PATHOPHYSIOLOGY AND NATURAL HISTORY
COARCTATION REPAIR

Increased forearm vascular reactivity in patients with hypertension after repair of coarctation

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ABSTRACT To determine whether altered vascular reactivity could contribute to hypertension after repair of coarctation, the change in forearm and calf vascular resistances to small intra-arterial infusions of norepinephrine were measured in six patients who had undergone surgical correction of coarctation of the aorta but still had upper extremity hypertension and compared with similar measurements made in five normotensive patients with mild heart disease. Only the mean upper extremity pressure was significantly greater in the group that underwent repair of coarctation (102 ± 11 vs 83 ± 5 mm Hg, p < .05, for mean arm pressures and 96 ± 13 vs 83 ± 7 mm Hg for mean leg pressures in patients who had coarctation vs normotensive patients, respectively). Forearm and calf blood flows were measured in the right arm and leg with a mercury-in-plastic strain-gauge plethysmograph. Forearm and calf vascular resistances were calculated by dividing mean arterial pressure of the appropriate extremity by the blood flow of that extremity. Norepinephrine was infused into the right brachial and femoral arteries of the patients at doses of 0.02, 0.05, 0.1, 0.2, 0.3, 0.5, and 0.7 µg/min. Resting forearm and calf vascular resistances were similar in both groups of patients. The norepinephrine dose-response curves showed that control patients required more than three times the norepinephrine to produce the same percent increase in forearm vascular resistance (after 0.2 µg/min forearm vascular resistance increased by 55% in the coarctation group, while the resistance in the control group increased by only 3%, p < .05). There was no difference between the two groups with regard to the dose-response curves for calf vascular resistance. These data suggest the presence in the resistance vessels anatomically positioned above the coarctation of abnormal vascular reactivity that may have persisted despite successful repair. Circulation 71, No. 3, 495-499, 1985.

AFTER successful repair of coarctation of the aorta, a significant percentage of patients will have resting hypertension.1-3 Furthermore, many patients who have undergone successful repair of coarctation and are normotensive at rest will have a hypertensive response to exercise in their right arms and may develop a residual gradient across the coarctation.4 Previous investigations have suggested that abnormalities of the vascular bed anatomically positioned before the coarctation (precoarctation vascular bed) may play a role in this hypertension. We have previously reported abnormalities of baroreceptor function in such patients5 and Samanek et al.6 have shown differences in maximal muscle blood flow between the upper and lower extremities of patients after coarctectomy, suggesting differences in resistance vessels in the precoarctation and postcoarctation vascular beds (those positioned after the stricture). With the use of specimens obtained at coarctectomy, Sehested et al.7 have shown in vitro and with histologic evidence that the precoarctation vessel wall is more rigid than the postcoarctation vessel wall.

Because of these findings, we hypothesized that the precoarctation vascular bed has abnormal vascular reactivity to adrenergic stimuli that persists after adequate repair of coarctation.7-9 To test our hypothesis, we assessed changes in both right forearm and calf vascular resistances in response to intra-arterial infusions of norepinephrine in patients who had undergone repair of coarctation and were mildly hypertensive and compared their responses with those of patients in a control group.

Materials and methods
Six patients who had undergone coarctectomy and were undergoing cardiac catheterization to assess the hemodynamic cause of their residual mild resting hypertension and severe
TABLE 1

