

## Delayed Onset Hypertension with Infrarenal Aortic Cross-Clamping in Dogs<sup>1</sup>

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The time course and mechanism of systemic hypertension associated with infrarenal aortic cross-clamping were investigated in 31 chloralose-anesthetized dogs after ligating the tail artery, the paired infrarenal lumbar arteries, and the circumflex iliac arteries bilaterally. Cardiac output, renal blood flow, and suprarenal and infrarenal mean arterial blood pressure were continuously monitored. Infrarenal aortic clamping (90 min) in the standard group ( $n = 6$ ) consistently decreased infrarenal blood pressure from  $90 \pm 6$  to  $13 \pm 1$  mm Hg within 1 min, while suprarenal blood pressure gradually increased over 20–30 min from  $88 \pm 7$  to  $144 \pm 8$  mm Hg, where it remained until declamp. The SHAM group (identical operation and instrumentation, without aortic clamping) ( $n = 5$ ) showed no statistically significant changes. After 90 min of clamp total peripheral and renal resistance nearly doubled but no statistically significant changes in cardiac output, heart rate, central venous pressure, renal blood flow, renin, or glomerular filtration rate were detected. Upon declamping, pressures returned to control levels within 20 min. Groups with bilateral nephrectomy ( $n = 9$ ) or unilateral iliac artery clamping ( $n = 7$ ) produced similar time courses and patterns of hemodynamic change. Ablation of afferent nerves from the left hind limb ( $n = 4$ ) eliminated the hypertension produced by left iliac artery clamping. The substantial delay (20–30 min) to the onset and full development of suprarenal hypertension, with near immediate infrarenal hypotension, is not consistent with a direct mechanical impedance effect. Hypertension in the presence of a bilateral nephrectomy or unilateral iliac artery clamping combined with its full reversal by nerve section strongly suggests that this is a reflex hypertension. This reflex mechanism of hypertension development has implica-

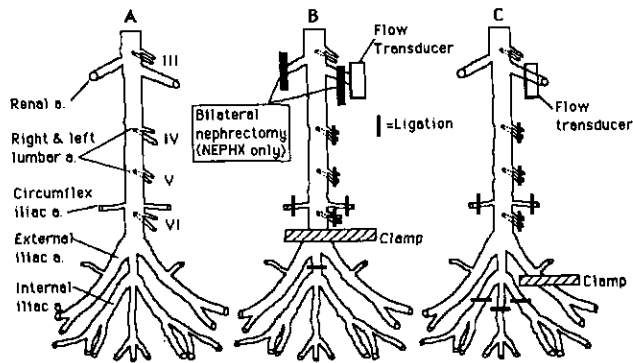
tions for intra- or perioperative events associated with hypertension management. © 1994 Academic Press, Inc.

### INTRODUCTION

Surgical repair of the diseased infrarenal aorta occasions prolonged clamping of the distal aorta to allow for its replacement with synthetic material. This procedure is performed approximately 60,000 times per year and is associated with a wide variety of perioperative complications. One potentially dangerous complication is the intraoperative development of systemic hypertension during cross-clamping. Clinical studies consistently report some pattern of systemic hypertension with infrarenal aortic cross-clamping; however, there is wide variability in the magnitude, duration, and management of this hypertension as well as the eventual clinical course of the patient [1, 2, 7]. Intraoperative hypertension is generally assumed to be a passive hydraulic event related to an increase in aortic impedance. The outcomes of laboratory investigations have also been varied and therefore the etiology or etiologies of this hypertension have not been fully clarified. The common finding of some degree of hypertension in both clinical and laboratory studies lead to this investigation of the pathophysiology of intraoperative hypertension. We have developed a highly reproducible and reliable dog model of infrarenal aortic cross-clamping with the long-term goal of improving the clinical management of intraoperative hypertension. Rather than assuming a passive hydraulic character of the hypertension we hypothesized that the increase in arterial pressure is substantially more complex and develops secondary to a reflex mechanism under the control of local factors as well as the central nervous system. Afferent signals from resting, hypotensive (presumed ischemic) hindlimbs would be integrated within the CNS and override baroreceptor control to elevate systemic arterial blood pressure. The elevation in pressure would serve to help restore perfusion pressure for the hindlimbs much like the Cushing cerebral ischemic re-

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**FIG. 1.** Schematic drawings of the experimental preparations. Represented in A is the dog infrarenal aorta with associated collateral vessels and branches. Depicted in B is the flow transducer on the left renal artery (STD group), bilateral nephrectomy (NEPHX group), collateral ligation, and infrarenal clamp application (STD and NEPHX). The ILIAC group instrumentation is shown in C: a flow transducer on the left renal artery, ligated collateral pathways, and the clamp application on the left external iliac artery just proximal to the deep femoral artery.

sponse does for the brain. This study tests this hypothesis under a variety of experimental conditions.

## METHODS

### General Preparation

Thirty-one male mongrel dogs weighing 16.0–22.0 kg were premedicated with morphine sulfate (1.5 mg/kg, sc), anesthetized with an intravenous injection of  $\alpha$ -chloralose (120 mg/kg) dissolved in half-normal (0.45%) saline at a concentration of 8 mg/ml, intubated, and ventilated with room air at 18–20 breaths/min with positive end-expiratory pressure of 6 cm of water (Harvard 607, South Natick, MA). Expired  $\text{CO}_2$  was continuously monitored and maintained between 4 and 5% (Beckman LB-2, Palo Alto, CA). An additional 2.5 mg/kg morphine sulfate (4.0 mg/kg for standard and sham groups described below) was given subcutaneously and anesthesia was supplemented by continuous infusion of  $\alpha$ -chloralose (12 mg/kg/hr, iv). Core body temperature was measured at the midesophagus and maintained at  $39 \pm 1^\circ\text{C}$  with heat lamps, blankets, and a proportional controller. An indwelling bladder catheter was placed to maintain an empty bladder. Subcutaneous needle electrodes recorded limb lead II EKG.

