Effects of Infrarenal Aortic Cross-clamping on Renal Hemodynamics in Humans

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While the systemic cardiovascular consequences of infrarenal aortic cross-clamping during aortic abdominal surgery are well documented, its repercussions on renal hemodynamics in humans have not been reported. In 12 patients, scheduled for elective aortic surgery, renal clearances, using ^{51}Cr EDTA and ^{125}I hippuran, were measured before, during, and after infrarenal aortic cross-clamping. A continuous infusion of mannitol 20% at a rate of 100 ml/h was administered throughout the study. Arterial and renal venous blood sampling, obtained at the midpoint of each period, permitted calculation of the extraction fraction of ^{125}I hippuran and accurate determination of renal blood flow and its cortical-extracortical distribution. Although cardiac output and systemic vascular resistance did not change significantly between the three study periods, infrarenal aortic cross-clamping decreased ^{125}I hippuran clearance by $29 \pm 15\%$ ($P < 0.05$) and renal blood flow by $38 \pm 14\%$ ($P < 0.001$). Simultaneously, an increase of $75 \pm 31\%$ in renal vascular resistance ($P < 0.05$) was observed and the extraction fraction of ^{125}I hippuran increased from 0.67 ± 0.05 to 0.74 ± 0.05 ($P < 0.01$). All of these changes, which indicate global diminution of renal perfusion with a redistribution of renal blood flow toward the cortical compartment, persisted for at least 1 h after release of the aortic clamp. Early signs of renal tubular damage, such as the appearance of lysozyme and ligandine in the urine, however, were never observed. The authors conclude that infrarenal aortic cross-clamping produces profound and sustained alterations in renal hemodynamics and may be harmful in patients with impaired renal function or when surgical occlusion of the aorta is prolonged. (Key words: Arteries: abdominal aorta. Kidney: blood flow; filtration.)

PREVENTION AND TREATMENT of the systemic hemodynamic consequences of infrarenal aortic cross-clamping occurring in patients during aortic abdominal surgery are well documented.[1-5] Even patients with cardiac or coronary insufficiency can tolerate this surgical procedure.[6,7] However, despite the progress in surgical and anesthetic management, decreased renal function still is observed after aortic abdominal surgery and remains an important problem in the postoperative period.[8-12] Although the pathogenesis of this renal impairment is not well understood, it probably is related to aortic cross-

clamping, which is mandatory during aortic abdominal surgical procedures. The results of numerous experimental studies investigating the effects of infrarenal aortic cross-clamping on renal perfusion[13-17] and intrarenal blood flow distribution[15-17] are not conclusive and do not provide sufficient information to understand the renal dysfunction occurring in humans after aortic abdominal surgery. The purpose of this study was to evaluate the renal consequences of infrarenal aortic cross-clamping in humans by measuring renal clearances, global renal blood flow, and its distribution between cortical and extracortical compartments in patients undergoing surgical procedures on the abdominal aorta.

Patients and Methods

Twelve patients, two women and 10 men, scheduled for elective aortic abdominal grafting surgery, gave their informed consent to participate in this study, which was approved by the Committee for Ethics in Clinical Research of our institution. Six patients were operated for aortoiliac occlusive disease and the other six for non ruptured aortic aneurysm. The age of the patients ranged from 55 to 75 yr (mean 64 yr). Only three subjects were affected by cardiovascular medication, one was taking digoxin and verapamil for atrial fibrillation and congestive heart failure, one labetalol for coronary artery disease, and one reserpine for systemic arterial hypertension. The remaining nine patients were free from medication and known diseases, besides their abdominal aortic pathology.

The patients were premedicated with morphine sulfate 0.1 mg/kg im 60–90 min before arrival in the operating room. Anesthesia was induced with bolus doses of fentanyl (5 μg/kg) and thiopental (3–5 mg/kg); tracheal intubation was facilitated with pancuronium bromide (0.1 mg/kg). Throughout the surgical procedure, anesthesia was maintained with nitrous oxide 60% in oxygen and fentanyl, which was infused continuously at the rate of $8-12 \ \mu g \cdot kg^{-1} \cdot h^{-1}$. Additional pancuronium was administered as needed. The patients were ventilated with a volume cycled ventilator and maintained at a Pa_{CO_2} between 35–40 mmHg and a Pa_{O_2} between 80–120 mmHg. Temperature was maintained above 35°C. The following variables were monitored continuously in all patients: heart rate, mean arterial pressure (MAP) using an indwelling arterial catheter, central venous pressure (CVP), and urinary output (UO).

