Plasma Renin Activity in Patients with Coarctation of the Aorta

A Comment on the Pathogenesis of Prestenotic Hypertension

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SUMMARY

In 10 patients with coarctation of the aorta, plasma renin activity was measured after recumbency and orthostatism in peripheral venous blood and, in some cases, in renal venous blood also. In nine of these patients, basic plasma renin values and those obtained under stimulatory conditions lay within normal range, and only in one patient were the values elevated. However, since this patient displayed the lowest gradient of mean arterial blood pressure proximal and distal to the stenosis, it can be regarded as improbable that the elevation in plasma renin activity was caused by the coarctation. Plasma renin activity in the renal venous blood of both kidneys, which was measured in three patients, showed no elevation.

On the basis of observations of other authors and of our own studies it can be concluded that the kidneys can contribute to the development of prestenotic hypertension in acute constriction of the aorta in experiments with animals, but in chronic coarctation in animals or in man the humoral or renal theory has no importance to the pathogenesis of hypertension.

Additional Indexing Words:
Renal theory  Experimental coarctation  Renin in peripheral and renal venous blood

COARCTATION of the aorta consists of a congenital narrowing of the thoracic aorta and is typically localized at the ligamentum arteriosum. An increase in arterial blood pressure above the site of stenosis and a decrease in blood pressure with a faint or impalpable pulse below it are characteristic of this disease. Three theories pertain to the pathogenesis of the prestenotic hypertension:

(1) mechanical, (2) neural, and (3) humoral or renal.

In the mechanical theory the narrowed aorta and the collateral arteries present increased resistance to the myocardium which must be overcome by an increase in arterial pressure. At the same time, blood flow increases as shown by Bing and associates and Blumgart and associates on the basis of flow measurements in the upper limbs; normal blood flow, however, was found by others in both limbs. The neural theory asserts that the hypertension is not dependent upon increased blood volume per unit of time or increased blood flow, but rather upon a vasomotor mechanism which causes an increase in peripheral resistance proximal to the site of coarctation.
The humoral or renal theory is based on experimental observations with animals in which the kidneys seem to have an important pathogenic function by producing humoral substances which give rise to prestenotic elevation in blood pressure.7-10

Since it is possible that renin or angiotensin could be this high blood pressure-inducing factor, we examined plasma renin activity (PRA) in 10 patients with coarctation. In all 10 patients PRA was determined in peripheral venous blood after recumbency and orthostatism, and in three of them, in the venous blood of both kidneys also.

Methods

Ten patients (cases 1 to 10) with coarctation of the aorta were examined, for whom the diagnosis was confirmed on the basis of clinical findings, x-rays, and particularly, blood pressure measurements above and below the site of the stenosis. The ratio of men to women was 6:4. The ages varied from 17 to 38 years (average, 27.6 ± 2.5). There was no evidence of congestive heart failure or of any other diseases. According to the angiographic films, patient 3 showed multiple, segmented renal artery stenoses which could be regarded as functionally meaningless as proved by split renal function tests and by renin determinations. The patients were receiving no antihypertensive or diuretic drugs at the time of this study.

Blood pressure was measured in the aorta above and below the obstruction by means of a 2-mm diameter polyethylene catheter. In three patients (cases 1, 5, and 9) blood pressure was measured simultaneously both above and below the site of coarctation. Plasma renin activity was determined according to the method of Boucher and co-workers.11 The patients received a normal salt diet of 110 mEq of Na/day. The blood for the PRA determination in peripheral venous plasma was drawn after the patient had been in the recumbent position at least 2 hr and again after at least 2 hr in the orthostatic position. In three patients (cases 1, 2, and 3), who likewise had reclined at least 2 hr, the PRA was measured in renal venous plasma from both sides. Each determination was carried out twice. The recovery value of all determinations was 78% ± 12%.