Two arterial catheters were placed, one in a muscular branch of the left femoral artery with the tip just distal to the inguinal ring as a measure of infrarenal blood pressure (IRBP) and the second in the left carotid artery with the tip at the level of the aortic arch as a measure of suprarenal blood pressure (SRBP). Note that throughout this report the terms “suprarenal” and “supra-clamp” are used interchangeably, as are the terms “infrarenal” and “infraclamp.” Two additional catheters

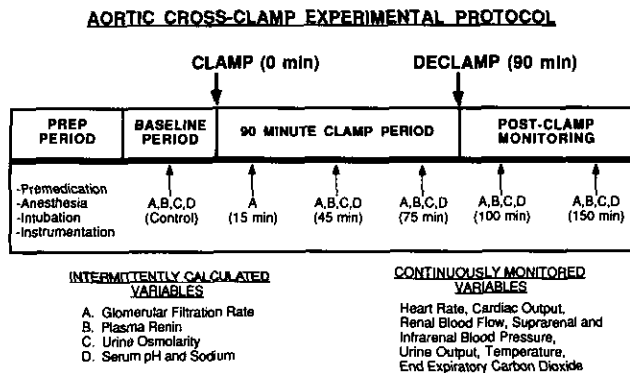
were placed into the left external jugular vein, one for central venous pressure (CVP) monitoring and the other for intravenous fluid administration. Each animal received a 500-cc bolus of 5% dextrose in water with 1.5 meq/kg of sodium bicarbonate intravenously followed by a continuous intravenous drip of half-normal saline at 8 ml/kg/hr to compensate for fluid loss and maintain hydration. Arterial blood pH was measured (pH/Blood Gas Analyzer 113, Instrumentation Laboratory, Lexington, MA) in the control period and corrected with intravenous sodium bicarbonate as needed to maintain a pH of  $7.40 \pm 0.03$ . A thoracotomy at the left fifth interspace allowed placement of an ultrasonic flow transducer on the pulmonary artery for continuous on-line cardiac output measurements (12 mm; Transonic Systems Inc., Ithaca, NY).

The infrarenal aorta was exposed via a retroperitoneal approach through a left flank incision. Collateral blood supply to the lower torso was interrupted by ligating the paired fourth, fifth, and sixth lumbar arteries, the large circumflex iliac arteries, and the arteries to the tail (Fig. 1A). An ultrasonic flow transducer (2 mm) was placed on the left renal artery for continuous on-line renal blood flow measurements in the groups with intact kidneys. Urine was continuously collected from a catheter (PE160) inserted into the left ureter. Thus each animal was continuously monitored for cardiac output, pulsatile and mean renal arterial blood flow, pulsatile and mean supra- and infrarenal arterial pressure, central venous pressure, ECG, heart rate, temperature, end-expiratory  $\text{CO}_2$ , and unilateral urine flow rate.

### Protocols and Experimental Groups

After the above basic preparation the animals were separated into five experimental groups and instrumented for specific protocols as described below.

**Standard aortic cross-clamp (STD).** An outline of the standard experimental protocol is provided in Fig. 2. Renal function as reflected by glomerular filtration rate (GFR) (inulin) and plasma renin activity were assessed and correlated with standard hemodynamic parameters and renal blood flow during the clamp/declamp sequence. After initial instrumentation and stabilization an arterial blood sample was taken for the baseline measurement of plasma sodium (Nova 6; Nova Biomedical, Waltham, MA), osmolarity (Micro Osmometer; Precision Systems, Sudbury, MA), pH (pH/Blood Gas Analyzer 113, Instrumentation Laboratory), and plasma renin activity. Blood and urine samples were taken at 15, 45, 75, 100, and 150 min after application of the clamp. A completely occluding Satinsky clamp was then placed on the infrarenal aorta avoiding the renal artery, as indicated in Figs. 1B and 2. Marked infrarenal hypotension was confirmed in each case by obtaining an IRBP of 10–20 mm Hg within minutes. The clamp was left in place for 90 min and then removed. No attempt was



**FIG. 2.** Outline of experimental infrarenal aortic cross-clamp protocol. Small arrows indicate sample times during the control period and at 15, 45, 75, 100, and 150 min during the protocol. Large arrows indicate application of the cross-clamp. GFR, plasma renin, urine osmolarity, and serum pH and sodium were calculated from blood and urine samples taken as indicated. All other variables were continually monitored throughout the protocol sequence.

made to attenuate or modify any potential declamp hypotension.

**Sham (SHAM).** Four sham-operated dogs were instrumented in a fashion identical to that of the STD group but without the aortic cross-clamp. All other measurements made in the STD group were also made in the SHAM group.

**Unilateral iliac occlusion (ILIAC).** In seven dogs, the clamp was placed not on the infrarenal aorta but rather on the left external iliac artery at a point just proximal to the branch point of the deep femoral artery for 90 min (Fig. 1C). Ligatures were placed on the internal iliac arteries bilaterally and the tail artery to obliterate these more distal collateral pathways. Unilateral hindlimb hypotension was confirmed by obtaining an IRBP of 10–20 mm Hg in the left leg.

**Bilateral nephrectomy (NEPHX).** In nine dogs bilateral nephrectomies were performed through flank incisions during the surgical preparation (Fig. 1B). The renal artery, renal vein, and ureter were identified and ligated on each side before removing the kidneys. Thereafter the protocol was identical to that of the STD group.

**Nerve section (N-SEC).** In four dogs the preparation was identical to that of the ILIAC group, however after  $46 \pm 5$  min of infrarenal aortic cross-clamping the ilioinguinal, lateral cutaneous femoral, genital, femoral, obturator, seventh lumbar, first sacral, and ischiatic nerves on the left side were sectioned in rapid succession via the retroperitoneal dissection. Ten milliliters of 1% lidocaine was then infiltrated over 20 cm of perispinous musculature, localized to the fascial planes around the sacral nerves. The clamp was removed after 90 min as in the other groups.

**Nerve intact (N-INT).** We detected no statistically significant differences in the blood pressure responses among the STD, ILIAC, and NEPHX groups and hence

have pooled the blood pressure data under a group called nerve intact (N-INT). All of the members of the N-INT group had intact afferent nerves and this pooled group is used for comparison with the nerve-sectioned animals.

### Inulin Assay

Inulin concentrations in blood and urine were determined by modification of the anthrone method described by Davidson and Sackner [5]. Blood samples were taken prior to and during inulin infusion at the midpoint of each 10-min urine collection. Inulin was given as a bolus (60 mg at 10 mg/min) and intravenous infusion (6 mg/min) for the duration of the protocol. Forty-five minutes after the inulin bolus two urine and two blood samples were obtained for GFR,  $\text{Na}^+$ , pH, renin, and osmolarity to serve as postinulin control measurements. A protein-free plasma supernatant was prepared by adding 4.5 cc of 10% trichloroacetic acid to 0.5 cc of heparinized plasma, incubated with anthrone reagent and read on a spectrophotometer (Spectronic 20; Bausch & Lomb, Rochester, NY) at 620 nm. The urine samples were diluted prior to incubation with anthrone. A five-point standard curve, as well as plasma and urine blanks, were processed with each assay. GFR (ml/min) was then determined using the standard formula of urine inulin concentration multiplied by urine flow rate divided by plasma inulin concentration:

$$\frac{\text{urine inulin concn} \times \text{urine output}}{\text{plasma inulin concn}}$$

### Renin Assay

Plasma samples were assayed for plasma renin activity using the timed generation of angiotensin I after the technique of Haber *et al.* [6] using a commercial radioimmunoassay kit (New England Nuclear, Boston, MA).