Pertinent clinical data from six children with repaired coarctation (patient Nos. 1 to 6) and five control patients (Nos. 7 to 11)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Diagnosis</th>
<th>Age (yr)</th>
<th>Age at repair of C of A (yr)</th>
<th>At rest</th>
<th>During treadmill exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rt. arm BP (mm Hg)</td>
<td>Rt arm-rt leg systolic gradient (mm Hg)</td>
</tr>
<tr>
<td>1</td>
<td>Patch aortoplasty</td>
<td>13.8</td>
<td>12.9</td>
<td>142</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>Patch aortoplasty</td>
<td>18.2</td>
<td>13.8</td>
<td>145</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>End-to-end anastomosis</td>
<td>14.4</td>
<td>6.8</td>
<td>141</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>End-to-end anastomosis</td>
<td>19.0</td>
<td>11.9</td>
<td>146</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>End-to-end anastomosis</td>
<td>17.1</td>
<td>6.8</td>
<td>141</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>End-to-end anastomosis</td>
<td>18.3</td>
<td>7.2</td>
<td>148</td>
<td>85</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>16.8</td>
<td>9.9</td>
<td>144</td>
<td>75</td>
</tr>
<tr>
<td>± SD</td>
<td></td>
<td>± 2.0</td>
<td>± 3.1</td>
<td>± 2</td>
<td>± 9</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td>NS</td>
<td>&lt; .05</td>
<td>NS</td>
<td>.06</td>
</tr>
<tr>
<td>7</td>
<td>Mild PS</td>
<td>14.0</td>
<td>—</td>
<td>115</td>
<td>76</td>
</tr>
<tr>
<td>8</td>
<td>TOF repair; mild PS</td>
<td>19.0</td>
<td>—</td>
<td>125</td>
<td>78</td>
</tr>
<tr>
<td>9</td>
<td>Mild PS</td>
<td>20.2</td>
<td>—</td>
<td>136</td>
<td>75</td>
</tr>
<tr>
<td>10</td>
<td>Mild AS</td>
<td>13.6</td>
<td>—</td>
<td>108</td>
<td>78</td>
</tr>
<tr>
<td>11</td>
<td>VSD repair</td>
<td>19.5</td>
<td>—</td>
<td>122</td>
<td>76</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>17.3</td>
<td>—</td>
<td>121</td>
<td>76</td>
</tr>
<tr>
<td>± SD</td>
<td></td>
<td>± 3.2</td>
<td>± 11</td>
<td>± 2</td>
<td>± 1</td>
</tr>
</tbody>
</table>

AS = aortic stenosis; AsAo = ascending aorta; C of A = coarctation of aorta; HR = heart rate; NS = not significant at p < .05; PS = pulmonic stenosis; Rt = right; TOF = tetralogy of Fallot; VSD = ventricular septal defect; ex = exercise.

*Catheterization vs control.

hypertension in response to exercise formed the experimental group; five patients with mild heart disease formed the control group (table 1). All patients were enrolled in the protocol as an adjunct to diagnostic cardiac catheterization. Informed consent was obtained from all according to guidelines established by institutional review.

Two separate norepinephrine infusions were given to each patient, one into the right brachial artery and one into the femoral artery contralateral to the site of percutaneous entry for catheterization. Each infusion was begun at a rate of 0.02 μg/min and increased in a stepwise fashion at 5 min intervals to a rate of 0.7 μg/min. During the selective infusion studies heart rate and mean arterial pressure remained unchanged (table 2).

Thus, selective infusion of norepinephrine was achieved without systemic effects.

Blood pressure was measured by indwelling catheter in the ascending aorta for forearm infusions and in the descending aorta for femoral infusions. Mean arterial pressure was calculated by electrical integration. Forearm and calf blood flows were measured by mercury-in-plastic strain-gauge plethysmography (D. E. Hokanson Inc.; EC-3 plethysmograph). For each infusion rate the average of four blood flows measured during the last minute of the infusion was considered the blood flow for that rate. Figure 1 illustrates characteristic tracings from one patient in each group. Vascular resistance was calculated by dividing mean arterial blood pressure by blood flow. Because a significant change in vascular resistance is defined as a 50% increase in resistance from baseline levels, percent change in vascular resistance from initial values was calculated for each patient at each norepinephrine infusion rate.5, 7 Dose-response curves for each patient group were then generated by plotting percent change in resistance (relative units) against norepinephrine concentration on semilogarithmic paper.

