Resting and Exercise Renal Blood Flows in Immature
Ovine Aortic Coarctation
Impact of Gradient Relief

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SUMMARY. The primary purpose of this study was to determine whether a neonatally induced thoracic aortic coarctation reduces renal blood flow during physiological stress (treadmill exercise), and whether relief of the gradient returned renal blood flow during exercise to normal. Two ancillary questions were also addressed: does a coarctation alter the responses of enteric and other visceral vascular beds to treadmill exercise? Eight newborn lambs that underwent sham thoracotomy with placement of left atrial lines served as controls; in seven lambs we also created a recently described form of dilatable juxtaductal coarctation. This preparation is unique in that, like human coarctation, the obstruction does not get worse as the animal grows. Rest and exercise vascular pressures and regional blood flows were determined 2–2 1/2 months after surgery. Coarctations were relieved with balloon dilation angioplasty catheters, inserted percutaneously. Postdilation rest and exercise hemodynamic studies were performed, at the same level of exercise, 24 hours after dilation. Renal blood flow did not change with exercise in the control animals. In lambs with coarctation, renal blood flow fell (~22%, P < 0.01) during exercise. Unexpectedly, an exercise-induced fall in renal blood flow (~22%, P < 0.001) persisted even after effective relief of the coarctation (descending aortic blood pressure fell 25% with exercise predilation, but remained unchanged with exercise postdilation). Blood flow to the terminal ileum and cecum followed a qualitatively similar pattern to that of renal blood flow in control, predilation, and postdilation lambs, and this pattern was distinct from that of other enteric and visceral organ flows. These results demonstrate an expected abnormality in the regulation of exercise renal blood flow in lambs with coarctation of the aorta; however, the persistence of this abnormality after effective gradient relief does not support the previously advanced theory that postcoarctation hypertension is largely nonrenal in origin. The apparent similarity between ileocecal and renal blood flow control under these circumstances may provide a clue to the known predilection of the terminal ileum to suffer ischemic injury. (Circ Res 53: 644–654, 1983)

EARLIER in this century, the hypertension above an aortic coarctation was attributed to abnormal aortic wall compliances (Blumgart et al., 1931; Bing et al., 1948). Subsequently, however, renal autotransplantation experiments indicated an important role of the kidney in producing this hypertension (Scott and Bahnson, 1951), presumably on the basis of impaired renal blood flow (RBF) (Parker et al., 1982). Despite this, previous attempts to document a coarctation-associated decrease in renal perfusion have either been unsuccessful (Harris et al., 1950; Fallo et al., 1978), or have required the unphysiological stresses of marked sodium restriction and/or general anesthesia (Bagby et al., 1975; Alpert et al., 1979). Thus, the mechanism by which a coarctation produces hypertension remains unresolved.

More recently, the advent of successful surgical correction for coarctation has uncovered a second abnormality of blood pressure control in that lesion: paradoxical postcoarctation hypertension, as recently reviewed by Nanton and Olley (1976). This hypertension frequently occurs not only acutely (i.e., in the first week after repair), but also may evolve into chronic hypertension. Recent studies into the genesis of acute postcoarctation hypertension, performed largely in humans, have implicated nonrenal causes, such as the "silent" residual obstruction seen late postoperatively (Freed et al., 1979), catecholamine excess (Rochini et al., 1976), and a resetting of the carotid sinus baroreceptor (Sehested et al., 1982). Animal studies into postcoarctation hypertension have been limited (Igler et al., 1981); surgically created "coarctations" are difficult lesions to correct at reoperation and previously have required a major thoracic operation. Thus, the possibility that a persistent abnormality in renal perfusion may contribute to the acute form of postcoarctation hypertension has not been explored.

We have recently described an experimental form of aortic coarctation in newborn lambs which is unique from all other such preparations in that the aortic gradient remains stable with animal growth (Lock et al., 1982). In this preparation, the coarctation can be successfully relieved without a thoracotomy by a balloon-tipped dilating catheter. We have used this preparation to address three questions:
How does a neonatally induced, nonprogressive aortic coarctation influence renal and visceral blood flows at rest? Does a modest physiologic stress (i.e., submaximal treadmill exercise) produce abnormalities in blood flow distribution in such animals? Does reduction of the aortic gradient restore resting and exercise blood flow patterns to normal in the immediate postcorrection period?

**Methods**

**Creation and Correction of Aortic Coarctation**

This dilatable form of aortic coarctation, and the protocol used for gradient relief, have been described in detail previously (Lock et al., 1982). Briefly, 3–21-day-old lambs underwent a left thoracotomy, the proximal descending aorta was dissected free for a distance of 2–3 cm, and the nonpatent ductus arteriosus was ligated and divided. A posterior wedge of aortic wall, comprising 50% of the aortic diameter, was resected posteriorly and repaired with running 5-0 polypropylene suture. The narrowed segment was then wrapped with 2-0 catgut suture (Fig. 1). In each lamb, we strove for an intraoperative gradient of 40–60 mm Hg, larger gradients being generally fatal in the immediate postoperative period. An 8F heparin-filled umbilical artery line was inserted into the left atrium via the appendage and secured. The thorax was closed, and the left atrial (LA) line was buried subcutaneously between the scapulae.