Results

Blood pressures above and below the coarctation were as follows: above the narrowing the systolic pressure varied from 116 to 172 mm Hg (mean ± se, 155 ± 18 mm Hg), the diastolic pressure from 66 to 103 mm Hg (mean, 88 ± 3 mm Hg), and the mean pressure from 84 to 128 mm Hg (mean, 113 ± 4 mm Hg). Distal to the coarctation the systolic pressure varied from 95 to 128 mm Hg (mean, 107 ± 3 mm Hg), the diastolic pressure from 64 to 94 mm Hg (mean, 80 ± 3 mm Hg), and the mean pressure from 76 to 102 mm Hg (mean, 89 ± 3 mm Hg). Accordingly, the gradients of the mean pressures lay

Table 1

| Plasma Renin Activity and Arterial Blood Pressure in 10 Patients with Coarctation of the Aorta |
|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Plasma renin activity (ng/100 ml plasma/3hr) | Arterial blood pressure (mm Hg) |
| Patient | Peripheral venous blood | Recumbent 2 hr | Upright 2 hr | Renal venous blood | Right | Left | Above the coarctation | Below the coarctation | Gradient of the means |
| No. | Name | Age | Sex | | | | Systolic | Diastolic | Mean | Systolic | Diastolic | Mean | |
| 1. | T.A. | 35 | M | | | | 163 | 103 | 128 | 114 | 94 | 102 | 26 |
| 2. | U.G. | 19 | M | | | | 171 | 94 | 119 | 107 | 86 | 94 | 25 |
| 3. | W.B. | 37 | M | | | | 139 | 89 | 110 | 128 | 89 | 101 | 9 |
| 4. | D.E. | 20 | M | | | | 116 | 66 | 84 | 97 | 64 | 76 | 8 |
| 5. | J.B. | 35 | F | | | | 151 | 79 | 106 | 95 | 70 | 81 | 25 |
| 6. | R.G. | 17 | M | | | | 166 | 86 | 117 | 103 | 73 | 80 | 37 |
| 7. | G.D. | 30 | M | | | | 136 | 85 | 104 | 96 | 76 | 83 | 21 |
| 8. | C.T. | 23 | F | | | | 169 | 85 | 115 | 111 | 69 | 84 | 31 |
| 9. | B.T. | 38 | F | | | | 172 | 93 | 121 | 109 | 83 | 91 | 30 |
| 10. | A.A. | 22 | F | | | | 168 | 100 | 125 | 112 | 94 | 102 | 23 |
| Mean | | | | | | | 212 | 663 | 553 | 490 | 155 | 88 | 113 | 107 | 80 | 89 | 24 |
| Standard Error (SE) | | | | | | | 45 | 100 | 122 | 55 | 18 | 3 | 4 | 3 | 3 | 3 |
Figure 1

Renin activity in peripheral venous plasma in patients with coarctation of the aorta.

between 8 and 37 mm Hg (average, 24 ± 3 mm Hg; table 1).

After the patients rested for at least 2 hr in the recumbent position, the PRA was within normal range in nine of the 10 patients (normal range, 0 to 400 ng/100 ml of plasma/3 hr of incubation). Within this range, the values varied between 50 and 260 ng/100 ml/3 hr. In patient 4, the PRA was elevated to 600 ng/100 ml/3 hr. The mean was 212 ± 45 ng/100 ml/3 hr. Patient 4 was also the only one of the 10 patients in whom the PRA rose above the normal range to 1500 ng/100 ml/3 hr after 2 hr in the upright position. The other values ranged between 320 and 740 ng/100 ml/3 hr (mean, 663 ± 100 ng/100 ml/3 hr) and thereby conform to those values which can be estimated in normal persons (normal mean, 652 ± 77 ng/100 ml/3 hr; see fig. 2). The increase in PRA after 2 hr standing was statistically significant (P < 0.001; fig. 1).

The PRA in renal venous blood which was examined in patients 1 to 3 was not elevated since PRA in renal venous blood normally is somewhat higher than it is in peripheral blood. Significant differences between the right and left sides were not encountered. The mean value was 553 ± 122 ng/100 ml/3 hr for the right kidney and 490 ± 55 ng/100 ml/3 hr for the left kidney.

