Renal Function During Extracorporeal Circulation At High and Low Flow Rates: *

Experimental Studies in Dogs

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THE DEVELOPMENT of effective pump-oxygenators has now focused attention upon the biochemical and physiologic effects of total bypass of the heart and lungs. These factors are of significance, as pointed out by Kirklin,[10] in cases of complex intracardiac procedures which may necessitate total bypass for periods of longer than an hour.

Numerous investigators have reported alterations in proteins, electrolytes, acid-base balance, and cellular elements of the blood during extracorporeal circulation with pump-oxygenators.[3, 5, 6] Nevertheless, it has been shown that an understanding of the factors which alter biochemical characteristics of the blood, adequate replacement therapy, and a pump-oxygenator which minimizes trauma to the blood can reduce these changes to a level compatible with consistently successful use of this technic. A study was made of the effect of total extracorporeal circulation upon specific organs and areas of the body; the central nervous system, heart, liver, and kidneys seemed most likely to be affected by a reduction of their blood supply or by changes in the composition of the blood and the circumstances of its delivery to the organ. This investigation is concerned with an evaluation of kidney function in the dog during and immediately following extracorporeal circulation with an artificial pump-oxygenator.

Methods

The Crafoord-Senning pump-oxygenator, described in detail elsewhere,[5] was used in these experiments. The blood is oxygenated on a series of perforated cylindrical rollers and returned to the arterial system from a pump delivering a flow of low pulsation at 280 beats per minute.

Freshly collected heparinized donor blood was used to fill the machine. The method of collection involved the partial replacement of blood volume of the donor dog with intermittent transfusion of blood salvaged from a previous experiment. This allowed a considerably larger amount of blood to be obtained from a single donor dog. However, some mixture of fresh with old blood was produced, which undoubtedly resulted in a higher level of plasma hemoglobin than might otherwise be present.

All animals were intubated and ventilated with an intermittent positive-negative pressure respirator.†

Urine collections were obtained by an indwelling catheter. To insure complete evacuation, each urine collection period

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was followed by two rinses of the bladder using 10 to 20 ml. of H_2O. The rinses were added to the urine and the total volume was analyzed.

For measurement of renal clearances, a catheter was introduced into the right renal vein. Three different technics were used in passing this catheter. In approximately the first one-third of the dogs, a Cournand catheter was inserted through the femoral vein into the inferior vena cava and manually directed into the renal vein through an abdominal incision. In the second third, the catheter was introduced fluoroscopically into the inferior vena cava through the jugular vein and again directed manually into the renal vein. In addition, in some dogs a sling-ligature was passed around the renal vein and tightened during collection of renal venous blood to prevent back-flow from the inferior cava. The trauma associated with laparotomy and manipulation of the gut and structures surrounding the renal vessels prompted us to use the indirect fluoroscopic technic of Odmann for catheterization of the renal vein in the last group of dogs.

After priming doses of para-aminohippurate (80 mg.), creatinine (50 mg.), and 5.5 per cent glucose in water (200 ml.), these substances were infused into a jugular vein and femoral vein at a constant rate throughout the rest of the experiment. The clearances of PAH and creatinine were used as measures of the renal plasma flow and glomerular filtration rate respectively.

Plasma and urine PAH * were measured by the method of Smith *et al.* Plasma and urine creatinine were determined by the method of Folin. Plasma and urine chloride were analyzed by the potentiometric method of Norberg. Plasma and urine sodium and potassium were measured using a flame photometer.

In all cases, the concentration of PAH and creatinine at the midpoint of the urine collection period was estimated by graphic interpolation on time curves of the arterial and renal venous concentrations.

Surgical Procedure

Adult mongrel dogs weighing from 11 to 22 Kg. were anesthetized intraperitoneally with sodium pentobarbital. Additional anesthesia was administered during the experiment as needed.

A left thoracotomy was performed through the fourth intercostal space. An arterial cannula was placed into the aorta through the left subclavian artery; a venous cannula was inserted through the auricular appendage into the right auricle. A sling-ligature was passed around the main pulmonary artery and occluded during perfusion to produce total heart-lung by-pass.

Heparin, 4 mg./Kg., was administered intravenously immediately prior to cannulation.

Operations were performed under clean, but not sterile, technic and all dogs were sacrificed following post-perfusion measurements.

