Decreased Renal Perfusion after Correction of Experimental Coarctation

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ABSTRACT. Hemodynamical changes in coarctation were studied with an experimental model. Coarctation of the thoracic aorta was induced in seven puppies at the age of 8 wk. After a 7-month follow-up period a corrective operation with a venous patch was performed. Two dogs were lost a few hours after the correction operation. The remaining five dogs were followed for 12 months postoperatively. Renal perfusion was measured with a ^{133}Xe washout method just prior to the operation, 1 h, 6 and 12 months postoperatively. The glomerular filtration rate was measured using the ^{51}Cr -EDTA method 1 wk before the operation, 3 wk, 2, 6, and 12 months after it. Six healthy adult dogs were used as controls for glomerular filtration rate measurements. Peripheral renin activity was measured at operation, just before the correction of aortic coarctation, $\frac{1}{2}$, 1 h, 1, 3, 7 days, 2 and 6 months after the correction operation. Renal perfusion decreased significantly ($p < 0.05$) immediately after the correction operation and rose again during the follow-up. Peripheral renin activity rose significantly ($p < 0.01$) from the preoperative values and was at its greatest 1 day after the operation. Later on, peripheral renin activity values returned to normal. Coarctated dogs had significantly ($p < 0.01$) lower glomerular filtration rate values than controls in each measurement except at the 2 months postoperative measurement. These results support decreased renal perfusion with resultant increased peripheral renin activity as part of the pathomechanism of the paradoxical hypertension observed after correction of coarctation. (*Pediatr Res* 22:445-448, 1987)

Abbreviations

CoA, aortic coarctation
RP, renal perfusion
PRA, plasma renin activity
GFR, glomerular filtration rate
BP, blood pressure

Operative correction of CoA was first performed approximately 40 yr ago (1). Despite the good overall postoperative results, there are complications and symptoms such as paradoxical hypertension and long-term hypertension occurring after the corrective operation of thoracic CoA (2-4). The pathomechanisms of paradoxical hypertension have been widely studied, but the postoperative hemodynamical changes are still unknown.

Attention has been paid to the possible role of the kidneys in

both short- and long-term postoperative findings. Rocchini *et al.* (5) found that renin activity was significantly increased immediately postoperatively. Before the studies of the activity of renin-angiotensin system it was suggested that a high set of the baroreceptors will increase the release of norepinephrine thus causing hypertension (6, 7). Also, there are certain structural changes found both in the aorta and coronary arteries which may contribute to the pathomechanism of long-term hypertension (8, 9).

Because the methods to accurately measure renal hemodynamics are invasive, we developed an experimental model to study hemodynamical changes in CoA (10). Herein we report the results on the studies of RP, PRA, and GFR performed preoperatively, at the operation, and postoperatively in dogs.

MATERIALS AND METHODS

Coarctation of the thoracic aorta was induced in seven puppies at the age of 8 wk with a silk ligature just distal to the origin of the left subclavian artery (10). The weights of the puppies varied from 1840 to 2620 g. After a 7-month follow-up period when the dogs were 9 months old, a correction operation was performed. At operation, the constriction of the thoracic aorta was corrected with a venous patch taken from the left external jugular vein. Two dogs were lost because of postoperative respiratory insufficiency due to anesthesia a few hours after the correction operation. There were no operative complications during the procedures. The remaining five dogs were followed for 12 months postoperatively. Thus the total follow-up time was 1 yr and 7 months in each dog.

RP was measured with a ^{133}Xe washout method just before and a $\frac{1}{2}$ h after correction of CoA (11). During the follow-up period RP was measured both 6 and 12 months postoperatively. The dogs were anesthetized with pentobarbital sodium (30-40 mg/kg), intubated and breathed spontaneously during the measurements. A 40-200 MBq (1-5 mCi) dose of ^{133}Xe in 1-2.5 ml of saline was used. The injection was given through a catheter placed into the aorta above the origin of the renal arteries via the femoral artery. BP was measured from the aortal catheter before and after the RP measurement with a strain-gauge transducer and a multichannel recorder (Hewlett-Packard Co., Palo Alto, CA).

The glomerular filtration rate was determined using the ^{51}Cr -EDTA method by taking blood samples 90, 150, and 210 min after an intravenous injection of ^{51}Cr -EDTA. GFR was calculated on the basis of the decrease in radioactivity in the blood samples. GFR was measured 1 wk before the operation and 3 wk, 2, 6, and 12 months after operation. Six healthy adult dogs living in the same laboratory environment and who were about the same age were used as controls for GFR measurements.