Glomerular filtration rate and renal plasma flow were measured using clearances of ^{51}Cr EDTA (C_{EDTA}) and ^{125}I hippuran (C_{HIP}), respectively. The labeled compounds were injected immediately after induction of anesthesia as a bolus of 60 μCi ^{51}Cr EDTA and 30 μCi ^{125}I hippuran. In addition, a continuous infusion of 72 μCi ^{51}Cr EDTA and 36 μCi ^{125}I hippuran in 500 ml mannitol 20% at a rate of 100 ml/h was administered throughout the study in order to obtain an adequate UO and stable blood levels of labeled compounds that were, respectively, less than 6 μg/l for ^{51}Cr EDTA and less than 100 μg/l for ^{125}I hippuran.

After an equilibrium period of 64 ± 17 min ($\bar{x}$ ± SD), urine was collected through an indwelling intravesical catheter during three consecutive periods: 1) before infrarenal aortic cross-clamping for 61 ± 16 min (preclamp); 2) during infrarenal aortic cross-clamping for 58 ± 20 min (perclamp); 3) after infrarenal aortic cross-clamping for 56 ± 11 min (postclamp).

At the midpoint of each period of urine collection, in order to calculate the extraction fraction of ^{125}I hippuran (E_{HIP}), arterial blood was withdrawn from the radial artery, and renal venous blood was sampled by the surgeon, who punctured the left renal vein close to the kidney and withdrew blood very slowly to avoid vena cava blood contamination. At the time of blood sampling in all patients, standard hemodynamic data were recorded, which in six patients included measurements of cardiac output (CO) in triplicate and pulmonary capillary wedge pressure using a quadruple lumen Swan-Ganz® 7F catheter and the thermodilution technique. Throughout the study, the blood loss was monitored and Ringer's lactate and blood were administered in order to maintain filling pressures and hematocrit (Ht) at preclamp levels.

In order to determine the possible influence of the anesthetic management on E_{HIP}, which cannot be measured noninvasively, E_{HIP} was measured in three additional nonanesthetized patients during aortic angiography. These measurements were performed before the injection of contrast medium. The patients were similar to the 12 anesthetized patients as regards age and existing pathology.

Plasma and urinary radioactivity of ^{51}Cr EDTA and ^{125}I hippuran were measured with an auto-gamma scintillation spectrometer (Packard 5230). C_{EDTA}, C_{HIP}, creatinine clearance (C_{CR}), E_{HIP}, renal blood flow (RBF), filtration fraction (FF), free water clearance (C_{H_2O}) and systemic and renal vascular resistances (SVR, RVR) were calculated using the following equations:

$$C_{EDTA} \text{ (ml/min)} = \frac{\text{urinary } ^{51}\text{Cr EDTA} \times \text{UO (ml/min)}}{\text{plasma } ^{51}\text{Cr EDTA}}$$

C_{HIP} and C_{CR} were obtained using the same formula by replacing ^{51}Cr EDTA with ^{125}I hippuran or creatinine.

$$E_{HIP} = \frac{\begin{array}{c}\text{arterial plasma } ^{125}\text{I hippuran} \\ - \text{ renal venous plasma } ^{125}\text{I hippuran}\end{array}}{\text{arterial plasma } ^{125}\text{I hippuran}}$$

$$RBF \text{ (ml/min)} = \frac{C_{HIP}}{E_{HIP}} \times \frac{100}{100 - Ht}$$

$$FF = \frac{C_{EDTA}}{C_{HIP}}$$

$$C_{H_2O} \text{ (ml/min)} = UO \text{ (ml/min)} - UO \text{ (ml/min)} \times \frac{\text{urinary osmolality}}{\text{plasma osmolality}}$$

$$SVR \text{ (dyn·s·cm}^{-5}) = \frac{MAP - CVP}{CO} \times 80$$

$$RVR \text{ (dyn·s·cm}^{-5}) = \frac{MAP - CVP}{RBF} \times 80$$

The renal fraction of CO is expressed as RBF/CO ratio.

Urinary lysozyme was measured using a modified method according to Favre et al.,[18] and ligandine was measured using the method of Habig et al.[19]

The results were expressed as means ± SD. All data of renal perfusion were normalized for body surface area of 1.73 m^2. The data obtained during three study periods were compared with one-way analysis of variance and statistical difference detected with the test of Scheffé, with $P < 0.05$ being considered significant.