After 2–3 months, predilation rest and exercise cardiac outputs, organ blood flows, and intravascular pressures were determined (see below). The same day, the lambs were anesthetized with ketamine (10 mg/kg), the right femoral artery was cannulated percutaneously, and the gradient across the coarctation site was determined by measuring the pressure on either side of the obstruction. In addition, the diameter of the aortic narrowing was measured directly from a lateral aortogram, using the catheter diameter to correct for magnification. Balloon dilation angioplasty was then performed with a polyethylene dilation catheter (Medi-tech, Inc. or Cook, Inc.) introduced percutaneously from the femoral artery. The diameter of the balloon, when inflated with saline, was chosen to be between 2½ and 3 times the angiographically determined diameter of the coarctation. A second aortogram and gradient determined the degree to which dilation had succeeded (Fig. 2). We then allowed the animal to recover overnight before determining postdilation rest...
and exercise outputs, organ flows, and intravascular pressures (see below).

So that the effects of exercise on organ flow distributions and intravascular pressures could be determined in a group of lambs which had never been exposed to aortic coarctation, sham thoracotomy was performed from the left chest when the lambs were between 3 and 21 days old. The proximal descending aorta was dissected, the nonpatent ductus arteriosus was ligated and divided, and a side-biting clamp was applied to the aorta for a total of 30 minutes in a fashion identical to that described above. However, the aorta was neither incised nor sutured. After 30 minutes of partial aortic occlusion, the clamp was removed, a left atrial line was placed, and secured as described above, and the chest was closed. These lambs then underwent training, rest and exercise studies, and dissection identical to that undergone by lambs in which a coarctation had been made. Finally, the absence of any aortic gradient was confirmed in each sham-operated lamb by direct pressure measurements.

Rest and Exercise Intravascular Pressures, Cardiac Outputs, and Organ Flows

Prior to dilatation, all lambs were trained to run on an animal exercise treadmill; in each case, the maximum speed that each lamb could reliably maintain for 7–10 minutes was recorded. On the day of study, lambs were anesthetized with ketamine (10 mg/kg, iv), the left atrial line was retrieved from its subcutaneous pouch, and catheters were placed in the ascending aorta and pulmonary artery from a cutdown over the right carotid artery and jugular vein, respectively. The position of all three catheters was confirmed fluoroscopically with contrast injections. In one lamb, the left atrial line had become dislodged during the 2½ months between thoracotomy and study; in that animal, a second soft arterial line was advanced retrogradely across the aortic and mitral valves and positioned in the left atrium. At least 75 minutes were allowed between the last dose of ketamine and the first hemodynamic study, ensuring a return to baseline hemodynamic status (Lock et al., 1980).

Intravascular pressures were measured with fluid-filled catheters, zeroed to midchest, connected to Statham p23Db transducers, and recorded on an E for M DR 12 multi-channel recorder. Resting pressures were measured with the lamb standing quietly on the treadmill; exercise pressures were determined after 3 and 8 minutes of exercise (see below). Mean pressures were obtained electrically.

Cardiac outputs and organ flows were determined with radiolabeled microspheres, by a protocol previously described (Einzig et al., 1980). Briefly, after sonication for 15 minutes in an ultrasonic bath, an injection via was filled to capacity with isotonic saline, and the “15 μm-radiolabeled (46Sc, 111Ce, 85Sr, and 99Ni) microspheres (Minnesota Mining and Manufacturing) were flushed for 10–15 seconds with 10 ml of saline into the left atrium at rest and during exercise; the number of beads actually injected ranged from 0.1 to 5.7 × 106. Blood was withdrawn from the ascending aorta at a continuous rate (7.5 ml/min) for a total of 2½ minutes to ensure complete microsphere collection; the radioactivity of that sample was used to determine tissue flow and cardiac output via the reference sample technique (Buckberg et al., 1971; Heymann et al., 1977). After the last microsphere injection, the lambs were killed by sedative overdose, and the carcass dissected to allow determination of organ flows.