Discussion

The opinion that prestenotic hypertension attendant upon coarctation is conditioned by a renal factor goes back to the experiments of Goldblatt and co-workers in 1939 in which compression of the aorta above the origin of the renal arteries caused an increase in blood pressure. Scott and associates conducted further experiments with dogs in 1951 and 1954, in which they also observed an elevated blood pressure following narrowing of the aorta proximal to the renal arteries. The blood pressure normalized, however, when one kidney was transplanted into the area of the neck, and the second was removed.

Similar observations were made by Svane and Jensen who found that the hypertension does not appear at all if unilateral nephrectomy and transplantation of the second kidney into the region above the coarctation precede experimental coarctation. At the same time, the activity of the juxtaglomerular apparatus in the kidney peripheral to the narrowing was raised and lowered when central to the stenosis. The observation time was 12 months. Determinations for PRA were not carried out.

Circulation, Volume XL, November 1969
Habib and Nanson\textsuperscript{13} experimented on young dogs aged 6 months to 2 years. They also went a step further in that they induced a progressive constriction of the aorta at several localizations above and below the origin of the renal arteries by means of a hygrophilic substance. During the observation period, hypertension manifested itself not only in those dogs in which the aorta was narrowed above the origin of the renal arteries, but also in the dogs in which aortic constriction occurred distal to the origin of the renal arteries. The blood pressure did not return to normal when one kidney was transplanted and the other was removed, but the blood pressure normalized when the narrowed part of the aorta was replaced by a prosthesis. The authors assumed that both the renal and the mechanical factors were important in the pathogenesis of the hypertension. In these experiments, PRA was not measured.

Yagi and co-workers\textsuperscript{14} carried out PRA measurements in their recently published experiments on dogs, in which PRA was measured in peripheral and renal venous blood before and after experimental coarctation. They observed an increase in PRA 1 to 24 hr after surgical stenosis which returned to normal 1 to 2 weeks after the operation although the prestenotic hypertension remained. The elevation in PRA was not dependent on an increased renin substrate concentration, as the angiotensinogen level during the PRA elevation manifested merely insignificant changes. This study showed that only the early, but not the chronic phase of the hypertension was accompanied by PRA stimulation.

Indication of augmented renin secretion in patients with coarctation are rarely found. Morris and associates,\textsuperscript{15} for instance, were able to define an elevated angiotensin level in nine patients with coarctation. However, the method used was not very sensitive, since it could not show evidence of pressor activity in normal persons. Simmons and co-workers\textsuperscript{16} confirmed a lowered responsiveness of the diastolic blood pressure to administration of exogenous angiotensin II in two patients with coarctation, while this responsiveness in two other patients was normal to elevated. However, this angiotensin infusion test allows only approximate conclusions as to the amount of the endogenous angiotensin.\textsuperscript{17} Even after surgical correction of the coarctation, Sealy\textsuperscript{18} found an elevated angiotensin level which had fluctuated within the normal range before the operation. He explained this augmentation as the result of increased excretion of catecholamines which can lead to renin stimulation\textsuperscript{19-21} and which would also be partially responsible for the paradoxical hypertension after surgical correction of coarctation.

Our own studies showed that stimulation of the renin-angiotensin system appeared in only one of our 10 patients. However, the stimulation of the PRA in patient 4 was probably not caused by the coarctation, since in this patient blood pressure proximal to it was the lowest of the group (table 1). As all diseases which may bring about an elevation in PRA\textsuperscript{22} could be eliminated from consideration through diagnostic procedures, no definite explanation can be given for this observation. Because of the clinical picture of this young patient, hyperreactivity of the autonomous nervous system could be considered as the cause of the stimulation of renin secretion.\textsuperscript{19, 23}

If elevated angiotensin activity actually does occur in patients with coarctation, a clear increase in diastolic pressure should be noticeable, since angiotensin II causes elevated peripheral resistance,\textsuperscript{23} and since its effect is seven times stronger than that of norepinephrine.\textsuperscript{24} In coarctation, however, the diastolic pressure proximal to the stenosis is normal to slightly elevated and, to quote an example, significantly lower than that of patients with essential and renovascular hypertension.\textsuperscript{25} Also in our patients there was, at the most, only slight elevation in diastolic pressure proximal to coarctation (mean, 88 ± 3 mm Hg).