Experimental Plan

After the initial priming doses of PAH, creatinine, and glucose/water were administered, serial observations were carried out. In each experiment separate studies were performed during the following periods:

Period I: Immediately after placement of necessary cannulae for collection of samples.

Period II: Following thoracotomy and placement of perfusion cannulae.

Period III: During the first half-hour period of EC.

Period IV: During the second half-hour period of EC.

* For convenience the following abbreviations are used in this article:
PAH—para-aminohippurate,
RPF—renal plasma flow,
GFR—glomerular filtration rate,
EC—extracorporeal circulation.

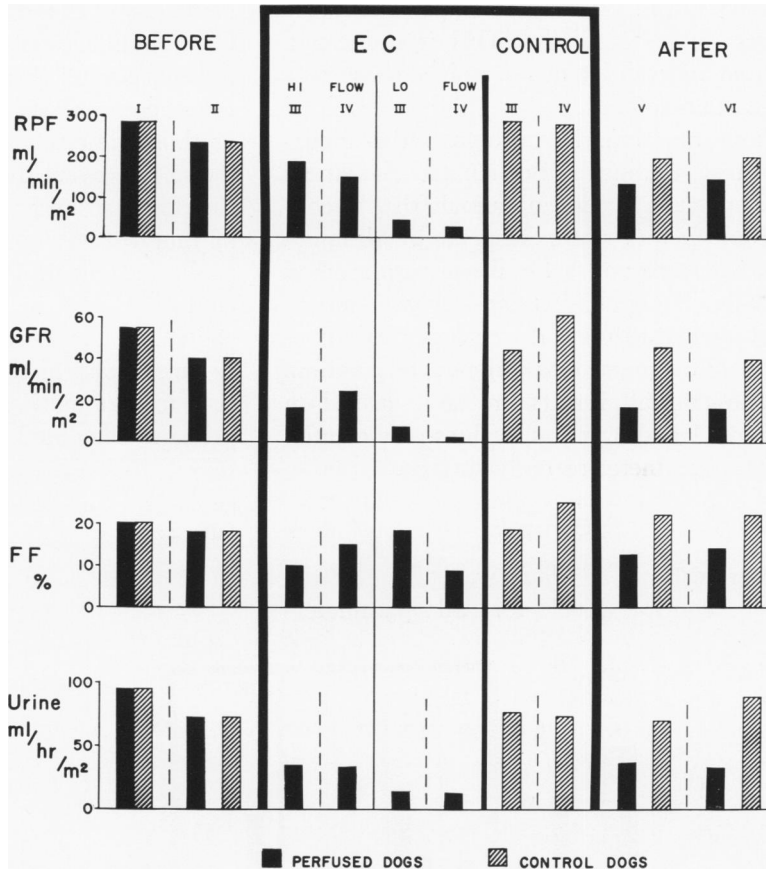

FIG. 1. In Periods I and II the values for control dogs and test dogs are identical and are represented as separate only in a figurative sense.

Periods V and VI: Consecutive one-hour periods following discontinuance of EC and return to normal cardiac output.

The following sequences of flows were used during the periods of extracorporeal circulation:

1. High flow throughout (95–105 ml./Kg./min.)
2. High flow during the first half hour followed by low flow during the second half hour (35–45 ml./Kg./min.)
3. Low flow followed by high flow.

A control group of nine dogs was treated in the same manner as the dogs subjected to extracorporeal circulation with the same operative maneuvers and time intervals, but without extracorporeal circulation being put into effect.

Results

Forty-seven dogs were studied using the above described technics. Nine animals were excluded because of technical errors, failure to excrete adequate urine, ventricular fibrillation, excessive hemolysis, or errors in laboratory analysis. In the remaining 38 animals, acceptability of the measurements in any given period depended upon urine production. Despite the appreciable quantities of isotonic glucose solution administered, urine flows were generally meager. In view of the difficulty of accurately collecting small quantities of urine, an arbitrary lower limit of 5 ml./hr. was set, below which measurements were regarded as unacceptable. Exception was made in the periods during which the animal was being perfused with a low flow rate, the resulting

urinary outputs during these periods rarely being above 5 ml./hr. This introduces a certain bias and tends to select those animals that maintained a higher level of kidney function. Nevertheless, the deviation from the mean of calculated clearances was so great in certain animals that uncontrolled factors were suspected. Although the flow rate and arterial pressure seemed adequate, they had inexplicably poor urinary output. Hence it was assumed these animals belonged to a different population.