Tissue samples (1–3 g) were obtained from the spleen (n = 1), liver (n = 1), and head and tail of the pancreas (n = 2). After removal of the renal capsule, medulla, and upper and lower poles, for one sample each in the right and left renal cortices. The total weight of the four full-thickness renal cortical samples was 11.23 ± 1.3 g. Full-thickness samples were also obtained from four different regions of the small and large intestine: the first 10–15 cm (2.17 ± 0.67 g) of the duodenum), the terminal 10–15 cm (2.47 ± 0.71 g) of the ileum, the first 8–12 cm (2.26 ± 0.69 g) of the cecum, and 9–12 cm (1.91 ± 0.60 g) of the middle portion of the large intestine. All renal cortical samples contained at least 356 spheres (average 5027 ± 5865 spheres). The mean number of microspheres in the intestinal samples was 730 ± 876/sample for the duodenum, 582 ± 512/sample for the ileum, 860 ± 814/sample for the cecum, and 394 ± 416/sample for the mid large intestine. Reference blood and tissue samples were counted for 10 minutes in a Packard AutoGamma scintillation spectrometer at window settings selected to correspond to the peak energies of the different nuclides. All counts were corrected for background and cross-over activity. Blood flow to each sample was calculated by solving the equation Ai/Fi = Ar/Fr, where Ai = tissue sample count rate, Ar = reference sample count rate, Fi = tissue sample flow rate (ml/min) and Fr = reference sample flow rate (ml/min). Tissue blood flow was divided by wet weight to express flow as ml/min per g of tissue. Computations were performed on a Hewlett-Packard 9831A computer (Einzig et al., 1980).

Treadmill exercise was performed on a Reliance animal treadmill, at a level grade, employing speeds of 2–3 miles per hour. After resting pressures and injection of microspheres for measuring resting flows had been determined, the treadmill speed was rapidly advanced to the speed which the animal was known to tolerate (see above), and the time of initiating exercise was noted. After 3 minutes of exercise, pressures and heart rates were recorded; the aortic and LA lines were detached from the transducers, and microspheres were injected between 4 and 4½ minutes of exercise. At the end of aortic sample withdrawal, the lines were flushed, and while the lamb was still exercising, repeat pressures were measured, in each case between 7 and 8½ minutes after exercise was instituted. The exercise protocol performed after coarctation relief was identical to that performed prior to gradient relief. Exercise intravascular pressures were taken as the values obtained at 3 minutes of exercise; in each lamb, for each variable, there was no significant change in any pressure or heart rate between 3 and 8 minutes of exercise.

Since we expected RBF during exercise to return to normal after gradient relief, and since accurate determination of the resting and exercise gradients across the coarctation site would require dissection of an artery in the hindlimb (a procedure which might compromise the ability of the lamb to exercise), no attempt was made to determine exercise coarctation gradients in these lambs. However, when analysis of the data (see below) indicated an unexpected fall in RBF with exercise even after the coarctation had been relieved, the presence of an undiminished exercise-induced coarctation gradient became a distinct possibility. Accordingly, in six other lambs, a limited dissection was carried out over the posterior tibial artery to obtain simultaneous pressures in the ascending and descending aorta during exercise before and after dilation. This was achieved in four of the six lambs; however, artifacts induced by running made identification of the systolic pressure difficult. In each, the postdilatation
intra-coarctation blood pressure was not measured in the same leg that was cannulated for passage of the dilation catheter, to avoid the possibility of femoral artery stenosis induced by the dilation procedure itself.

Data Analysis

Since the primary purpose of these experiments was to determine the impacts of both exercise and coarctation relief on RBF, the statistical significance of changes in RBF and intravascular pressures were tested with the Student’s paired t-test. To determine the impact of either exercise or gradient relief on individual organ flows, the paired t-test was modified, using the Bonferroni method. To determine the significance of changes in overall visceral organ blood flow, caused either by exercise, the presence of a coarctation, or the relief of a coarctation, an analysis of variance was employed (Wallenstein et al., 1980). All data are expressed as the mean ± SD.

Results

Creation and Correction of Aortic Coarctation

Eight lambs underwent a sham thoracotomy; each survived, none had any measurable aortic gradient at the time of study, and each underwent a full rest and exercise protocol. In three of these lambs, lateral aortography did not demonstrate any aortic distortion, due to the dissection and clamp application, which might have produced an exercise gradient.

A total of 13 lambs underwent both coarctation creation and LA line placement in the newborn period; one expired of pneumonia prior to any study. One lamb died unexpectedly during dissection of the carotid artery prior to the predilation exercise study, one lamb suffered a ruptured aortic wall at the time of dilation and exsanguinated, and one lamb suffered a ruptured femoral artery, secondary to dilation catheter placement, and eventually died from intra-abdominal blood loss. One lamb had neurological impairment after the predilation exercise study, and could not exercise effectively after dilation. Finally, the LA line became dislodged between the first and second exercise study in one lamb, with the result that all radioactivity injected postdilation was ultimately found in the left pleural space.

The hemodynamic and angiographic results of coarctation creation and subsequent dilation in the seven remaining lambs are listed in Table 1. The mean systolic gradient, measured during ketamine anesthesia just before dilation, was 37 mm Hg, with a coarctation diameter of 4.8 mm. Although balloon dilation angioplasty did not restore the aortic anatomy to normal in any lamb (Fig. 2), it did cause a substantial increase in the diameter (77%) and a decrease in the systolic gradient (82%) across the narrowed site (Table 1).