Results

The preoperative renal function was in the normal ranges for all patients as evidenced by the C_{CR} of 83 ± 23 ml/min.[20] On arteriography, the size of both kidneys was normal, the secretion of contrast medium was symmetric, and adequate and the renal vessels were free of any pathology.

Hemodynamic, respiratory, and metabolic variables remained stable during the study; vasopressors, vasodilators, or bicarbonate never were administered. The Ht was maintained at 38 ± 4%, 36 ± 3%, and 37 ± 4% in the preclamp, perclamp, and postclamp period, respectively, by administering whole blood (700 ± 85 ml).

Systemic hemodynamic results are summarized in table 1. No significant change in any variable measured was observed before, during, and after infrarenal aortic cross-clamping.

Renal hemodynamic and functional data are presented in table 2. Besides UO, C_{EDTA}, and FF, the other variables measured varied significantly during perclamp period, without returning to basal values during the first hour of observation after release of the aortic clamp. Infrarenal aortic cross-clamping produced a significant decrease of 29 ± 15% in C_{HIP}, 38 ± 14% in

TABLE 1. Systemic Hemodynamic Variables Measured at Midpoint of Preclamp, Perclamp, and Postclamp Period ($\bar{x} \pm$ SD)

		Preclamp	Perclamp	Postclamp
Heart rate (beats/min)	n = 12	77 ± 12	70 ± 13	68 ± 12
Mean arterial pressure (mmHg)	n = 12	100 ± 12	104 ± 9	96 ± 12
Central venous pressure (cmH$_2$O)	n = 12	6 ± 4	6 ± 3	7 ± 3
Pulmonary capillary wedge pressure (mmHg)	n = 6	10 ± 2	10 ± 1	11 ± 2
Cardiac output (l/min)	n = 6	4.8 ± 0.9	4.0 ± 0.8	4.4 ± 0.9
Systemic vascular resistance (dyn·s·cm^{-5})	n = 6	1,570 ± 403	1,946 ± 513	1,682 ± 427

RBF and a significant increase of 75 ± 31% in RVR. E$_{HIP}$ increased also significantly from 0.67 ± 0.05 to 0.74 ± 0.05; individual variations are presented in figure 1. All these changes remained significantly different in the postclamp period when compared with the preclamp data, but not different when compared with perclamp data. The E$_{HIP}$ measured preoperatively in three patients under local anesthesia was similar to the preclamp data, respectively, 0.65, 0.67, and 0.70.

Individual variations of RBF/CO ratio during the three investigation periods are presented in figure 2. The mean values decreased from 0.25 ± 0.03 in the preclamp period to 0.17 ± 0.04 and 0.15 ± 0.07 in the perclamp and postclamp period, respectively. Significant changes were noted only between preclamp and postclamp values.

Lysozyme and ligandine were not detected in any urine sample during the study. The following variables did not change significantly at any time: C$_{CR}$ was 83 ± 23, 64 ± 13, and 65 ± 18 ml/min and C$_{H_2O}$ was −1.01 ± 2.01, −1.28 ± 0.88, and −1.48 ± 0.41 ml/min in the preclamp, perclamp, and postclamp periods, respectively.

Discussion

Measurements of C$_{HIP}$ and E$_{HIP}$ allow for an accurate evaluation of the renal perfusion. It generally is agreed that C$_{HIP}$ corresponds to the cortical or effective renal plasma flow.[21,22] By dividing C$_{HIP}$ by E$_{HIP}$, total renal plasma flow can be calculated.[20] From these values, information can be obtained about the distribution of the total renal plasma and/or blood flow between cortical and extracortical fractions.[23,24]

This study demonstrated a profound alteration in renal hemodynamics during occlusion of the aorta below the renal arteries, characterized by a 75% increase in RVR and a 38% decrease in RBF, whereas systemic cardiovascular variables did not change significantly. Although there was a tendency toward a decrease in CO, the observed changes in renal perfusion can be attributed mainly to infrarenal aortic cross-clamping, since the anesthetic drugs and mannitol were administered continuously throughout the study, ventilatory management was unchanged, and blood volume was maintained at the preclamp level. With one exception,[14] most experimental studies reported no change in RBF during infrarenal aortic cross-clamping.[13,15–17] These conflicting data may be explained by differences in species, in techniques of measurement of RBF, and in preoperative kidney function. In addition, the patients investigated were suffering from severe arteriosclerosis, which can explain the low E$_{HIP}$ calculated in the preclamp period. In the experimental studies, the animals were most probably free from any vascular disease.