The over-all results are summarized in Figures 1 and 2 with all values recalculated per square meter of body surface.

Controls

Period I in all dogs was taken as the basic control level for all parameters studied. In the group of animals carried throughout all periods as controls without extracorporeal circulation, in Period II (thoracotomy) the changes were the same as those described below for the test animals. However, the transient character of the decreases in function during the trauma of thoracotomy is evident from the return to normal during Periods III and IV in the control dogs, in which the clearances showed no statistical difference from Period I. In contrast to the restored kidney function, in Periods III and IV the mean arterial pressure remained slightly lower * than in

* Asterisks are used here and subsequently as an index of calculated statistical significance as follows:

* $.01 < P < .05$
** $.001 < P < .01$
*** $P < .001$

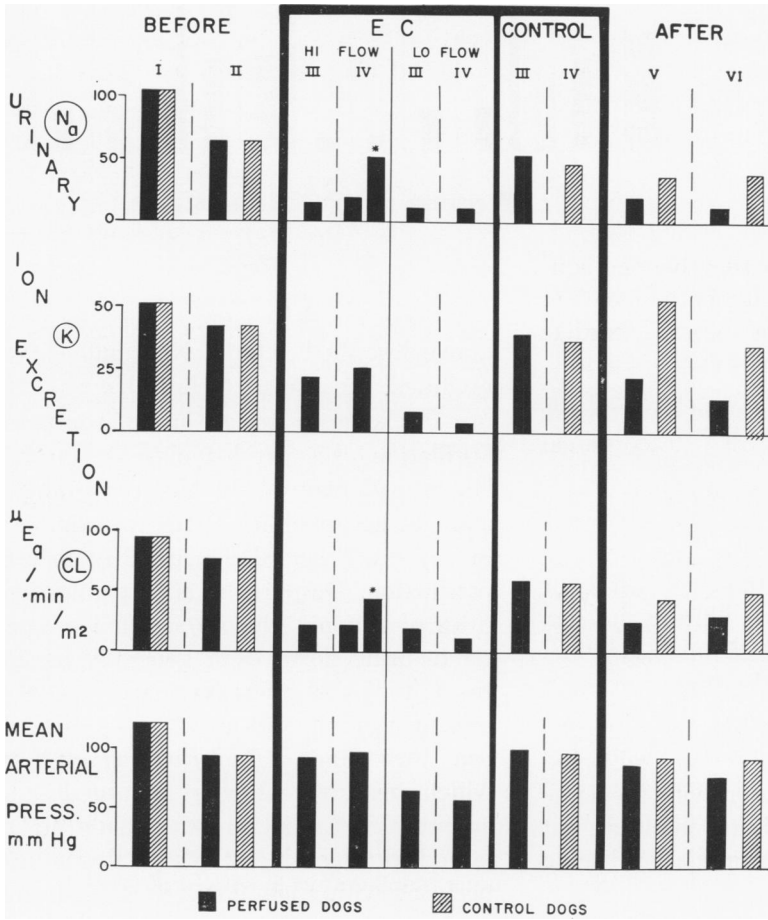

FIG. 2. In Periods I and II the values for control dogs and test dogs are identical and are represented as separate only in a figurative sense. * indicates high flow in Period IV following a low flow in Period III; the accompanying bar represents high flow following high flow. In all other parameters there was no significant difference between high flow following low flow and high flow following high flow and these data are therefore presented as a single group.

Period I. As a consequence, only the first period from all dogs is used as the reference period in the statistical testing of changes in mean arterial pressure, whereas Periods III and IV in the control animals together with Period I in all animals constitute the reference group for all other parameters except sodium excretion.

Period II—Surgical Trauma. During the surgical trauma associated with thoracotomy, there was a decrease in all measured kidney functions and blood pressure. This depression in function is significant for renal plasma flow,*** glomerular filtration rate,** and mean arterial pressure,*** but less so * for excretion of urine and electrolytes.

Periods III and IV: EC—High Flow Rate. Perfusion with a high flow rate did not produce a significant decrease in arterial pressure as compared to control animals in the same periods. Nevertheless, there was a significant decrease in renal plasma flow *** and glomerular filtration rate,*** in excretion of potassium *** and chloride,*** and in urine volume ** and sodium excretion.** There were no significant differences between Period III and Period IV in those dogs that had a high flow rate in both periods. However, the sodium excretion was significantly higher ** during a high flow period following a low flow period than in dogs in whom a high flow was maintained throughout the perfusion. The same tendency was apparent for chloride excretion, but without probable significance.