Rest and Exercise Pressures and Cardiac Outputs

The exercise loads and duration of exercise for each group of lambs are listed in Table 1; these variables were similar for each group. The changes in heart rate, intravascular pressures, and cardiac outputs at rest and during exercise are shown in Table 2. In the sham-operated lambs, there was a 57% increase in heart rate, and a similar (60%)
increase in cardiac output with exercise. Although systolic aortic blood pressure rose (96–115 mm Hg) and diastolic blood pressure fell with exercise (73–60 mm Hg), there were no significant changes, induced by exercise, in mean aortic, left atrial, or pulmonary arterial blood pressures.

The rise in heart rate (35%) and cardiac output (47%) during exercise in the lambs with aortic coarctations was not significantly different from those of control lambs (57 and 60%, respectively). Again, although systolic blood pressure rose (from 126 to 140 mm Hg) and diastolic blood pressure fell (98–93 mm Hg) with exercise, there were no significant changes in mean aortic, left atrial, and pulmonary arterial blood pressure induced by exercise in the lambs with coarctation. Thus, other than the fact that baseline blood pressures in the ascending aorta are higher in lambs with a coarctation, the general hemodynamic response to treadmill exercise in lambs with a significant, long-standing coarctation is minimally different from that of control lambs.

The exercise-induced rise in heart rate (41%) and cardiac outputs (65%) in the coarcted lambs, 1 day after gradient relief, is similar to that of both control lambs and their own predilation values. Baseline aortic blood pressures were returned to normal levels (mean ascending aortic pressure = 87 mm Hg) after dilation. However, there was a substantial and unexpected increase in systolic (100–127 mm Hg), diastolic (77–89 mm Hg), and mean aortic blood pressures (87–108 mm Hg) induced by exercise in these postdilation lambs (Fig 3). Not only was the exercise-induced rise in aortic blood pressure significant ($P < 0.001$), it was also significantly greater postdilation than predilation ($P < 0.001$), in these same lambs, and was significantly greater than the change observed in sham-operated lambs ($P < 0.01$, unpaired $t$-test). There were no changes in left atrial or pulmonary arterial blood pressures, induced by exercise in postdilation lambs. Thus, 24 hours after gradient relief, lambs that have had a long-standing aortic coarctation have normal resting hemodynamics. However, exercise produces an abnormal rise in aortic blood pressure in these lambs, in the face of normal changes in heart rate, cardiac output, and left atrial pressures.

### Rest and Exercise Blood Flow Distributions

#### Renal Blood Flows

In the sham-operated lambs, RBF was well-preserved during exercise. There was less than a 5% fall in combined RBF (Table 3). Although resting

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Visceral Rest and Exercise Blood Flow Distributions</th>
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<tbody>
<tr>
<td>Renal blood flow</td>
<td>Terminal ileal blood flow</td>
</tr>
<tr>
<td>Sham-operated lambs</td>
<td>Rest</td>
</tr>
<tr>
<td>(n = 8)</td>
<td>Exercise</td>
</tr>
<tr>
<td>Coarctation predilation</td>
<td>Rest</td>
</tr>
<tr>
<td>(n = 7)</td>
<td>Exercise</td>
</tr>
<tr>
<td>Coarctation postdilation</td>
<td>Rest</td>
</tr>
<tr>
<td>(n = 7)</td>
<td>Exercise</td>
</tr>
</tbody>
</table>

All flows are expressed in ml/min per g.
* $P < 0.05$.
† $P < 0.01$. 

FIGURE 3. Exercise-induced changes in systolic and diastolic ascending aortic blood pressures in control, predilation, and postdilation animals.
RBF was normal in the coarcted, predilation lambs (8.9 vs. 8.5 ml/g per min), exercise produced a significant, 22% (P < 0.01) fall in RBF. Thus, the physiological stress of treadmill exercise unmasks an abnormality of RBF in aortic coarctation not present at rest.

The response of RBF to gradient relief by a balloon dilation catheter was entirely unexpected; resting RBF was slightly lower postdilation than it had been predilation. In addition, RBF fell even further with exercise postdilation, from 6.7 to 5.2 ml/min per g (P < 0.001).

Other Visceral Blood Flows

Hepatic, splenic, pancreatic, duodenal, terminal ileal, cecal, and sigmoid colonic blood flows were also determined in all three groups at rest and on exercise (Table 3). In general, blood flow to visceral organs other than terminal ileum and cecum behaved as one might have anticipated; there was a fall in organ blood flow with exercise in the sham-operated lambs of variable statistical significance, and a similar or larger fall was observed in the coarcted lambs. After dilation, the resting blood flows remained largely unchanged. Further, the magnitude of the exercise-induced decrease in blood flow in postdilation lambs was generally smaller than that observed prior to dilation. These generalizations apply to the liver, spleen, duodenum, and pancreas.