Plasma renin activity was determined using reagent kits from Clinical Assays, Inc., Cambridge, MA according to the manufacturer's instructions. The measurements were performed at operation, just before the correction of CoA and $\frac{1}{2}$ and 1 h after the

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operation. Later, PRA was measured 1, 3, and 7 days and 2 and 6 months after the correction operation.

Development of hypertension was followed by measuring BP regularly from the left front leg of the dogs with an ultrasound device (Arteriosonde, Roche). For this measurement, no anesthesia was necessary. Earlier we found that indirectly measured values correlated well with directly measured values (11).

Cardiac output was measured by thermodilution simultaneously with RP measurements immediately before and a ½ h after the correction operation.

Significance values of differences measured at the different occasions were analyzed first with a two-way analysis of variance and if this gave a significant *F* value, analysis was continued with a paired *t* test. Our "goal" was to test the differences of the values before and after the correction operation. The paired comparisons were thus made only with these values. The differences to the values of the control group were tested with an unpaired *t* test.

RESULTS

The mean weight of the dogs after follow-up time was 11.9 kg, weight varying from 10.9 to 13.2 kg. Hypertension above the coarctation developed in each dog, the mean BP being 216/124 mm Hg, as measured indirectly. The dogs remained hypertensive even after the correction operation (Fig. 1).

One dog had a significant systolic gradient, *i.e.* 15 mm Hg, after the correction operation. Three dogs had no gradient and one dog had a 5 mm Hg gradient in the thoracic aorta postoperatively in anesthesia. At operation, pulse pressure below the coarctation rose significantly from the mean value of 9 mm Hg (SD 5) before the correction to the value of 22 mm Hg (SD 6, $p < 0.01$) postoperatively. The mean BP values in the distal aorta remained at the same level; it was 82 mm Hg (SD 16) before and 86 mm Hg (SD 12) after the operation. Cardiac output remained about the same and was 2.4 l/min (SD 0.9) preoperatively and 2.2 l/min (SD 0.7) 1 h postoperatively.

RPs decreased significantly from preoperative values of 2.83 (SD 0.75) to 2.39 (SD 0.45) ml/min/g ($p < 0.05$) immediately after the correction operation (Fig. 2.) and rose again during the follow-up (Fig. 3.). PRA rose significantly ($p < 0.01$) from the preoperative values of 2.8 (SD 1.69) $\mu\text{g/liter/h}$ and was at a maximum 1 day after the operation and was 6.4 (SD 3.99) $\mu\text{g/liter/h}$ (Fig. 4.). Later, PRA values returned to normal (Fig. 5.).

The GFR rose temporarily as compared to the preoperative values 2 months postoperatively (Fig. 6.). The mean GFR of the control group was 55.3 ml/min (SD 11.1). When comparing this to the respective value of coarctated dogs, they had significantly ($p < 0.01$) lower values in each measurement except at the 2-month postoperative measurement.

Fig. 1. Blood pressure (mean, SD) in the proximal aorta before correction of CoA and 3 days, 7 days, 2, 6, and 12 months postoperatively. Measured indirectly without anesthesia in five dogs.

Fig. 2. RP values before and 1 h after correction of CoA in five dogs. The decrease from 2.83 to 2.39 ml/min/g is statistically significant ($p < 0.05$).

Fig. 3. Mean RP preoperatively and 1 h, 6 and 12 months after correction of CoA in five dogs. The mean value 1 h after the operation is significantly decreased ($p < 0.05$).

DISCUSSION

Paradoxical hypertension after CoA operation occurs in 37–100% of operated patients (3, 7). Gastrointestinal and neurological symptoms occur in 2–28% of patients (3, 12). The significant decrease in RP and the significant increase in PRA after the correction operation found in our study may well be the basic pathomechanism responsible for the rise in BP occurring 1 to 2 days after the operation in coarctated patients. We did not measure BP systematically during the first 2 days after the operation and so any possible paradoxical hypertension was not detected. On the 3rd postoperative day BP was not increased as compared to preoperative values. Also PRA activity was decreased to nearly preoperative values.

In the dogs with corrected CoA BP remained higher than in the controls. In our earlier study we found significant morphological changes in the aortal wall (8). Failure of reversal of these structural changes may be the cause of the permanent hypertension in the coarctated dogs.