Periods III and IV: EC—Low Flow Rate. During perfusion with a low flow rate there was a pronounced fall in arterial pressure,*** clearances,*** and urine *** and electrolyte excretion *** as compared to the levels during high flow rate; the exception was sodium excretion which decreased less significantly.* Function during low flow in Period IV did not differ significantly from that obtained during low flow in Period III.

Periods V and VI. *In control* dogs the RPF and GFR were significantly ** lower in Periods V and VI than in the reference periods. Urine output and potassium and chloride excretion, however, were not reduced. Sodium excretion differed from the other ions. After the high excretion in the first period, there appeared to be a reduction increasing with time. This reduction was not significant for Periods II, III, or IV, but attained significance * for Periods V and VI of the control dogs.

After EC the RPF and GFR were only slightly lower than in the high flow EC periods, but there was a significant reduction *** as compared to Periods V and VI in control dogs. The mean arterial pressure,* urine output,*** sodium,** chloride,** and potassium * excretions were significantly lower than in the corresponding Periods V and VI in control dogs. Showing the same tendency as noted in the control dogs, after perfusion there was a further significant * reduction in sodium excretion.

In all cases there was a good correlation between the degree of reduction of kidney function and the decrease in mean arterial pressure.

The concentrations of sodium, potassium, and chloride in the blood were notably constant in spite of the EC flow rate or the general condition of the dogs.

Discussion of Experimental Methods

In examination of the values obtained, it appears that our mean PAH clearance of 286 ml./min./m.^{2} body surface agrees well with the published data; Houck [9] reported a value up to 266 ml./min./m.^{2} Our figure of 54.9 ml./min./m.^{2} for glomerular filtration is lower than Houck's value of 84.4; consequently, our filtration fraction is lower than reported values by Houck and by Stanler, Katz, and Rodbard.[15]

Philips *et al.*,[13] point out that because of the low plasma PAH content of renal venous blood, rapid in vitro diffusion of PAH

takes place from the cells to the plasma. With suitable technics an extraction ratio of 87 per cent may be obtained. However, in our experiments no attempt was made to institute rapid cooling and centrifugation of renal venous samples. As a rule, all samples were centrifuged one and one-half hours or more after the last had been collected; hence equilibrium should have been reached between cells and plasma, and from the data of Philips *et al.*, one may expect a maximum reduction in the extraction ratio of 20 to 25 per cent. Our mean value for extraction ratio of 60.5 per cent is in agreement with this. This does not, however, impair the validity of the values for purposes of comparison. In confirmation of this, the renal plasma flow values calculated from arterial PAH levels alone (assuming 100 per cent extraction) show the same direction of change with the experimental conditions as the renal plasma flow calculated from the arterial-venous difference in PAH.

Discussion of Results

Previous work in this laboratory has shown that there is moderate impairment of hepatic function at low flow rates [2] and that oxygen consumption during EC is dependent on flow rate, almost to the exclusion of variations in arterial pressure.[1] We proposed to investigate whether this relation held for renal function as well.

During EC when the flow rate was reduced by one-half, the renal plasma flow and glomerular filtration rate were reduced to one-third of the previous levels or less; the filtration fraction did not change significantly in this case. Certain factors may account for this disproportionate fall in the apparent effective renal blood flow and filtration rate:

1. A selective redistribution of blood flow resulting in a shunting of blood away from the kidney and favoring the perfusion of more vital parts of the body.
2. Shunts within the kidney itself, bypassing the glomerular and tubular capillaries.
3. Errors associated with the use of PAH as an indicator of renal plasma flow under conditions of low systemic pressure.

With the reduction of flow rate, arterial pressure fell from a mean of 95 mm. Hg to a mean of 58 mm. Hg. Since we were unable to devise a method for maintaining high arterial pressures with low flow rates without producing marked renal vasoconstriction, it was not possible to separate the specific effects of lowered systemic blood pressure and lowered perfusion flow rates.