Thus, the values of C$_{EDTA}$, C$_{HIP}$, FF, and E$_{HIP}$ measured in the preclamp period are compatible, as postulated by Reubi,[20] with a situation where some nephrons had been destroyed and replaced by nonfunctioning inert tissue that are still perfused, while the remaining nephrons function normally. This hypothesis is supported by histologic data.[25] Since the blood perfusing the inert kidney tissue does not clear the labeled compounds, a slight decrease in C$_{EDTA}$ and C$_{HIP}$, and a

TABLE 2. Renal Hemodynamic and Functional Changes Produced by Infrarenal Aortic Cross-clamping and Declamping ($\bar{x} \pm$ SD, n = 12)

	Preclamp	Perclamp	Postclamp
Urinary output (ml/min)	4.45 ± 3.42	3.10 ± 1.58	3.03 ± 1.69
^{51}Cr EDTA clearance (ml/min)	90 ± 27	71 ± 18	71 ± 30
^{125}I hippuran clearance (ml/min)	429 ± 118	298 ± 77*	267 ± 109†
Extraction fraction of ^{125}I hippuran	0.67 ± 0.05	0.74 ± 0.05†	0.75 ± 0.06†
Renal blood flow (ml/min)	1,034 ± 254	622 ± 135‡	566 ± 226‡
Filtration fraction	0.22 ± 0.06	0.25 ± 0.06	0.27 ± 0.06
Renal vascular resistance (dyn·s·cm^{-5})	7,901 ± 2,617	13,517 ± 4,144*	14,884 ± 6,124†

Statistical difference from preclamp data: $*P < 0.05$, $\dagger P < 0.01$, $\ddagger P < 0.001$.

normal value for FF are expected; whereas E_{HIP} is decreased markedly, since it represents a more sensitive index of the amount of normal renal tissue. In addition, E_{HIP} also can be influenced by other factors such as ventilation,[26] saline and mannitol infusion,[27,28] or anesthetic drugs.[29-31] However, the E_{HIP} values obtained in the three nonanesthesized patients with advanced arteriosclerosis were similar to our preclamp data; RBF and RBF/CO ratio in the preclamp period were in normal ranges, and C_{CR} did not change during the preclamp period when compared with preoperative values. All these data suggest that the anesthetic management probably did not affect at any time the intrarenal blood flow distribution or global renal perfusion and function.

The significant decrease in C_{HIP} and the significant increase in E_{HIP} observed during aortic cross-clamping in each patient (fig. 1) indicate a global diminution of the renal perfusion with redistribution of the RBF toward the cortical compartment; this phenomenon is beneficial and can prevent the development of acute tubular necrosis. The intrarenal blood flow redistribution in favor of the cortex during occlusion of the aorta was not found in experimental studies where no change or decrease in cortical blood flow was demonstrated.[15-17] It is difficult to define the protective role of mannitol, which has been shown to preserve cortical[32] as well as total renal perfusion[14] during infrarenal aortic cross-clamping in animals. In this study, mannitol was administered only in order to obtain adequate UO and more accurate renal measurements. Furthermore, the absence of a significant decrease in C_{EDTA} in the presence of an important reduction in RBF demonstrates preservation of the intrarenal autoregulatory mechanism.

The renal hemodynamic deterioration observed during infrarenal aortic cross-clamping persisted for at least 1 h after the release of the aortic clamp. No systemic cardiovascular changes can explain that phenomenon, since blood volume remained stable and CO tended to increase. Therefore, the absence of early recovery at the end of aortic occlusion could be related to a sustained renal vasoconstriction, which may be secondary to stimulation of the renin–angiotensin system induced by the clamping of the aorta as demonstrated in humans[33,34] as well as in experimental animals.[16,17]