Animal care complied with the Principles of Laboratory Animal Care (formulated by the National Society for Medical Research), the Guide for the Care and Use of Laboratory Animals (NIH Publication No. 80-23, revised 1985), and The University of Michigan Committee on Use and Care of Animals (Approval No. 2425A-Dogs).

### Statistical Analysis and Calculated Values

Hemodynamic variables were recorded continuously. Sample points were obtained every 10 min for the STD, SHAM, ILIAC, and NEPHX groups and reported as such. For comparison between the N-INT and N-SEC groups, points were obtained at preclamp, maximal MAP increase during clamp (30–50 min), just prior to declamp (90 min of clamp time), and 30 min after declamping (150 min from clamping). Student's paired *t* test corrected for repeated measures (Bonferroni) was utilized to compare the MAP, CO, HR, CVP, RBF,

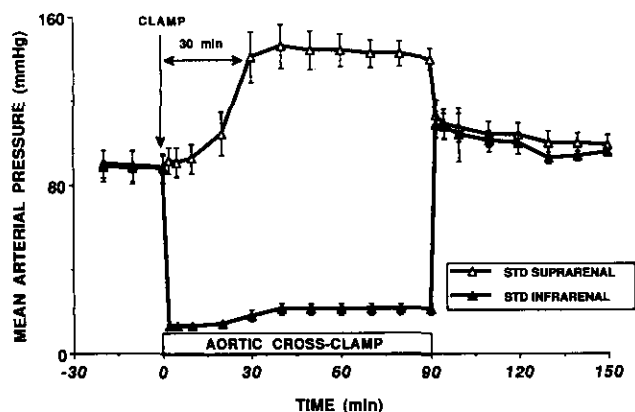


FIG. 3. Time course of STD suprarenal and infrarenal mean arterial pressures is shown before, during, and after the application of the infrarenal aortic cross-clamp. The rectangular box on the horizontal axis indicates the 90-min aortic cross-clamp. Suprarenal pressure increased gradually over time (20–30 min) and was significantly greater than the control level at 90 min ( $P = 0.0002$ ). Infrarenal pressure, in marked contrast to the SRBP pattern, decreased rapidly after clamp application and was significantly lower than the control level at 90 min ( $P = 0.0003$ ). Upon removing the cross-clamp, both pressures rapidly returned toward their control levels.

renin, GFR, TPR, and renal resistance data within each group between the 10-min preclamp and 90-min (just prior to declamp) samples, as well as with the 60-min declamp. Unpaired Student's *t* tests were used to compare the MAP, CO, HR, CVP, renal blood flow (RBF), renin, GFR, TPR, and Renal Resistance data among groups using the Bonferroni correction. A level of  $P < 0.05$  was accepted as statistically significant. ANOVA was used to detect differences in data among the STD, ILIAC, and NEPHX groups as indicated under Results. Total peripheral resistance was calculated by dividing SRBP (mm Hg) by cardiac output (ml/min). Renal resistance was calculated by dividing SRBP (mm Hg) by renal blood flow (ml/min). Results are reported as means  $\pm$  1 SE. Statistics were performed on a Macintosh II utilizing the Statview 512 software.

## RESULTS

Prior to aortic cross-clamping SRBP and IRBP were essentially equal ( $88 \pm 7$  and  $90 \pm 6$  mm Hg, respectively) in the STD group (Fig. 3). Upon application of the clamp, IRBP dropped immediately—reaching  $13 \pm 1$  mm Hg within 1 min—and remained at this level until the 30-min time point. In marked contrast, SRBP did not immediately increase; rather, it gradually and progressively increased, beginning 20 min after clamping and reaching a maximum plateau pressure of  $144 \pm 9$  mm Hg by 30 min into the clamp period. Thus, systemic supraclamp hypertension was 56 mm Hg (64%) above baseline just prior to declamp ( $P = 0.0002$ ). Following 20–30 min of aortic clamping, IRBP also began to gradu-

ally increase from its initial low of  $13 \pm 1$  to  $21 \pm 3$  mm Hg. This slow, progressive IRBP increase occurred over the same time frame as the increase in SRBP. At 90 min, the IRBP was significantly lower than the control level ( $P = 0.0003$ ). Declamping quickly returned both SRBP and IRBP to a similar level, slightly higher than control levels, where they stayed until 10 min postclamp. There were no postclamp differences between the IRBP and the SRBP. The striking aspect of this observed response is the delayed onset of the suprarenal hypertensive response as opposed to the immediate drop in infrarenal arterial pressure associated with the aortic clamping.

Figure 4 (top) shows the SRBP response in the NEPHX, ILIAC, STD, and SHAM groups. The SHAM group showed no significant change in pressure during the course of the experiment. Note the nearly identical pattern of response to the aortic cross-clamp in all three clamp groups (i.e., all non-SHAM groups) despite their different interventions. With placement of the clamp there is a slow and gradual increase in SRBP over 20 to 30 min. At 30 min into the clamp period the SRBP increase is at its maximum (43% above baseline) and remains elevated for the duration of the clamp application. All three clamped groups show a statistically significant increase when preclamp levels (–10 min) are compared to 90-min levels (NEPHX,  $P = 0.001$ ; ILIAC,  $P = 0.003$ , STD,  $P = 0.0002$ ). ANOVA performed on all three groups at 90 min shows no significant difference among the groups. All pressures returned toward control levels after removal of the cross-clamp.

Figure 4 (bottom) shows the CO response in these same four groups after clamping. The NEPHX group has a lower baseline CO secondary to bilateral nephrectomy. CO in the SHAM group tended to decrease throughout the protocol, causing an approximately 25% reduction when the control level is compared to the 90-min level ( $P = 0.003$ ). The patterns in the non-SHAM groups are similar: there is an initial slight increase in CO with clamp application followed by a gradual return to baseline levels. There were no statistically significant changes in CO between control and 90 min. After 50 min of aortic clamping, CO was statistically higher ( $P < 0.05$ ) in the STD group than that in the SHAM group, and although less than its control level, remained elevated when compared to that in the SHAM group for the duration of the experiment. When the three clamp groups are compared at 90 min there is a significant difference, with the NEPHX group being lower than the other two groups (NEPHX vs ILIAC,  $P = 0.004$ ; NEPHX vs STD,  $P = 0.007$ ). With declamping there is a transient increase with rapid return to baseline levels.

