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Plasma renin activity in coarctation of the aorta before and after surgical correction

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SUMMARY In 37 patients with coarctation of the aorta, arterial blood pressure and ambulant plasma renin activity (PRA) were determined before and, in 15 patients, after surgical correction. The systolic blood pressure was raised in all the cases and the diastolic pressure was raised in 30 patients. Ambulant PRA was increased in 11 patients when compared with normal subjects of similar age. Twelve of the 15 operated patients had a significant decrease of systolic pressure after operation. Eight had raised PRA, and in 7 of these PRA fell to normal after operation and the blood pressure also fell; in 1 patient the decrease of PRA was unaccompanied by a fall in blood pressure. Though there was no significant correlation between the changes in blood pressure and PRA after operation it seems possible from our results that the renin-angiotensin system may be activated and contribute to the raised arterial pressure which occurs in patients with aortic coarctation.

Several attempts have been made to establish the pathogenesis of the hypertension which occurs in coarctation of the aorta; essentially three theories have been proposed: a mechanical theory (Blumgart *et al.*, 1931; Bing *et al.*, 1948; Gupta and Wiggers, 1951), a neurogenic theory (Pickering, 1936; Prinzmetal and Wilson, 1936), and a renal humoral theory (Goldblatt *et al.*, 1939; Page, 1940; Scott and Bahnson, 1951; Harrison and Alton, 1954; Scott *et al.*, 1954; Timmis and Gordon, 1964; Svane and Jensen, 1967; Habib and Nanson, 1968). Studies in dogs have shown that constriction of the aorta is followed by a prompt increase in PRA (Yagi *et al.*, 1968) and though this returns to normal within 10 days, it is possible that other mechanisms, possibly not associated with renal ischaemia, maintain the hypertension. In studies in man a number of authors have found supine PRA in coarctation to be within normal limits and have reported normal responses to various stimuli such as the erect position or sodium depletion (Kirkendall *et al.*, 1959; Brown *et al.*, 1965; Amsterdam *et al.*, 1969; Kroetz *et al.*, 1968; Werning *et al.*, 1969; Strong *et al.*, 1970). However, others have reported raised PRA which returned to normal after corrective operation (Morris *et al.*, 1966; Pickens, 1967; Sealy, 1967). In contrast, Markiewicz *et al.* (1975) found low supine values for PRA which rose after operation. In view of these divergent results, we have

measured PRA and blood pressure in 37 patients with coarctation. In 15 of the patients we repeated these measurements after corrective surgery.

Subjects and methods

Observations were made on 37 patients (25 male, 12 female) with coarctation of the aorta, aged 2 to 49 years (Table). All the patients were admitted to the Cardiology Centre of the University of Padua. During the study the patients were maintained on a normal sodium diet (120 mmol per day for adults and about 2 mmol/kg per day for the children), and none had received any antihypertensive or diuretic drug for at least 15 days. The diagnosis of coarctation of the aorta was made from the clinical findings and plain x-ray film. Cardiac catheterisation and angiocardiology confirmed the presence of a significant coarctation at the level of the isthmus, with a systolic arterial pressure gradient across the obstruction (at least 10 mmHg), or a demonstrable collateral circulation bypassing the stenotic area, or both. None of the patients had any other significant disease.

The following procedure was used: the arterial pressure (mean of 3 measurements) was measured in the right arm 3 hours after rising with a Riva-Rocci type sphygmomanometer, using Korotkoff sounds I and IV to determine systolic and diastolic pressure, respectively. Immediately after the blood pressure measurement a blood sample was taken for

Table PRA and blood pressure in patients with coarctation studied before and after operation