The low pressures encountered during low flow and after EC, and to a lesser extent during high flow, present a serious problem in the evaluation of changes in renal plasma flow. Corcoran and Page [4] have shown that at low arterial pressures, diodrast clearances are no longer valid indicators of renal plasma flow. This may well be true for PAH also and could be explained by the "partitioning" of renal blood flow. Some nephrons are able to secrete diodrast, or PAH, at lower arterial pressures than others; in this case part of the substance may be allowed to move to the venules without being secreted, or may be secreted, but due to low filtration pressure may not be excreted. This phenomenon has been demonstrated in reverse fashion by Edling *et al.*,[7] who showed that with increasing hydrostatic pressure transmitted through the ureters to the kidney tubules, excretion in the kidney ceased, presumably because of a decreased pressure differential available for filtration and excretion. In this circumstance, the injection of a radiopaque iodine compound (Umbradil) clearly outlined the kidney, indicating that the compound had been secreted in

the tubular cells but could not leave the kidney. They similarly showed that a prior lowering of the blood pressure by hemorrhage or vasodilatory drugs could produce a similar effect even when no attempt was made to increase the hydrostatic pressure in the ureter. One may, therefore, think of two factors which both tend falsely to raise the renal plasma flow as determined by the extraction of PAH:

1. Re-absorption from tubular cells and interstitial fluid during relatively high flow following low flow increases the renal venous concentration of PAH, thus lowering the extraction ratio and raising the calculated renal plasma flow.
2. PAH, secreted during a previous period of low flow but still not excreted, is washed into the bladder by the increased filtration during subsequent high flow, thus increasing the total amount of PAH excreted and hence the calculated renal plasma flow.

The rate of hemolysis of this pump-oxygenator is well below the level at which renal damage due to increase in plasma hemoglobin might be expected under ordinary circumstances.[5] Maluf [11] has shown that large amounts of hemoglobin may be administered to a well hydrated dog without producing signs of renal damage. However, dehydration and shock markedly reduce the quantities of hemoglobin which may be given without renal impairment. Thus, low flow with consequent low arterial pressure might reduce materially the nephrotoxic level of plasma hemoglobin, and renal damage conceivably could result in cases in which slight transfusion reactions produced an increase in the plasma hemoglobin. In these acute experiments the possibility of some renal damage after low flow cannot be eliminated; observation of renal function twenty-four hours or more following extracorporeal circulation together with late histologic examination of the kidney would help to clarify this point.

In these experiments no carbon dioxide was added to the oxygenating atmosphere and it is therefore probable that a moderate respiratory alkalosis existed during the period of perfusion. Although the excretion of electrolytes may be affected, neither acidosis nor respiratory alkalosis appreciably change renal plasma flow or glomerular filtration rate. In view of the acute nature of these experiments, these factors were not controlled.

Control dogs showed no significant reduction in renal function in the first two hours of the experiment, but during the third hour a decrease in most functions was evident. Selkurt *et al.*[14] reported a reduction of 15 per cent after three hours in a dog subjected to heparinization, cannulation, laparotomy, and isolation of the renal vein; this figure is less than the reduction obtained in our control dogs.

Previous studies [1] have shown oxygen consumption to reach control levels at flow rates of approximately 100 ml./Kg./min., and this figure was taken as "high flow" in these experiments. However, this flow is still 20 to 35 per cent below the normal cardiac output in anesthetized dogs after thoracotomy. Although arterial pressure was fairly well maintained at "high flow rates," it was generally below the original levels and it is not surprising that a decrease in renal blood flow and renal function should result. Unfortunately, in the control dogs cardiac output was not determined, and it is possible that maintenance of a higher circulatory rate in these animals than the "high flow rate" used during extracorporeal circulation may account in part for the better maintenance of renal function in those animals. The similarity of arterial blood pressures does not necessarily indicate equal perfusion rates, since there is some reason to believe that peripheral vascular resistance is altered during extracorporeal circulation.

Despite the fact that a certain decrease in renal function occurred, the demonstration that a good level of total function was maintained at high flow rates may be of greater significance. This is in agreement with the findings of Morris *et al.*,[12] who found in patients that renal function during perfusion was maintained at levels generally consistent with circulatory rate and arterial pressure.

Conclusions

1. Renal function as measured by renal plasma flow, glomerular filtration rate, and electrolyte excretion was significantly depressed during extracorporeal circulation, even at "high flow rates."

2. There was a much more severe depression of renal function during extracorporeal circulation at low flow rates than at high flow rates.

3. Renal function during extracorporeal circulation appeared to be dependent on the existing rate of flow or arterial pressure and was not influenced significantly by prior flow rates. An exception may exist when low flow rate enhances an already existing susceptibility to renal damage, such as from hemolysis.

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