Renal blood flow, glomerular filtration rate, and plasma renin activity for the STD and SHAM groups are presented in Fig. 5. The RBF and GFR data reflect the left kidney only (left renal artery flow transducer and left ureteral catheterization). RBF, measured continuously throughout the experiment, showed a gradual de-

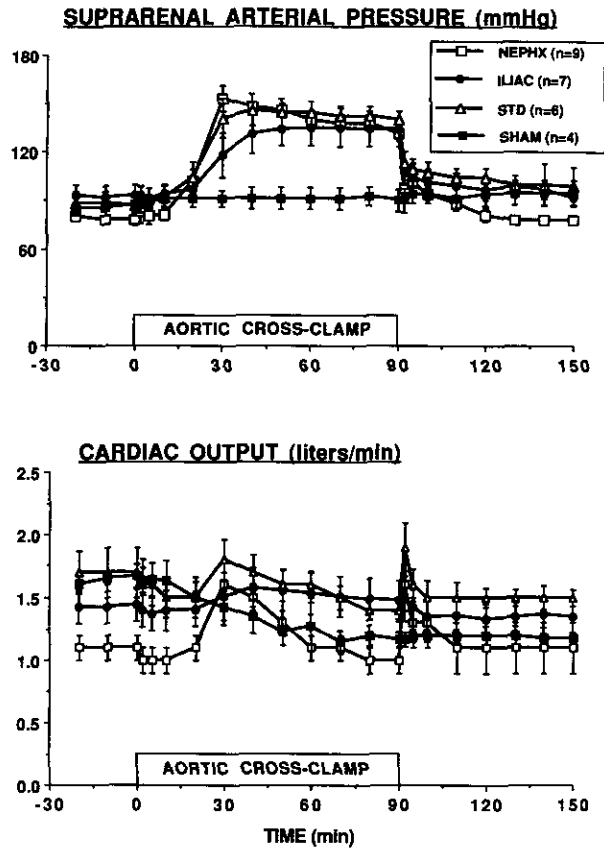


FIG. 4. Time course of suprarenal arterial pressure (top) and cardiac output (bottom) in the NEPHX, ILIAC, STD, and SHAM groups. The rectangular box along the horizontal axis indicates the 90-min aortic cross-clamp. Suprarenal pressure (top) gradually increased in all three clamp groups (i.e., non-SHAM) after clamp application. At 90 min, the NEPHX, ILIAC, and STD pressures were all significantly elevated above their respective control level (NEPHX,  $P = 0.001$ ; ILIAC,  $P = 0.003$ ; STD,  $P = 0.0002$ ). All pressures returned toward control levels after removal of the clamp. The SHAM group showed no statistically significant pressure changes. Cardiac output (bottom) in the three clamp groups increased initially upon clamp application and then gradually returned to baseline levels. There were no statistically significant decreases in CO in any of the clamp groups. Removal of the clamp produced a transient increase with a rapid decline to baseline levels. Note that the lower baseline cardiac output in the NEPHX group is secondary to the bilateral nephrectomy. Cardiac output in the SHAM group tended to decrease throughout the protocol.

crease in both the STD and SHAM groups, but there were no statistically detectable differences between the two in the rate or magnitude of decline. No statistical significance was found between  $-10$  and  $90$  min. GFR in the STD group was higher throughout the protocol; however, no statistically significant differences within or between groups were detected. Plasma renin levels tended to decrease in both groups, although not significantly.

The TPR response in the NEPHX, ILIAC, STD, and SHAM groups is similar; with clamp application TPR increases gradually, not immediately (Fig. 6, top). This increase is more gradual than the increase in MAP, and

with declamping there is a decrease to baseline levels. The increased resistance can be partially accounted for by gradual changes in the anesthetized preparation over the 3-hr experimental period, as evidenced by the TPR data from the SHAM group. Interestingly, the progressive increase in TPR is coincident with the progressive return to baseline of the CO data. This reciprocal relationship accounts for the more stable MAP throughout this period. The increase in TPR is statistically significant in all three groups when baseline data ( $-10$  min) is compared to the 90-min time point (NEPHX,  $P = 0.003$ ; ILIAC,  $P = 0.03$ ; STD,  $P = 0.0001$ ). There is no difference among the three groups at the 90-min time point. The NEPHX TPR appears to increase higher than those of the other groups, but this presumably is secondary to the nephrectomy. Furthermore, the initial increase in NEPHX CO (Fig. 4, bottom), which appears as the largest CO increase, returns to its baseline level as the TPR increases.

The pattern of increase in renal resistance in the STD and ILIAC groups (Fig. 6, bottom) is similar to the pattern seen with MAP: a gradual and statistically signifi-

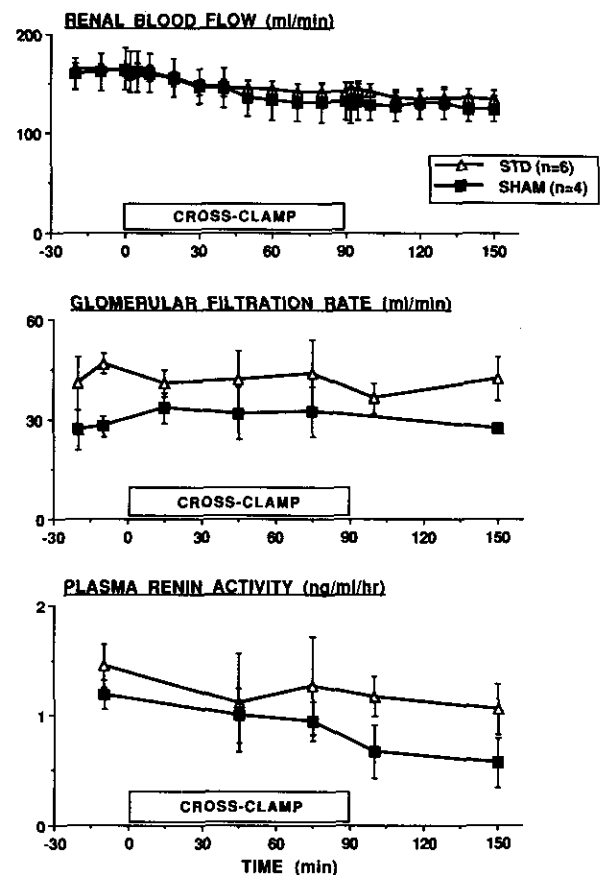
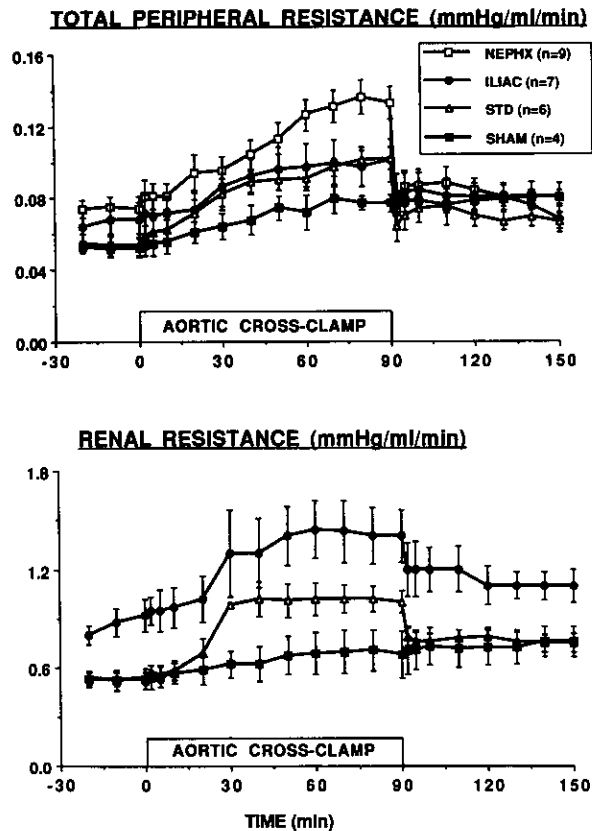