Case No.	Age (y)	Sex	Upright PRA (ng/ml per 3 h)		Blood pressure (mmHg)			
			Before operation	After operation	Before operation		After operation	
					Systolic	Diastolic	Systolic	Diastolic
1	6	M	18.4	—	140	90	—	—
2	4	M	9.8	—	130	100	—	—
3	2	M	10.2	—	120	95	—	—
4	18	M	2.4	3.2	180	100	170	100
5	5	M	9.0	8.9	140	90	120	90
6	15	M	16.0	7.6	150	100	130	90
7	16	M	23.6	4.6	160	90	160	90
8	4	F	6.4	—	160	90	—	—
9	10	M	9.4	—	130	100	—	—
10	29	F	8.6	—	170	100	—	—
11	6	F	6.2	—	130	100	—	—
12	49	F	2.4	—	185	105	—	—
13	18	M	6.2	—	150	100	—	—
14	27	F	10.3	9.2	190	100	125	85
15	20	M	3.2	—	170	110	—	—
16	33	F	7.5	—	155	85	—	—
17	6	F	3.6	3.6	140	90	120	90
18	17	M	3.1	2.2	180	80	170	90
19	37	M	5.8	—	190	90	—	—
20	17	M	32.0	5.7	140	90	120	70
21	8	M	15.2	—	130	80	—	—
22	5	M	15.0	—	140	100	—	—
23	20	M	5.8	—	195	85	—	—
24	15	M	4.8	4.0	180	100	130	90
25	38	M	10.0	4.5	200	110	130	90
26	32	M	8.7	2.7	145	75	110	70
27	15	M	21.3	6.3	225	95	200	70
28	10	M	3.5	2.8	150	90	120	90
29	10	M	4.4	—	145	105	—	—
30	11	F	8.8	—	190	130	—	—
31	6	M	5.2	—	130	90	—	—
32	48	M	1.4	—	210	90	—	—
33	39	F	5.0	—	175	95	—	—
34	48	M	4.2	—	180	100	—	—
35	17	F	34.0	6.4	160	100	140	90
36	15	F	9.6	0.5	170	110	130	70
37	22	F	3.6	—	145	75	—	—

the determination of PRA. In 15 operated patients, the same procedure was repeated 20 days after operation, at least 7 days after the discontinuance of all pharmacological therapy. PRA was determined by radioimmunoassay of angiotensin I generated during 3 hours incubation at 37°C, by the method of Stockigt *et al.* (1971), with the omission of rapid boiling at the end of the 3-hour incubation.

The results are reported as mean \pm standard error of the mean. Significance of differences was analysed by Student's *t* test for paired data. In those patients who had operation a reduction of at least 20 mmHg systolic was taken as the criterion for improvement in blood pressure.

For the evaluation of the PRA results the patients were subdivided into 2 groups, the first consisting of 13 patients from 2 to 10 years of age and the second of the 24 patients over 10 years of age. These values were compared with those obtained from 60 normal subjects on the same sodium intake and divided into the same age groups. For each control group the mean \pm 2 SD was calculated.

The arterial pressures were compared with those of the normal subjects of their same age (Master *et al.*, 1950; Moss and Adams, 1962; Londe, 1966; Loggie, 1969; Long *et al.*, 1971).

Results

BASAL VALUES IN ALL PATIENTS STUDIED (Table)
In the 37 cases studied the systolic blood pressure ranged from 120 to 225 mmHg and the diastolic pressure ranged from 75 to 130 mmHg. In all cases the systolic blood pressure was above normal for age though the diastolic was raised in only 30.

The PRA ranged from 1.4 to 34 ng/ml per 3 hours. When the PRA values obtained from the patients were compared with those of age matched normal subjects, the values were raised in 3 of 13 patients in the younger age group (normal range 2.4 to 14 ng/ml per 3 hours) and in 12 of 24 patients in the older group (normal range 3.4 to 7.4 ng/ml per 3 hours). In the first group the mean PRA was 8.9 ± 1.8 ng/ml per 3 hours, not significantly

different from the normal group of the same age. In the second group PRA was significantly greater (9.9 ± 1.8 ng/ml per 3 hours) than in the age-matched control group (5.1 ± 0.3) ($P < 0.05$).