In contrast, blood flow to the terminal ileum and cecum behaved in a different fashion. Flow was well preserved to these organs during exercise in the sham lambs (changes of +4% and −2%, respectively), but blood flows to the terminal ileum and cecum fell substantially with exercise in the coarcted lambs (−32 and −23%). Finally, dilation had no apparent beneficial effect on exercise-induced falls in organ blood flow to either the terminal ileum or the cecum. In each of these respects, terminal ileal and cecal blood flow responses mimicked the renal responses to both exercise and gradient relief. The response of colonic blood flow to either exercise or gradient relief is intermediate; blood flow is perhaps less well preserved during exercise (−18%), but there is little beneficial effect of balloon dilation on the exercise-induced decrease in flow. These changes are summarized in Table 4.

The percentage differences in the responses of renal, terminal ileal, and cecal blood flow on the one hand and the rest of the viscera on the other are illustrated in Figure 4. On the x axis, we have plotted the percent fall in blood flow, induced by exercise, in the sham-operated lambs. On the y axis are plotted the influences of gradient relief on exercise-induced blood flow decreases (expressed as the fall in blood flow, predilation minus the fall in blood flow, postdilation, divided by the fall in blood flow, predilation).

Miscellaneous Studies

When preliminary inspection of the data indicated that there was a fall in renal blood flow after gradient relief, that this exercise-induced fall in RBF might persist even after coarctation dilation, and that aortic blood pressure might rise more with exercise after dilation than before, several further studies were incorporated into the protocol to attempt to shed light on these issues. Thus, adrenal blood flow was found not to change with exercise in six sham-operated lambs (5.28 vs. 5.99 ml/min per g); in six coarctation, predilation lambs (3.88 vs. 3.72), and in only three coarctation, postdilation lambs (4.86 vs. 7.20). Similarly, there were no apparent changes in aortic wall blood flow, measured in five sham-operated lambs and in four coarctation, pre- and postdilation lambs (Table 5), that were induced either by exercise or by gradient relief. Finally, we measured ascending and descending aortic blood pressures in four lambs at rest and with exercise. Exercise caused large artifacts in the descending aortic pressure tracing, making systolic and diastolic pressures difficult to identify; thus, only mean pressures are reported. Although exercise clearly increased the mean gradient across a coarctation site, both predilation (from 49 mm Hg at rest

<table>
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<tr>
<th></th>
<th>Terminal ileal blood flow</th>
<th>Cecal blood flow</th>
<th>Hepatic blood flow</th>
<th>Pancreatic blood flow</th>
<th>Splenic blood flow</th>
<th>Colonic blood flow</th>
<th>Duodenal blood flow</th>
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<tbody>
<tr>
<td>Sham-operated lambs</td>
<td>−5%</td>
<td>+4%</td>
<td>−2%</td>
<td>−52%</td>
<td>−36%</td>
<td>−27%</td>
<td>−15%</td>
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<td>(n = 8)</td>
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<tr>
<td>Coarctation predilation</td>
<td>−22%</td>
<td>−32%</td>
<td>−23%</td>
<td>−25%</td>
<td>−44%</td>
<td>−85%</td>
<td>−31%</td>
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<td>(n = 7)</td>
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<tr>
<td>Coarctation postdilation</td>
<td>−22%</td>
<td>−30%</td>
<td>−25%</td>
<td>−12%</td>
<td>−26%</td>
<td>−45%</td>
<td>−33%</td>
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Table 4: Visceral Rest and Exercise Blood Flow Distributions
to 73 mm Hg on exercise) and postdilation (from 10 mm Hg at rest to 32 mm Hg on exercise), the gradient increased predilation due to a fall in descending aortic blood pressure (from 78 to 59 mm Hg), whereas, in postdilation lambs, it was due to a rise in ascending aortic blood pressure (from 94 to 117 mm Hg). Of interest, the descending aortic blood pressure in postdilation lambs remained not only constant with exercise, but as high as or higher than descending aortic blood pressure in the resting, precoarctation lambs (see Table 4). Thus, the fall in aortic pressure with exercise (−25%) in these predilation lambs was similar to the fall in RBF predilation (−22%) previously described. Since aortic pressure did not fall with exercise postdilation, the exercise-induced fall in RBF postdilation would appear to be due to renal vasoconstriction. A similar argument applies to blood flow changes in the terminal ileum and cecum.

**Discussion**

The primary purpose of the experimental studies described above was to provide a direct test of an old, widely held, but as yet unproved hypothesis, that decreased RBF contributes to the genesis of coarctation-associated hypertension. Thus, rest and exercise RBF were measured in lambs with and without a thoracic aortic coarctation. The advent of an experimental form of aortic coarctation, dilatable with a balloon-tipped catheter (Lock et al., 1982), obviated the need for a thoracotomy for gradient relief, and allowed us to address a second question: does gradient relief acruly restore resting and exercise RBF to normal values?