FIG. 5. Time course of renal blood flow, glomerular filtration rate, and plasma renin activity in the STD and SHAM groups. Renal blood flow showed a tendency to decrease in both groups. There were no significant changes detected in any of the three parameters either within or between groups.

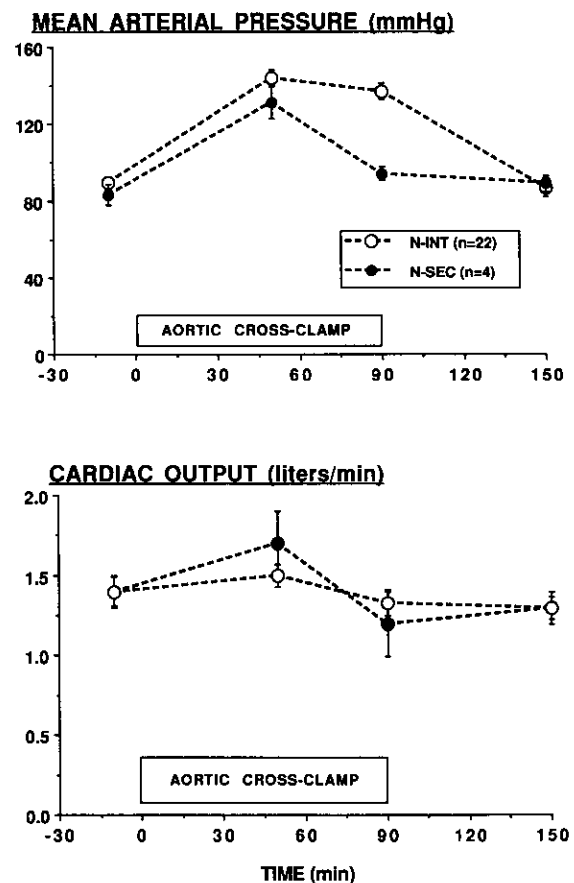


**FIG. 6.** Time course of total peripheral resistance (top) and renal resistance (bottom) in the NEPHX, ILIAC, STD, and SHAM groups. All three clamp groups (i.e., non-SHAM) exhibited gradually increasing TPR (top) with application of the clamp and were significantly higher than control levels at 90 min (NEPHX,  $P = 0.003$ ; ILIAC,  $P = 0.03$ ; STD,  $P = 0.0001$ ). Removal of the clamp immediately returned TPR to baseline levels. Renal resistance (bottom) in both clamp groups gradually increased, upon clamp application, and was significantly higher at 90 min than control levels (ILIAC,  $P = 0.007$ ; STD,  $P = 0.0008$ ). The two clamp groups are different both at  $-10$  min ( $P = 0.003$ ) and at 90 min ( $P = 0.02$ ). Clamp removal produced a return to control levels. The SHAM group showed an increase in both TPR and renal resistance throughout the experimental period.

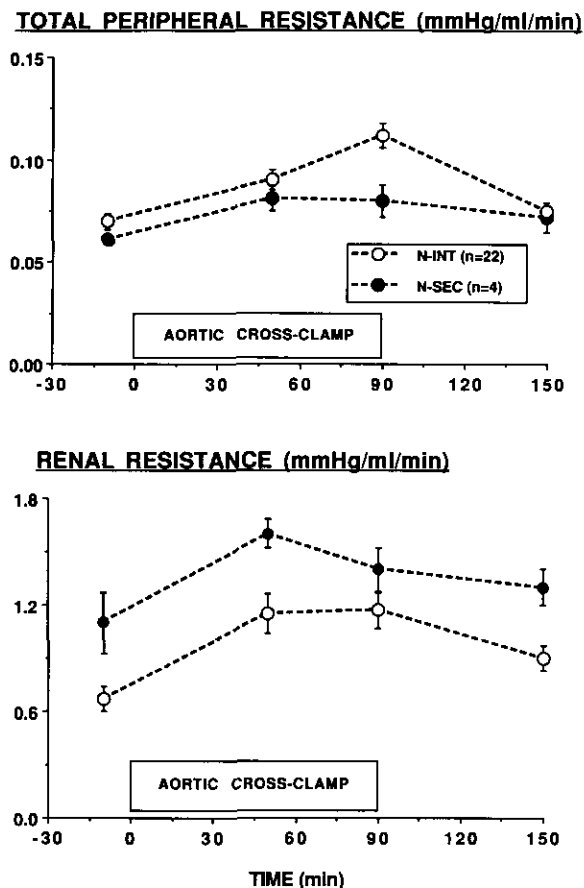
cant increase after clamp application until a plateau is reached after 30 min and a rapid decrease upon removal of the clamp toward control levels. The resistance in both groups is significantly elevated at 90 min when compared to  $-10$  min (ILIAC,  $P = 0.007$ ; STD,  $P = 0.0008$ ). The resistance in the ILIAC group is greater than that of the STD group at both  $-10$  min ( $P = 0.003$ ) and 90 min ( $P = 0.02$ ). Renal resistance in the SHAM group slowly increased throughout the protocol.