Statistics. Within each group mean ± SEM percent change in vascular resistance was calculated at each infusion rate; results in the two groups were compared by a two-factor analysis of variance for repeated measures (profile analysis). Slope coefficients for the last four infusion points were calculated for each group by linear regression analysis. Since the assumption of normally distributed data could not be assessed as a result of the small sample sizes, statistical analyses comparing patients who

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had coarctation and control patients were completed with both parametric (Student's t test) and nonparametric (the median test) procedures. The findings were quite similar. Thus, means, SDs, and the results of the median tests are presented. In particular, the slope coefficients were then compared by the median test, which was also used to compare prestudy variables in the two groups, and to compare the prestudy values with those at the infusion rate at which vascular resistance increased by 50% in the coarctation group.

Results

Pertinent prestudy data are presented in table 2. Patients in the coarctation group had a significantly higher resting systolic blood pressure than the control patients and were mildly hypertensive. These patients had small peak systolic gradients across the repaired aorta, as assessed by intra-aortic pressure measurement and cineangiography. Initial forearm and calf resistances were not statistically different.

The changes in forearm blood flow at increasing norepinephrine infusion rates in two patients, one from each group, are depicted in figure 1. The patient who had undergone coarctectomy experienced a decrease in forearm blood flow at a lower norepinephrine infusion rate compared with the control patient.

The percent change in forearm vascular resistance at increasing norepinephrine infusion rates for all the patients is depicted in figure 2. Profile analysis demonstrated that the responses of the patients in the two groups were not parallel (p > .02). In particular, at an infusion rate of 0.2 μg/min, forearm vascular resistance in the coarctation group increased 55% while in the control group resistance increased only 3% (p > .01). The control group did not develop a 50% increase in forearm vascular resistance until the infusion rate reached 0.7 μg/min, three times the rate inducing a similar response in the coarctation group. Slope coefficients calculated from the last four infusion points showed a more rapid increase in resistance in the coarctation group (230% change/μg/min in the coarctation group vs 103% change/μg/min in the control group; p = .008). Thus, the coarctation group has a much lower threshold for response to adrenergic stimuli in the forearm vascular bed and a more rapid response as well.

Figure 3 depicts the change in calf vascular resistance at increasing infusion rates. Both groups had similar dose-response curves, with a 50% increase in resistance achieved at an infusion rate of 0.5 μg/min. Thus, there was no difference in vascular reactivity in
FIGURE 2. Percent changes in forearm vascular resistance at increasing norepinephrine infusion rates for the coarctation (●) and control (○) groups. In the patients who had undergone coarctectomy there was a significantly more rapid rise in vascular resistance (p = .02, profile analysis).

the two groups in the calf, a postcoarctation vascular bed.

Discussion

Infusion of small concentrations of norepinephrine into a peripheral vascular bed and measurement of changes in blood flow have been used to assess vascular reactivity in patients with systemic hypertension. Studies have shown that patients with essential hypertension require much lower concentrations of norepinephrine to produce a 50% increase in vascular resistance than do normotensive control subjects. The present study has demonstrated a significant increase in forearm vascular reactivity in mildly hypertensive patients who have undergone successful coarctectomy when compared with that in normotensive patients with mild heart disease. However, unlike other studies of vascular reactivity and hypertension, we have demonstrated that this change in vascular reactivity is not uniform throughout the body. While forearm vascular reactivity is abnormal, calf vascular reactivity is not, despite the fact that five of six of the patients who underwent coarctectomy also had mild hypertension in their legs. Since we observed a difference in forearm vascular reactivity only, our results suggest this difference in vascular reactivity is not merely due to the presence of mild residual hypertension, but rather probably results from secondary structural alterations of the pre-coarctation vascular bed that persist despite adequate repair of coarctation. In addition, even though neither we nor other investigators have studied the relationship between changes in vascular reactivity of the forearm and changes in other vascular beds, we feel it is reasonable to assume that in our patients with repaired coarctation, the right forearm vascular bed is probably representative of other vascular beds in the upper half of the body. Further studies in animals will be necessary to prove whether this assumption is accurate or not.