Since radiolabeled microspheres were used to assess RBF, we were also able to address several ancillary questions: e.g., are all visceral organs equally susceptible to stress-induced ischemia in a coarcted animal? Of interest, clinical studies have identified a post-coarctectomy syndrome of ischemic bowel disease associated with signs of mesenteric arteritis. Virtually all previous reports of this syndrome (Sealy, 1953; Lober and Lillehei, 1954; Ring and Lewis, 1950) have demonstrated a marked predilection for bowel ischemia to occur in the terminal ileum and cecum. Furthermore, clinical experience with a newborn form of ischemic bowel disease has also noted a strong tendency for the terminal ileum

**TABLE 5**

<table>
<thead>
<tr>
<th>Ascending and Descending Aortic Blood Pressures in Four Lambs</th>
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<tr>
<td>Predilation</td>
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<td></td>
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<tr>
<td>Mean ascending aortic pressure</td>
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<td>Mean descending aortic pressure</td>
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</table>
and cecum to suffer ischemic damage (Touloukian et al., 1967; Stevenson et al., 1969; Briski et al., 1982). Is there a discernible physiological basis for this known predisposition of the terminal ileum to suffer ischemic damage?

Response to Exercise in Normal Lambs

Since the flow distribution responses to exercise in immature animals have not previously been reported, we performed sham thoracotomies with left atrial line insertion in eight lambs and subsequently determined their exercise responses. Broadly speaking, these results in juvenile lambs are quite similar to previously published results from adult animals (Van Citters and Franklin, 1969; Vatner et al., 1971; Pannier and Leusen, 1977). Aortic systolic pressure rises while there are minimal changes in mean aortic, left atrial, or pulmonary artery pressures. Although there was considerable scatter in the blood flows to various visceral organs, blood flow to most of the viscera (including the liver, pancreas, and spleen) tends to fall with isotonic exercise, RBF was unchanged, and the fall in overall enteric blood flow (=10%) was insignificant. These results are indistinguishable from those previously reported for adult dogs, and do not shed further light on the previously noted apparent discrepancy between canine and human RBF responses to exercise (Rowell, 1974).

Unlike previous workers, we measured regional, rather than total, gut blood flow at both rest and exercise. Within the gut, exercise-induced changes were not uniform; blood flow to the terminal ileum and cecum was best preserved with exercise, whereas flow to the duodenum and sigmoid fell.

Response to Exercise in Coarcted Lambs

The surgically induced coarctations produced a substantial (41%) increase in mean resting aortic blood pressures. Despite this, the resting blood flows and their responses to exercise in coarcted lambs were surprisingly normal. In fact, exercise-induced changes in heart rate, cardiac output, and intravascular pressures, were minimally different from those in normal lambs.

The major hemodynamic abnormality we observed in the coarcted lambs was a significant, 22% decrease in RBF with exercise, which occurred in the face of normal resting RBF's. There was also a nonsignificant tendency for blood flow to most visceral organs to fall more with exercise in the face of a coarctation. This was especially true for the terminal ileum and cecum; i.e., although organ flow was completely preserved in those organs during exercise in control lambs (see above), it fell 32 and 23%, respectively, in the face of a coarctation. Thus, it would appear that, in the presence of a neonatally produced aortic coarctation, regional flow during exercise is nonsignificantly decreased for most visceral organs, but is significantly decreased in the kidneys, terminal ileum, and cecum.

Response to Exercise in Lambs after “Correction” of Aortic Coarctations

Although most of the results described to this point might have been anticipated, the response of the postdilation lambs to exercise was surprising in a number of respects. Firstly, although mean aortic pressure rose less than 5% with exercise in the first two groups of lambs, exercise produced a substantial (25%) increase in mean aortic pressure in the postdilation group. This abnormality could not be attributed to concomitant “abnormal” changes in cardiac output or left atrial pressure with exercise. Analysis of the aortic pressures indicated that, although the exercise rise in systolic aortic pressure was similar for sham, predilation, and postdilation lambs (20, 12, and 26%, respectively), diastolic blood pressures fell significantly in both sham (17%) and predilation (6%), but actually rose 16% (P < 0.02) in the postdilation lambs (Fig. 3).

The behavior of the blood flows to the visceral organs after gradient relief was also somewhat unexpected. Although gradient relief tended to blunt the fall in organ blood with exercise for most visceral organs (including the liver, spleen, duodenum, and pancreas), the exercise-induced fall in blood flow to the kidneys, terminal ileum, and cecum was entirely undiminished by coarctation relief. Thus, the three visceral organs whose flow was best preserved during exercise in control animals are precisely the same three organs whose exercise flow is least improved by relief of an aortic coarctation (Fig. 4).

Four of the physiological observations detailed above warrant further discussion. (1) Neonatally induced aortic coarctation causes no measurable disturbances at rest, but induces a fall in renal blood flow during treadmill exercise. (2) Relief of an aortic coarctation is associated with fall in renal blood flow, measured 24 hours after dilation, and a persistence of the exercise-induced fall in RBF. (3) Exercise produces an unexplained rise in mean and diastolic aortic blood pressures after, but not before, release of an aortic obstruction. (4) The regulation of blood flow to the terminal ileum and cecum during exercise and before and after coarctation relief is different from that of other visceral organs, but is indistinguishable from that of renal vessels.