Stimulation of the PRA by 2 hr in the orthostatic position was also less pronounced than it is, for instance, in renovascular hypertension after salt deprivation or ortho-
PLASMA RENIN ACTIVITY

statism or both.26-33 It was, instead, comparable to that of normal persons.12, 34 Therefore, the basic and stimulative values of the PRA lay between the findings in primary aldosteronism in which extremely low values are to be found35 and those in renovascular hypertension in which extremely high values can be measured36-38 (fig. 2).

The PRA in renal venous blood was likewise not elevated. This finding seems to us to be especially important, since in some cases of renovascular hypertension the PRA in peripheral blood is normal while that in renal venous blood is elevated.29 We also found normal PRA in renal venous plasma in those patients (cases 1 and 2) in whom the gradients of the mean pressures were relatively high (26 and 25 mm Hg). Despite a high pressure gradient, the renal hemodynamics do not seem to be significantly changed, which, however, is an important condition for PRA stimulation according to contemporary views.28, 30 For instance, Kirkendall and associates37 could find no reduction of renal blood flow or of glomerular filtration rate in 21 patients with coarctation. These parameters did not manifest themselves until congestive heart failure developed as a complication. The results differed significantly from those on patients with essential hypertension. These authors presumed that a general increase in peripheral resistance is not typical for coarctation and that renal factors are not responsible for the hypertension that accompanies it. Whenever increased PRA with coarctation is found peripherally or centrally, the question still remains whether the elevated angiotensin activity actually is causing the hypertension, since there is no parallel relationship between PRA and blood pressure.22 Furthermore, it is important in such cases to eliminate the existence of renal arterial stenosis, as narrowing in the aorta sometimes appears in combination with narrowing in the renal arteries.38 One of our patients (case 3) displayed this combination of coarctation and renal arterial stenosis on both sides.

On the basis of the above-mentioned findings of other authors on animals and of our own studies, the kidneys seem to have an importance in the pathogenesis of hypertension in acute coarctation. After experimental constriction of the aorta, a temporary rise in PRA can be found. In the chronic phase of experimental hypertension or in human hypertension attendant upon coarctation, PRA is not elevated.

Thus, the presence of elevated angiotensin activity despite normal PRA and the existence of a so-called relative hyperreninism cannot be completely excluded.22, 39 Justification for this assumption is found in the fact that several days to weeks after experimental production of renovascular hypertension40-43 or coarctation44 the originally raised pressor activities or PRA return to normal despite the remaining hypertension. Furthermore, the PRA which had been elevated as a result of constriction of the renal artery goes back to normal after removal of the contralateral kidney without simultaneous reduction of the high blood pressure.44 However, lowering in blood pressure can be obtained if those animals with normal renin levels are given by injection antirenin or a renin inhibitor.45, 46

At the present time, it cannot be said with certainty whether the kidneys are essential in the hypertension of coarctation through increased secretion of vasopressor substances or possibly through decreased production of vasodepressor agents47, 48 or whether the neural and mechanical aspects should be given priority as responsible for the high blood pressure. On the basis of our own findings, the humoral or renal theory seems to be of less importance in the pathogenesis of prestenotic hypertension in patients with coarctation of the aorta.

Addendum

Recently Amsterdam et al.49 found normal PRA values in peripheral venous blood in 16 children with coarctation of the aorta. They also suggested that the hypertension associated with coarctation of the aorta is not associated with increased activity of the renin-angiotensin system.

Acknowledgment

We want to thank our technical assistants, Mrs. Barbara Bindschedler, Miss Brigitte Haupt, Mrs.
Deborah Pelli, Miss Ilse Tauber, and Miss Hanne Weiand for their valuable help.

References
28. Del Greco, F., Simon, N. M., Goodman, S.,
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Circulation. 1969;40:731-737
doi: 10.1161/01.CIR.40.5.731
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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