodium-potassium ratios, and no maternal-child correlations of these ratios.

Discussion

Young women with a history of gestational hypertension 3–6 years earlier had slightly higher blood pressures than a group of control women who had remained normotensive throughout pregnancy. Overall, mean PRA and plasma aldosterone did not differ significantly in these two groups of women, although renin and aldosterone were suppressed in women with a history of hypertension in pregnancy who were taking oral contraceptive agents at the time of follow-up. Conceivably, renin-aldosterone suppression in these women may have been related to higher...
blood pressures in contraceptive users and/or to some other effect of oral contraceptives on renin release. Reclassifying all women based on follow-up blood pressures, blood pressure differences among groups were greater and simultaneous measurements of renin were inversely related to blood pressure.

Excluding subjects using oral contraceptives, 30% of the women with a history of hypertension in pregnancy had a low PRA in response to exercise. Among these women, both elevated arterial pressure and low renin were maintained over time, and PRA was also suppressed in the children of mothers with low renin. Thus, low renin may not only be an appropriate physiologic response to relatively higher arterial pressures, but within families may also be a marker of "pre-hypertension." These results are consistent with an earlier observation of Fasiola et al. that patients with essential hypertension and their first degree relatives, aged 15–30 years, have suppressed renin release in response to exercise. However, in contrast to the report of Fasiola in our younger subjects, suppression of PRA in children of mothers with low renin was observed before but not after blood pressure.

In a separate population of young adults we have reported that both renin and aldosterone were suppressed in subjects with higher blood pressures. In that population both males and females were included. Blood pressures were higher in males, and aldosterone was more convincingly suppressed in males than in females. In the current study, aldosterone was not suppressed in young women with low renin. Similarly in patients with low renin essential hypertension, aldosterone production is frequently normal, and it has been suggested that normal aldosterone in the presence of low renin may reflect increased sensitivity of the zona glomerulosa to circulating concentrations of angiotensin.

In normotensive adults, some but not all investigators have described an inverse association between nonstimulated PRA or plasma renin concentration and arterial pressure. The inverse association between blood pressure and renin has been attributed to an effect of age in that blood pressure increases and plasma renin activity decreases with increasing age. In the present study, all subjects ranged in age from 17 to 24 years, and within this constricted age range there was no association between blood pressure and age. Consequently, the inverse association between renin and blood pressure is clearly not related to an effect of age.

Independent of blood pressure, PRA was also related to race. Other investigators have also demonstrated that plasma renin activity is decreased in black adults and children and there is a relatively high prevalence of low renin hypertension among blacks. Based on a single overnight urine collection, in the present study low renin in blacks was not related to racial differences of sodium excretion. However, a single urine collection may not be an adequate estimate of dietary sodium intake, and additional studies will be required to determine if low renin in blacks is related to increased sodium intake and/or decreased capacity to excrete sodium. Among white women, PRA was also lower in subjects using oral contraceptive agents. This may in part be related to higher arterial pressures of women using these agents and to a reciprocal suppression of renin in response to stimulation of renin substrate synthesis by oral contraceptives.

The demonstration that PRA is inversely related to blood pressure in these normotensive young adults suggests that renin suppression in patients with low renin essential hypertension is an appropriate response to elevated arterial pressure. In the presence of hypertension, "normal" renin may reflect inappropriate renin secretion due to underlying renal disease such as decreased renal cortical blood flow as a consequence of nephrosclerosis.

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References


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