Exercise-Induced Falls in RBF in Coarctation

Since the pioneering work of Scott and Bahnson (1951), most physiologists have assigned an important role to relative renal ischemia in the genesis of coarctation-associated hypertension. Despite multiple attempts to document decreased renal blood flow with aortic coarctations under baseline conditions, they have been unsuccessful (Harris et al., 1950; Fallo et al., 1978). More recently, several groups have adduced indirect evidence from plasma renin levels obtained under conditions of nonphysiological stress, that renal blood flow can be impaired by an aortic coarctation (Bagby et al., 1975;
Alpert et al., 1979). In that light, therefore, our observation of exercise-induced reductions in RBF in lambs with an aortic coarctation provides, for the first time, direct confirmation of a widely held hypothesis.

Paradoxical Behavior of Exercise RBF after Coarctation Relief

The finding that relief of a coarctation gradient has no beneficial effect on the exercise-induced fall in RBF in the postcoarctation lambs was entirely unexpected. "Protection" of the renal bed from a high, postcoarctectomy driving pressure seems unlikely, as gradient relief lowered ascending pressure, rather than raising descending aortic pressure. Although previous workers have shown that blood pressure may remain high after coarctectomy on the basis of a "resetting" of the carotid sinus baroreceptor (Sealy et al., 1953; Igler et al., 1981), hypertension on that basis should be mediated by sympathetic (Rocchini et al., 1976), and thus should show no special selectivity for renal vascular vasocstriction. A third possibility is that the dilation did not successfully relieve the obstruction. However, such was not the case; predilation exercise reduced mean descending aortic pressure (—28%) to a degree similar to the fall in RBF (—22%); postdilation, mean descending aortic pressure actually rose slightly with exercise (+1%) despite a fall in RBF of 22%, indicating exercise-induced renal vasocstriction. Perhaps coarctation relief adds a new low-resistance circuit in parallel to the high resistance circuits of the upper body, and thus may act to "steal" flow from abnormal terminal ileal and cecal ischemia. Indeed, in normal lambs, we observed the opposite; blood flows to the terminal ileum and cecum were better preserved during exercise than to any other visceral organ. However, whereas an aortic coarctation did appear that the hypertension after coarctotomy is due chiefly to increased diastolic blood pressures on exercise. Since exercise-induced hypertension after gradient relief cannot be attributed to abnormal changes in cardiac output, left atrial pressure, or heart rate, it would appear that the hypertension after coarctotomy is due to diminished exercise-induced systemic vasodilation in these lambs.

Regulation of Terminal Ileal and Cecal Blood Flow

The predilection of the gut on either side of the ileocecal value to suffer ischemic damage is well known to the surgeon, neonatologist, and cardiologist (Sealy, 1953; Lober and Lillehei, 1954; Ring and Lewis, 1956; Touloukian et al., 1967; Stevenson et al., 1969; Briski et al., 1982). To date, there have been no studies directed at identifying the cause of this peculiar distribution of ischemic lesions, although ill-defined anatomic considerations have been invoked in the past (Ring and Lewis, 1956). Our data do not support an anatomic reason for terminal ileal and cecal ischemia. Indeed, in normal lambs, we observed the opposite; blood flows to the terminal ileum and cecum were better preserved during exercise than to any other visceral organ. However, whereas an aortic coarctation did

**Table 6**

<table>
<thead>
<tr>
<th></th>
<th>Left ventricular blood flow</th>
<th>Right ventricular blood flow</th>
<th>Total brain blood flow</th>
<th>Biceps femoris blood flow</th>
<th>Triceps muscle blood flow</th>
<th>Masseter muscle blood flow</th>
<th>Pulmonary trapping (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham-operated</td>
<td></td>
<td></td>
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<tr>
<td>lambs (n = 8)</td>
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</tr>
<tr>
<td>Rest</td>
<td>1.92 ± 0.74</td>
<td>1.37 ± 0.57</td>
<td>0.85 ± 0.20</td>
<td>0.15 ± 0.09</td>
<td>0.10 ± 0.08</td>
<td>0.06 ± 0.03</td>
<td>6.45 ± 1.86</td>
</tr>
<tr>
<td>Exercise</td>
<td>3.16 ± 0.91</td>
<td>2.96 ± 0.84</td>
<td>0.93 ± 0.28</td>
<td>0.64 ± 0.44</td>
<td>0.74 ± 0.29</td>
<td>0.06 ± 0.03</td>
<td>5.50 ± 1.79</td>
</tr>
<tr>
<td>Coarctation pre-</td>
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<td>dilution (n = 7)</td>
<td></td>
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<tr>
<td>Rest</td>
<td>2.58 ± 0.62</td>
<td>1.74 ± 0.28</td>
<td>0.91 ± 0.18</td>
<td>0.31 ± 0.13</td>
<td>0.31 ± 0.03</td>
<td>0.15 ± 0.12</td>
<td>5.33 ± 3.20</td>
</tr>
<tr>
<td>Exercise</td>
<td>3.46 ± 0.65</td>
<td>3.00 ± 0.56</td>
<td>0.99 ± 0.14</td>
<td>0.99 ± 0.54</td>
<td>0.78 ± 0.31</td>
<td>0.08 ± 0.05</td>
<td>5.01 ± 1.05</td>
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<tr>
<td>Coarctation post-</td>
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<td>dilution (n = 7)</td>
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</tr>
<tr>
<td>Rest</td>
<td>2.01 ± 0.36</td>
<td>1.43 ± 0.40</td>
<td>1.00 ± 0.15</td>
<td>0.12 ± 0.04</td>
<td>0.09 ± 0.02</td>
<td>0.09 ± 0.04</td>
<td>4.43 ± 3.38</td>
</tr>
<tr>
<td>Exercise</td>
<td>4.52 ± 2.16</td>
<td>4.11 ± 2.12</td>
<td>0.94 ± 0.15</td>
<td>0.65 ± 0.31</td>
<td>0.94 ± 0.49</td>
<td>0.07 ± 0.03</td>
<td>4.24 ± 2.24</td>
</tr>
</tbody>
</table>