In Fig. 7 (top) the mean values for MAP in the N-SEC group are compared to the mean values of the other three groups combined (N-INT). The four points shown correspond to (1) control levels ( $-10$  min), (2) a point at which a maximal MAP response is seen (40–50 min), (3) a point just prior to declamping (90 min postclamp), and (4) 30 min postdeclamp. The first two time points depict the same conditions in the N-INT and N-SEC groups.

The third time point (just prior to declamping) compares the groups after the nerve sectioning and lidocaine infiltration in the N-SEC group. Note the initial increase in both groups consistent with the clamp application. In the N-INT group the MAP decreases only slightly from  $143 \pm 4$  to  $137 \pm 4$  ( $P = 0.04$ ) from the midpoint of clamp application until just prior to declamping. The MAP in the N-SEC group, however, returns to its control level after nerve sectioning, a large decrease from  $131 \pm 8$  to  $93 \pm 4$  ( $P = 0.004$ ) despite maintenance of the clamp application. The difference in pressure between the two groups is significant after the nerve sectioning ( $P = 0.002$ ). Upon removal of the clamp there is no change in MAP in the N-SEC group, while in the N-INT group there is a decrease to its control level as seen in Fig. 4 (top). The initial small rise in CO with



**FIG. 7.** Mean arterial pressure (top) and cardiac output (bottom) in the N-INT and N-SEC groups. Both groups show an increased MAP 45 min into the clamp application (top). At 90 min, MAP was still elevated in the N-INT group, while the N-SEC MAP had returned nearly to its control level, which was significantly decreased ( $P = 0.004$ ) compared to 45 min. The difference between the two groups at 90 min was also significant ( $P = 0.002$ ). Removal of the clamp had no effect on the N-SEC MAP while the N-INT pressure decreased to its control level. Cardiac output (bottom) increased slightly with clamp application in both groups. Nerve severing during the clamp application significantly reduced cardiac output ( $P = 0.02$ ). After clamp removal both groups returned to control levels.



**FIG. 8.** Total peripheral resistance (top) and renal resistance (bottom) in the N-INT and N-SEC groups. TPR increased initially in both groups (top) with clamp application. The N-INT group was increased further ( $P = 0.0005$ ) at 90 min compared to 45 min, while nerve sectioning kept TPR constant for the remainder of the clamp application. The difference between the two groups at 90 min was significant ( $P = 0.04$ ). After clamp removal both groups returned to control levels. Renal resistance increased initially in both groups (bottom) with clamp application. Nerve sectioning reduced renal resistance slightly, but not significantly. Clamp removal returned both groups to control levels.

clamp application is eliminated in the N-SEC group ( $P = 0.02$ ) but persists in the N-INT (Fig. 7, bottom).

TPR increases initially in both groups (Fig. 8, top) with application of the cross-clamp. Between 45 and 90-min the N-INT group continues to increase significantly ( $P = 0.0005$ ), while at the same time the N-SEC TPR does not increase after nerve sectioning. In addition, the TPR at 90 min is statistically higher in the N-INT group than that in the N-SEC group ( $P = 0.04$ ). Figure 8 (bottom) shows that the renal resistance changes are similar in both groups, with no statistically significant differences detected.

There were no significant changes detected in heart rate with the onset of the clamp (Table 1). Heart rate decreased significantly in the STD and N-INT groups ( $P = 0.003$  and  $P = 0.009$ , respectively) between the

clamp max point and the predeclamp point. Removal of the clamp returned heart rates in all groups back to baseline levels. Central venous pressure increased slightly but significantly with clamping only in the ILIAC group ( $P = 0.048$ ). Between the clamp max point and the predeclamp point the ILIAC group again showed a slight increase ( $P = 0.047$ ). Declamping returned CVP in all groups to baseline levels.

Table 2 contains the plasma sodium, osmolarity, and arterial pH data for the SHAM and STD groups at control (preclamp), 45 and 75 min after application of the aortic cross-clamp, and at 10 and 60 min postdeclamp (100 and 150 min from clamping, respectively). The sodium and osmolarity data within each group were consistent throughout the duration of the experimental protocol. There was a statistically significant decrease ( $P < 0.05$ ) in arterial pH in the STD group during clamping (0.067 pH units), but no detectable change in arterial pH in the SHAM group.

## DISCUSSION

### *Clinical Problems/Significance*

Infrarenal aortic reconstruction to treat aneurysmal and occlusive disease is a commonly performed and well-standardized surgical procedure; however, published mortality rates in nonselected series still approximate 4 to 7%. Cross-clamping can be associated with complex hemodynamic disturbances including supraclamp (systemic) arterial hypertension, infraclamp hypotension, and a decrease in cardiac output [1, 2, 7]. Clinical studies in this area are often focused on management of intraoperative hypertension and are confounded by the many therapeutic attempts at controlling or lowering blood pressure prior to or during aortic cross-clamping or compensating for the declamp hypotension [8, 9]. This study viewed intraoperative aortic cross-clamp hypertension as a physiologic reflex rather than a passive hydraulic event, which has both mechanistic and potential clinical implications. The latter includes opportunities for more precisely targeted interventions and, alternatively, the recognition that nonspecific intraoperative interventions to control blood pressure, such as vasodilators or negative inotropes, may further stimulate the reflex arc and exacerbate the adverse cardiac and renal effects that are already operative.

### *Model Considerations*

The literature regarding experimental models of infrarenal aortic cross-clamping is quite variable. In such reports, the extent of infraclamp hypotension is not often documented and continuous measurements of SRBP, IRBP, cardiac output, renal blood flow, and renal function are unavailable. Many of the differences could be due to differences in species, type of anesthetic, or body temperature. Our model consistently produced

**TABLE 1**  
**Heart Rate and Central Venous Pressure**

Group	Variable	Preclamp	Clamp max	Predeclamp	Declamp
STD	HR	100 ± 12	106 ± 20	87 ± 12*	95 ± 7
SHAM	HR	107 ± 7	85 ± 5	113 ± 43	90 ± 12
ILIAC	HR	105 ± 10	96 ± 12	89 ± 13	87 ± 10
NEPHX	HR	89 ± 9	85 ± 7	72 ± 5	98 ± 16
N-SEC	HR	85 ± 13	93 ± 11	89 ± 12	88 ± 13
N-INT	HR	97 ± 6	94 ± 7	82 ± 6*	94 ± 7
STD	CVP	5.3 ± 0.7	5.3 ± 0.6	4.9 ± 0.9	5.2 ± 0.6
SHAM	CVP	4.4 ± 0.7	4.0 ± 0.5	4.5 ± 0.8	4.5 ± 0.9
ILIAC	CVP	4.5 ± 0.4	5.2 ± 0.4*	5.7 ± 0.6*	5.0 ± 0.4
NEPHX	CVP	4.3 ± 0.3	4.5 ± 0.4	4.9 ± 0.6	4.3 ± 0.5
N-SEC	CVP	5.0 ± 0.7	4.6 ± 0.4	5.4 ± 0.5	5.5 ± 0.5
N-INT	CVP	4.6 ± 0.3	5.0 ± 0.3	5.2 ± 0.4	4.8 ± 0.3