It would have been of great interest to continue the measurements until they returned to control values. However, this was not possible, because we felt it was unethical to prolong the surgical procedure only in order to perform direct renal vein sampling. In order to assess other important factors that could influence renal hemodynamics, such as prolonged anesthetic management or surgical stimulation, it would have been very helpful to perform similar determinations in a
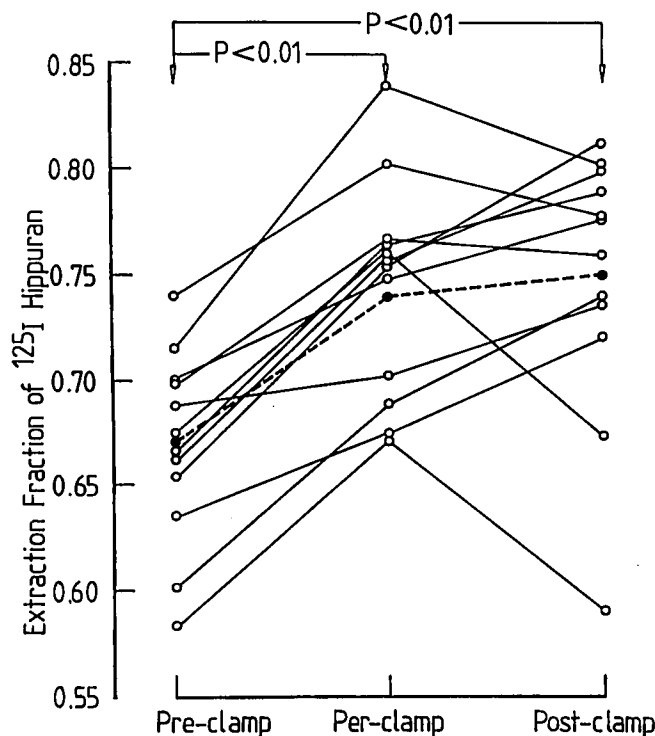

FIG. 1. Individual (O———) and mean (● – – –) changes of extraction fraction of ^{125}I hippuran during three investigation periods.
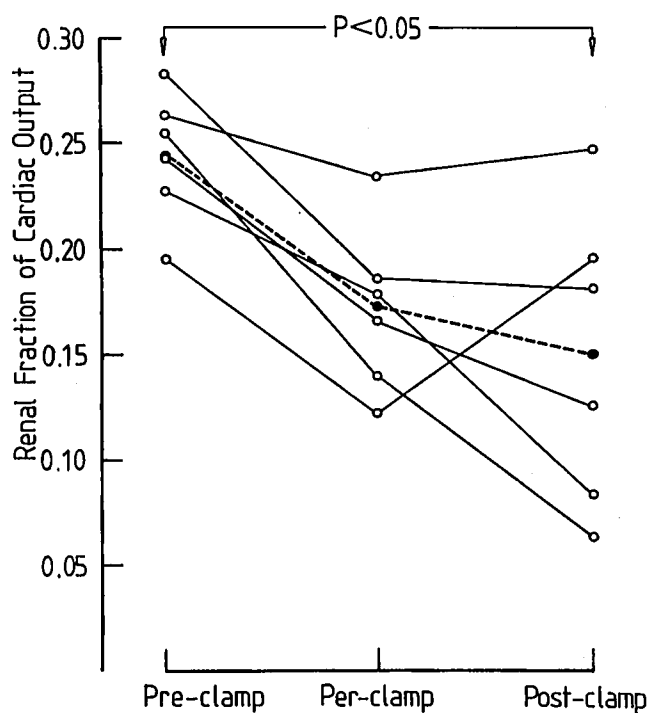

FIG. 2. Individual (O———) and mean (● – – –) variations of renal fraction of cardiac output in the six patients monitored with Swan-Ganz® catheter.

control group. For methodologic reasons, we considered it unethical to use such invasive measurements in patients suffering from advanced arteriosclerosis undergoing peripheral vascular surgery, who would represent the only appropriate control group. Fentanyl and nitrous oxide, however, which were administered continuously throughout the study, are most probably not responsible for the sustained decrease in renal perfusion in the postclamp period, since it was reported that 100 μg/kg of fentanyl in humans,[35] and 1 mg/kg in animals[36] in combination with nitrous oxide did not affect renal function and perfusion. The highest total dose of fentanyl administered in this study was under 50 μg/kg.

With the anesthetic management described, which was intended to maintain CO, extracellular fluid volume, and Ht, the changes observed in renal perfusion did not produce any detectable renal lesion. Integrity of the proximal tubular cells was demonstrated by the absence of lysozyme[18] and ligandine[37] in the urine, while the integrity of the distal segment of the nephron was evidenced by a negative C_{H_2O}.

In conclusion, infrarenal aortic cross-clamping produced profound and sustained alterations in renal hemodynamics, which may have been more profound without administration of mannitol. The observed changes were close to the point where acute tubular necrosis occurs, therefore, this study emphasizes the importance to maintain adequate CO and renal perfusion pressure to avoid acute renal failure after aortic abdominal grafting surgery. In addition, in patients with obvious preoperative renal dysfunction or who undergo prolonged aortic cross-clamping kidney damage may occur. Further studies are needed to devise methods that would provide better protection of the kidney during aortic cross-clamping such as hypothermia or for example renin or calcium antagonists.

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