* Studied at rest and on exercise (2.6 miles/hr) predilation, and 24 hours postdilation. All flows are expressed in ml/min per g of tissue. No attempt was made to assess the statistical significance of any flow changes in this table.
not decrease resting ileocecal flow, it did produce an exercise-induced fall in ileocecal blood flow. Of considerable interest, however, the terminal ileum and cecum resembled the kidneys in their response to gradient relief. Terminal ileal flow fell after coarctotomy, and exercise-induced ischemia to both organs persisted undiminished after gradient relief.

These results, instead of implicating an anatomic hindrance to flow, suggest something else. The kidneys and the ileocecal region of the gut may share some neurohumoral vasconstrictor mechanism which becomes very important in the face of a longstanding, neonatally produced aortic coarctation. Again, this study provides no data which might allow us to identify such a mechanism.

Methodologic Advantages and Pitfalls

There are several aspects of the methodology used in this study which not only enhance its value, but also limit the conclusions that can be drawn. Unlike all previous reports of constrictive hemodynamic lesions in growing animals, this form of coarctation closely mimics human disease, in that the gradient remains constant with animal growth (Lock et al., 1982). Since the obstruction can be relieved without thoracotomy, the lambs can be studied, with exercise, very shortly after gradient relief and without the confounding effects of a major operative procedure. Finally, since an extensive mediastinal dissection through old scar tissue is not required to relieve the obstruction, the possibility of damage to sympathetic nerves can be avoided.

In addition, there are some weaknesses which warrant discussion. Since multiple organs were sampled, accuracy of the flow determinations might have been hampered by small microsphere numbers in each sample; however, all renal and nearly all intestinal samples contained at least 400 microspheres. Since 24 hours elapsed between the first and last bead injections, we considered it possible that microspheres were released from the capillaries; however, there were no differences in systemic shunting of microspheres as approximated by pulmonary counts in the pre- and postdilation injections, and the resting renal blood flows were similar in sham and predilation lambs.

What is most important is the fact that—because of the design of the study—the cause of the persistent fall in RBF postcoarctotomy cannot be established. There are several reasons for this. Descending aortic blood pressure during exercise was not measured in all lambs, so that actual renal vascular resistance could not be calculated. Although it would appear (at first glance) that this measurement would be easy to obtain, such is not, in fact, the case. Percutaneous entry of at least one femoral artery was necessary for dilation; in these pulseless lambs, entry proved difficult, and frequently both femoral arteries were used. Thus, the use of a chronically implanted femoral artery line (which may or may not allow exercise in these lambs) as previously described (Weismann and Clarke, 1981) would not have been feasible in many lambs. Passage of a catheter from a neck vessel across the coarctation site to measure descending aortic blood pressures would have required removal of the catheter at the time of dilation; repassage of the catheter through the coarctation after a recent dilation would have placed the lambs at risk from transvascular rupture (Lock et al., 1982). Although we used a limited tibial dissection to gain information about the descending aortic pressure, it proved impossible to pass the catheter to a central aortic position, resulting in considerable motion artifact during exercise. Finally, since previous workers have suggested that nonrenal factors cause postcoarctation hypertension, we did not expect to find persistence of a renal abnormality after coarctation relief. As a result, no studies were performed to determine the duration or possible mediators of the decreased RBF.

In summary, these studies have provided direct experimental support for the long-standing hypothesis that physiological renal "ischemia" contributes to the genesis of coarctation-associated hypertension in immature animals. At the same time, it has raised a larger number of questions: Why does the exercise-induced decrease in RBF persist after coarctation relief? How long does it last? Why do systemic vessels fail to vasodilate with exercise after coarctation relief? Why does the apparent control of ileocecal blood flow seem to resemble that of the kidneys rather than that of other visceral organs? The answers to such questions may ultimately bear on the therapy of such diverse childhood diseases as postcoarctation hypertension and neonatal necrotizing enterocolitis.

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