*Note.* Heart rate (beats/min) and central venous pressure (mm Hg) throughout the protocol in all experimental groups. Significance is shown with asterisks (\*). Heart rate in the STD and N-INT groups was significantly decreased at predeclamp compared to clamp max (STD,  $P = 0.003$ ; N-INT,  $P = 0.009$ ) before returning to baseline levels upon clamp removal. Central venous pressure in the ILIAC group was increased at clamp max compared to preclamp ( $P = 0.048$ ) and was increased at predeclamp compared to clamp max ( $P = 0.047$ ), before returning to baseline levels after removal of the clamp.

hindlimb hypotension ( $13 \pm 1$  mm Hg) and presumably ischemia. This was accomplished with infrarenal aortic cross-clamping and by ligating the collateral branches located between the renal and iliac arteries. Collateral ligation has both laboratory [10, 11] and clinical relevance in that active bleeding from infrarenal lumbar vessels is virtually always dealt with by ligation rather than reimplantation. Distal hypotension in the nonexercising limb is the sine qua non for the delayed reflex systemic hypertension that we observed.

In clinical reports, the extent of infrarenal clamp hypotension is generally undocumented and likely varies widely. Our own empiric observations have indicated that during uncomplicated aneurysm repair, clamping the infrarenal aorta produces downstream hypotension comparable to that reported for this animal model. Brisk back bleeding has been used by some as evidence of ade-

quate perfusion pressure, but such pressures are well below opening pressure in the capillary beds. Vigorous bleeding such as might occur with a vena cava laceration is a familiar example of low-pressure bleeding ( $5\text{--}7$  mm Hg) which can be profuse but is well below critical capillary opening pressures. Our model parallels the clinical setting and establishes a consistent and reproducible hypotension below the aortic clamp.

#### Potential Mechanisms

The mechanical impedance theory explains the systemic arterial hypertension associated with aortic clamping as a passive hydraulic event that increases afterload secondary to placement of the clamp. In this study the drop in IRBP was immediate with clamping and the 64% increase from baseline in supraclamp pres-

**TABLE 2**  
**Plasma Sodium, Osmolarity, and pH**

	Time (min)				
	Preclamp	45	75	100	150
STD Na (meq/dl)	142 ± 2	141 ± 2	143 ± 1	142 ± 1	144 ± 2
SHAM Na (meq/dl)	143 ± 0	141 ± 1	140 ± 1	139 ± 1	140 ± 1
STD osmolarity (mOsmole/kg)	303 ± 3	305 ± 1	303 ± 1	300 ± 3	299 ± 4
SHAM osmolarity (mOsmole/kg)	301 ± 1	305 ± 3	302 ± 3	303 ± 8	293 ± 9
STD pH	7.385 ± 0.008	7.372 ± 0.016	7.347 ± 0.011*	7.318 ± 0.013*	7.340 ± 0.011*
SHAM pH	7.395	7.39	7.395	7.39	7.395

*Note.* Plasma sodium, plasma osmolarity, and arterial pH for the STD and SHAM groups during the experimental period. Significance is shown with asterisks (\*). Arterial pH in the STD group was lower than the preclamp value at 75, 100, and 150 min ( $P < 0.05$ ). Sample sizes are  $n = 6$  for STD and  $n = 4$  for SHAM, except for SHAM pH where  $n = 2$ .



sure developed over a 20- to 30-min time period. It was delayed in onset and slowly progressive; such is not consistent with a simple increase in mechanical impedance, but rather with an active physiological reflex engendered to counter lower torso hypotension and/or ischemia. Other laboratories have reported related aspects of the systemic response to aortic cross-clamping [10, 11]. Declamping quickly returned both SRBP and IRBP to similar levels, which were significantly higher than baseline, but which gradually returned to baseline 10 to 15 min postclamp.

Other etiologies have been set forth to explain cross-clamp hypertension, including a generalized sympathetic discharge and renal mechanisms. Neither is a likely explanation because a generalized sympathetic discharge would produce marked positive inotropic and chronotropic effects as well as a marked reduction in renal blood flow. There were no significant changes in HR, CVP, or RBF during the experimental period and only small increases in CO (Fig. 4, bottom), thus virtually obviating massive sympathetic discharge as a primary consideration. Past studies have shown reduction in RBF and GFR [14] or histological damage [15], while others show no change [16, 17] and some have shown a rise in plasma renin activity with aortic cross-clamping [18, 19]. In this study no measurable change in plasma renin activity, RBF, or GFR was observed. In addition the cross-clamp was purposefully placed well below the renal arteries. Furthermore, the same delayed hypertensive response occurred after removing both kidneys. Thus, a predominantly renal etiology is unlikely.

### Proposed Reflex

Prior studies have provided evidence that skeletal muscle contains nerve afferents that can elicit a reflex pressor response when stimulated by exercise [12, 13, 20, 21]. We are proposing that the hypertensive response seen in our study is a classical reflex, albeit occurring in resting muscle (Fig. 9). The initial stimulus would be the hypotension/hypoperfusion/ischemia in the hind limb secondary to the aortic cross-clamp (the exact stimulus could be any one of a host of physiological variables, such as O<sub>2</sub>, CO<sub>2</sub>, pH, temperature, etc.). The delayed nature of the pressor response suggests that one or more of these "indicators" of ischemia needs to accumulate and reach some type of "activation threshold" triggering the pressor response. This stimulus could be perceived by a receptor located in the hind limb; stretch receptors, baroreceptors, chemoreceptors, or a nociceptor are likely candidates. A neural or humoral afferent pathway then signals the brain which initiates a series of effector mechanisms to increase systemic arterial pressure and thus overcome the initial stimulus. The efferent pathway may be neural or humoral but must act to increase either TPR or CO.