VALUES OBTAINED BEFORE AND AFTER OPERATION (Table)

The systolic blood pressure was above normal for age in all 15 patients and fell significantly in 12 after operation. The diastolic pressure was above normal in 12 patients and fell in 7 cases after operation. In 8 patients the PRA values were above normal; in 6 of these both PRA and systolic blood pressure fell after operation. In one case there was a fall in PRA, but no fall in blood pressure; conversely in one case the PRA remained unchanged, though there was a fall in both systolic and diastolic pressure.

Discussion

The prevailing view in recent papers is that there is no relation between the renin-angiotensin system and arterial hypertension secondary to coarctation of the aorta. This view is based on reports by several authors of PRA values which were more or less normal in patients with coarctation (Kirkendall *et al.*, 1959; Brown *et al.*, 1965; Kroetz *et al.*, 1968; Amsterdam *et al.*, 1969; Strong *et al.*, 1970; Markiewicz *et al.*, 1975); furthermore, they found that the renin-angiotensin system was normally responsive to various stimuli. On the other hand, some authors, albeit in a small number of cases, have found high PRA values (Morris *et al.*, 1966; Pickens, 1967; Sealy, 1967). These studies contrast with our findings that PRA was high in 40 per cent of 37 cases. Close scrutiny of our data and that of other studies, especially that of Strong *et al.* (1970), reveals differences which may explain these contradictory results. The first point that must be kept in mind is the difficulty in establishing normal values in a study of patients of varying ages, especially when there is a high percentage of patients in the paediatric age group. It is well known, and we have confirmed this, that for a given sodium intake (per kg body weight), PRA values are higher in the first few years of life than in adulthood, and that PRA values decrease to near adult levels at puberty. We, therefore, defined the upper limits of normal in 2 separate age groups. Furthermore, the biological method used by other authors for PRA determination may be less sensitive than the radioimmunoassay technique used in our study. Finally, all the patients we studied were evaluated after a long period in the upright position, whereas in most of the previous studies the patients were usually studied supine. The importance of this stimulus is

apparent from the recent experiments by Bagby *et al.* (1975) in dogs with chronic coarctation of the aorta. Under normal basal conditions, no variations in renal haemodynamics or renin activity were evident, but sodium deprivation caused a significant decrease in renal perfusion along with an exaggerated rise of PRA. These authors suggested that sodium deprivation disturbs renal perfusion usually held in equilibrium by compensating factors.

It is possible that in patients with coarctation of aorta maintenance of the upright position, as in our study, may act as a stimulus to renin activity so that the modest reduction in critically balanced renal perfusion provokes an excessive renin response. This phenomenon could explain the very high values which we found in some of our patients. Certainly hyper-responsiveness to postural change has been shown to exist in patients with renal artery stenosis in whom the upright position may cause a very large increase of PRA, and indeed this stimulus has been used to amplify the differences in PRA between a normal kidney and one with renal artery stenosis (Michelakis *et al.*, 1969).

Although we did not find any correlation between the level of the blood pressure and PRA, the possibility that angiotensin might contribute to the maintenance of hypertension is suggested by experiments on animals with experimental renal artery stenosis where the administration of antirenin antibodies or of angiotensin II analogue Saralasin may restore a normal blood pressure even when the PRA is normal (Davis *et al.*, 1974; Laragh, 1975). Furthermore, it has been shown recently in 2 patients with coarctation of the aorta that the administration of Saralasin can reduce arterial pressure (Ribeiro and Krakoff, 1976).

It was possible to measure PRA values both before and shortly after operation in 15 patients, in 12 of whom systolic pressure was significantly reduced by operation. Of particular interest were those 7 patients who had a raised PRA before surgery in whom a fall in blood pressure and also of PRA was observed after operation.

At this time, the relation between the activity of the renin-angiotensin system and the hypertension which occurs in patients with coarctation is not easily understood from conflicting published reports or from contradictory data produced by our own study.

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