Fig. 4. PRA before and 1 day after correction of CoA in five dogs. The activity rose significantly (mean value from 2.8 to 6.4 $\mu\text{g}/\text{liter}/\text{h}$, $p < 0.01$).

Fig. 5. Mean PRA before and after correction of CoA. The mean value 24 h postoperatively is significantly increased ($p < 0.01$).

Fig. 6. Mean GFR values before and 3 wk, 2 and 6 months after correction of CoA in five dogs. Six healthy dogs were used as controls. *GFR is significantly lower ($p < 0.01$) as compared to controls.

Rocchini *et al.* (5) found increased PRA in patients operated on for coarctation. PRA is stimulated in different kinds of stress conditions and its increase may have been caused by the operation only. The finding of a postoperative decrease in RP strongly supports the pathophysiological importance of a high PRA in paradoxical hypertension. The postcoarctectomy syndrome with paradoxical hypertension, abdominal pain and tenderness, intestinal bleeding, fever, and leucocytosis has been suggested to be caused by severe, reactive vasospasm (12). Our finding of decreased RP after correction of CoA supports this mechanism.

Collateral circulation in coarctation is so well developed that there is no decrease in RP, even though the aorta is closed (10). Thus the magnitude of the circulation is normal, but there is a remarkably decreased pulsation in the circulation. The only marked postoperative hemodynamical change in the circulation below the coarctation was increased pulse pressure. Cardiac output and blood pressure remained at about the same level. It may be that the sudden pulsative blood flow causes a vasoconstriction in the vessels of the kidneys and leads to a decrease in RP. Another possibility to the vasospasm of renal vessels could be an increased activity of the renin-angiotensin system. We found, however, a decreased RP 1 h after correction of CoA and at that time PRA was still normal.

Moreno *et al.* (13) speculated that hypoperfusion distal to CoA during correction operation is the cause of the postcoarctectomy syndrome. The excellent collateral circulation that develops in severe CoA as in our experimental model, does not support this (10). It should be remembered, however, that the development of collateral circulation is dependent on the severity of the constriction. In mild CoA cases collateral circulation is poorly developed and thus the closure of the aorta may lead to ischemic damages. Yet the most serious form of these kinds of complications is the paralysis of the lower limbs postoperatively, with a frequency of about 0.4% (14).

Stimulation of the adrenal medulla to secrete more catecholamines is a common theory to explain the pathomechanisms of the postcoarctectomy syndrome. Benedict *et al.* (15) measured the concentrations of norepinephrine, epinephrine, and the activity of dopamine- β -hydroxylase in the urine of patients undergoing coarctectomy and compared these results to those of control patients who had other types of major operations. As expected, concentrations of these hormones rose in both groups, but much less in the control group (15). Earlier, Sealy (6) reported similar results, observing a good BP response to sympathetic blocking agents. In a situation of decreased blood flow and imminent ischemia it is logical to find increased secretion of epinephrine and norepinephrine.

We found previously that RP was not permanently decreased in our experimental CoA as compared to the control dogs (11). In the present study there was a significant decrease in GFR as compared to the controls. This difference disappeared temporarily 2 months after the CoA operation. Even though there was a change in GFR, no difference was found in other function studies of the kidneys. Bagby *et al.* (16) found that in normal conditions in their experimental CoA, kidney function studies were comparable to that of the controls. When the coarctated animals were stressed with dehydration or furosemide, there was a significant decrease in the function of the kidneys of the CoA animals as compared to the controls. It seems that our finding of decreased GFR has no clinical importance in normal situations, but it may mean that the reserve capacity of the kidneys in CoA is significantly decreased.

Observations of a small number of patients undergoing CoA operation have shown that PRA increases and may cause paradoxical hypertension postoperatively (5). Parker *et al.* (17) found a decrease in BP during an angiotensin antagonist (Saralasin) test in six of eight patients after correction of aortic coarctation, indicating the role of the renin-angiotensin system in the pathomechanism of paradoxical hypertension.

There are no studies available regarding the hemodynamic changes in patients after a correction operation. The present results in dogs implicate decreased RP which causes increased PRA and high blood pressure as part of the pathomechanism. It may be that the blood flow also is decreased in the mesenteric arteries. Our findings are clinically important and thus they indicate the urgent need of this kind of study in patients after coarctectomy.

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