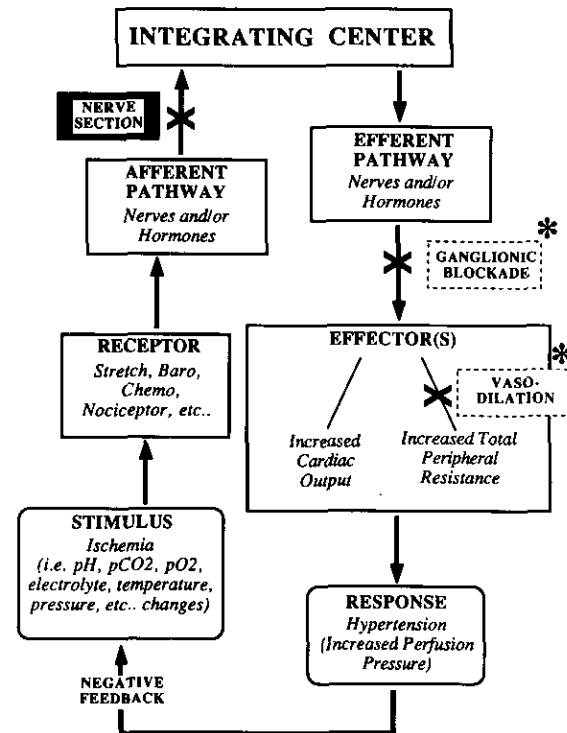


FIG. 9. Proposed generalized reflex arc for the hypertensive response to aortic cross-clamping. Nerve sectioning is shown disrupting the afferent pathway. Dissection of the efferent limb, as indicated by the asterisks (\*), is described elsewhere [22].

### Afferent Pathway

Julius and co-workers have reported a hypertensive response in studies on dogs [23] and man [24] with application of lower body compression. The pressure responses they observed were lessened by 70% with spinal anesthesia. The blockade by spinal anesthesia suggests the activation of a neural reflex similar to that which we ablated with the nerve-sectioning protocol. In addition, Freund *et al.* [25] found that stimulation of small sensory fibers during hindlimb ischemia elicits a centralized pressor response while the use of peridural anesthesia blocked this response. Dorsal root section also abolished the pressor response to occlusion of circulation to exercising hindlimb muscles in cats [20].

Aortic cross-clamping may be associated with increases in systemic concentration of catecholamines [26] and renin activity [18, 19], which could act centrally or have a clear vasoconstrictive capability. Gelman *et al.* [27] showed that vasoconstrictors (angiotensin and catecholamines) are released during aortic cross-clamping and can cause an increase in resistance in an isolated hind limb in the dog. This vasoconstriction was eliminated by the administration of an  $\alpha$ -adrenergic blocker as well as an angiotensin-converting enzyme inhibitor. Several studies in which both the aorta and the inferior vena cava were occluded have shown less of a hyperten-

sive response compared to aortic cross-clamp alone [12, 28, 29], supporting the hypothesis that a factor released from the ischemic hindlimb may be the initiating stimulus. Two observations argue against this position in the current series of experiments. First, the elimination of the response by nerve section would not have stopped the efflux of such mediators from the limb and second, the one-limb versus the two-limb protocol should have given half the response if the involved mediators were released on the basis of tissue mass. We cannot, however, exclude a contributing role for circulating factors in this response.

The systemic hypertension is maintained throughout our protocol because the initial hindlimb ischemic stimulus is not eliminated by the increased systemic pressure. In effect, the negative feedback loop is never allowed to close. Clamping the aorta following ligation of collateral vessels minimizes the transmission of the 56 mm Hg increase in systemic pressure (88 to 144 mm Hg) to the hindlimb as indicated by only an 8 mm Hg increase in infraclamp pressure (13 to 21 mm Hg) (Fig. 3), thus maintaining the afferent ischemic signal from the hindlimb. In the clinical situation there may be increased flow to the ischemic lower extremities utilizing the now increased perfusion pressure if abundant preformed collateral exists. Such collateral perfusion would gradually terminate the afferent signal necessary for the reflex hypertension if the collaterals were highly efficient.

#### *Efferent Pathway*

In the STD group there was a marked increase in renal resistance and a somewhat slower increase in TPR (Fig. 6) associated with the increase in SRBP (Fig. 4). The stronger association between renal resistance (Fig. 6, bottom) and SRBP favors a dominant role for increased renal resistance as the responsible effector mechanism. This vasoconstriction mechanism explaining the pressor response was previously suggested in exercise-induced hypertension [12]. Rowell and O'Leary [13] have reviewed a reflex hypertension occurring with exercise which is rapid in onset (2–3 min), and related to both muscle mass involved and the intensity of the exercise. While both responses involve hypertension, the time course (2 to 3 min vs 20 to 30 min) and initial conditions (exercise vs rest) are substantively different.

It is argued that the ultimate response of this proposed reflex arc is an active increase in MAP elicited specifically to overcome the initial stimulus, hypotension/hypoperfusion of the hindlimbs. In the bilateral nephrectomy protocol the hypotensive hindlimb sent the same afferent signal, but the available effector mechanisms for producing hypertension were altered. Rather than a resistance change, the reflex shifted to increased cardiac output (Fig. 4, bottom). The resulting systemic arterial hypertension would function to minimize the hindlimb ischemia similar to the observations of Lind *et al.* [30]

and MacDonald *et al.* [31]. They concluded from studies of the pressor response to isometric arm exercise that when one mechanism of increasing blood pressure is ineffective, another is called forth to effect the same pressor response, strongly suggesting the reflex nature of both responses. If this sequence were operable, one would predict that even a single hypotensive limb would send afferent signals sufficient for an increase in perfusion pressure. In our study only one limb was made hypotensive in the ILIAC group and a similar hypertension was produced. The most compelling demonstration of the reflex character of the response to aortic cross clamping was the sectioning of the nerves from the limb. By cutting the neural traffic from the limb and essentially eliminating the hypertensive response we have given strong evidence that afferent information coming from the hypotensive limb is necessary for the maintenance of the hypertension. We cannot completely exclude the possibility of nerve sectioning also eliminating efferent nerve traffic but it is highly improbable that efferent nerve traffic to a single limb could produce or sustain systemic hypertension.

In summary, these studies suggest a novel reflex systemic hypertension which occurs in response to confirmed hindlimb hypotension produced by infrarenal aortic cross-clamp. This reflex hypertension: (1) is progressive but delayed in onset (20–30 min), (2) originates from resting hind limb, and (3) can be produced by an active increase in either vascular resistance or cardiac output. We have sequentially altered the afferent limb (by nerve section and unilateral clamp application) and efferent limbs (nephrectomy) of this proposed reflex to further test the hypothesized reflex mechanism of the response. Better understanding of the potential reflex nature of the developing hypertension in the laboratory setting may ultimately lead to more appropriate clinical management strategies and avoid nonspecific antihypertensive therapies which may have considerable potential for adverse cardiac and renal effects.

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