Previous studies using a norepinephrine infusion technique to assess vascular reactivity have assessed changes in resistance by comparing those at each level of infusion to simultaneous measurements in the contralateral extremity. We did not feel reliable measurements in the left arm could be made in our patients with coarctation because the left subclavian artery may have been involved with the coarctation process itself or the repair. We therefore used resting right forearm or calf resistance measurements as our baseline value. We feel these measurements were reliable for two reasons: First, at low infusion rates, there was no significant change in resistance measurements, suggesting that there was little change in basal sympathetic tone during the study. Second, at higher infusion rates, significant changes in extremity resistance occurred without a significant change in systemic blood pressure, suggesting that the infusion did not have a systemic effect.

Another factor of importance for interpretation of the dose-response curves is the difference in basal forearm blood flow between our two groups of patients. Since the blood concentration of a drug depends not
only on the amount of the drug injected per unit of time but also upon the blood flow into which it is admixed, it is possible that the differences between our patient groups could have solely been due to differences in resting basal blood flow. As can be seen from table 2, on the average patients in the control group had lower basal blood flow than patients who had coarctation, so that if the difference between the groups was solely the result of differences in blood flow the patients in the control group would have had increased vascular reactivity. We therefore do not believe that the differences observed between the two groups of patients was solely due to differences in resting blood flows.

The results of this study are consistent with those of other studies that have suggested that coarctation produces significant vascular injury to the precoarctation vascular bed. Samanek et al.6 using a 133Xe clearance technique, demonstrated differences in maximal muscle blood flow during exercise in the precoarctation and postcoarctation vascular beds of 58 patients who had undergone coarctectomy an average of 11.5 years before the study. In the control group there was no difference in maximal blood flow in the upper and lower extremities. The blood pressures of the subjects in this study were not reported. Sehested et al.7 demonstrated in vitro and with histologic evidence that there was an increased rigidity of the precoarctation vascular bed in pathologic specimens obtained at coarctectomy. Precoarctation specimens showed more collagen and less smooth muscle than did postcoarctation specimens and coarctation specimens also showed greater contractility in vitro when stimulated with potassium, noradrenaline, or prostaglandin F2α. These characteristics were not observed in normal aortas. Beekman et al.8 have shown abnormal aortic baroreceptor function in the same group of patients with repaired coarctation reported in the present study. A possible explanation for this abnormality could be diminished distensibility of the precoarctation vascular bed caused by the vascular changes described by Sehested et al.7 and in the present study.

Although we have not documented a direct pathophysiologic relationship between abnormalities in forearm vascular resistance and the hypertension observed in patients who have undergone coarctectomy, we believe this abnormal vascular reactivity may play a role in the pathogenesis of exercise-induced hypertension. During exercise, cardiac output and catecholamine levels both increase. The precoarctation bed may be more sensitive to catecholamines than the postcoarctation bed, creating a disproportionate increase in vascular resistance in the former. Under these conditions, blood would be shunted across the site of the repaired coarctation into the postcoarctation vascular bed. If the repair site were either less distensible than the normal aortic tissue and/or slightly smaller than the normal descending aorta, a gradient could be created, and hypertension would develop in the precoarctation vascular bed. To confirm this hypothesis, an assessment of vascular reactivity in normotensive patients who have undergone coarctectomy must be undertaken. To date, however because of the invasive nature of these studies we have been unable to assess vascular reactivity in such patients.

In summary, we have demonstrated abnormal forearm vascular reactivity and normal calf vascular reactivity in patients who have undergone coarctectomy and have mild residual hypertension. These data can be explained by the presence in the precoarctation resistance vessels of abnormal vascular changes that persist despite successful repair. These vascular abnormalities may be related to the increased incidence of hypertension seen after repair of coarctation.

References
Increased forearm vascular reactivity in patients with hypertension after repair of coarctation.
S S Gidding, A P Rocchini, C Moorehead, M A Schork and A Rosenthal

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