Effect of Retransfusion After Hemorrhagic Hypotension on Intrarenal Distribution of Blood Flow in Dogs

SERGE CARRIÈRE and BERNARD DAIGNEAULT with the technical assistance of FRANÇOIS ROCHEFORT

From the Department of Medicine and Clinical Laboratories, Maisonneuve Hospital, and the University of Montreal, Montreal, Canada

ABSTRACT Hemorrhagic hypotension in anesthetized dogs produces a marked decrease of the cortical blood flow, whereas the medullary blood flow is well preserved. These animals were maintained at blood pressures of 50 mm Hg during a 3 hr period after which their blood pressures were restored by the reinfusion of blood or dextran, or both. In the first group of animals, the reinfusion of blood reestablished the blood pressure to control values, but the cortical blood flow was still nonuniformly decreased whereas the medullary blood flow appeared to be increased. In the second group of animals, phenoxybenzamine failed to protect the kidney completely since after blood reinfusion, the same anomalies described for the preceding group were found in 7 out of 10 dogs. The animals of the third group were reinfused with 50% of the shed blood and 10 ml/kg of a 10 g/100 ml solution of low molecular weight dextran. The modifications of the intrarenal distribution of the blood flow were less marked in this group although the blood flow rate of the inner cortex and the outer medulla was always elevated under these conditions. The reinfusion of low molecular weight dextran alone (20 ml/kg of a 10 g/100 ml solution) restored the blood pressure to levels slightly lower than those observed under control conditions but reestablished a normal pattern of intrarenal blood flow. The reinfusion of high molecular weight dextran was inefficient in correcting completely the anomalies of the renal blood flow. Mechanisms such as the increased sympathetic tone, the liberation of angiotensin, and the intravascular cellular aggregation could possibly account for the persisting anomalies of the renal circulation after reinfusion and are discussed.

INTRODUCTION

An increased renal vascular resistance has been observed repeatedly during hemorrhagic hypotension (1–6). Most studies are in agreement that the renal blood flow decreased more proportionately than the fall in blood pressure. This is true not only during hypotension but even after the reinfusion of blood when the renal vascular resistance remains elevated for some time following restoration of blood pressure to normal values (6–9). The cortical ischemia observed during the hypotensive period (10–13) readily explains the reduced renal blood flow since the outer medullary blood flow is relatively well maintained during hemorrhagic hypotension (11, 12). This last point, however, is still subject to controversy (10, 13).

The data concerning the intrarenal distribution of the blood flow after restoration of blood pressure following hemorrhagic hypotension are sparse (12, 13) and incomplete. In these studies, no definite conclusions could be established concerning the modifications of the cortical circulation because of the inconsistent results obtained in a small number of experiments. On the other hand, Aukland suggested that the outer medullary hydrogen clearance is increased to values which are comparable to control conditions by reinfusion of blood after hemorrhagic hypotension.

In the present study, the modifications of the cortical and medullary circulation have been evaluated in animals submitted to hemorrhagic hypotension and in whom the blood volume and blood pressure were restored by reinfusion of blood or dextran, or both.

This paper was presented in part at the Fourth International Congress of Nephrology in Stockholm, Sweden, 24 June 1969.

Received for publication 4 May 1970 and in revised form 13 July 1970.

METHODS

Fasted, mongrel dogs (20–30 kg) were anesthetized with pentobarbital (25–30 mg/kg) and were given additional doses as required during the experiments. The stem of a Y-shaped cannula was introduced into a femoral artery; one end was connected to a Statham strain gauge for pressure recording, while the second was connected with siliconized Tygon tubing to a sterile siliconized glass reservoir into which the animal was bled. Both renal arteries were exposed through flank incisions and catheterized with polyvinyl chloride catheters by a method previously described (14). Once the surgical preparation was completed, a 30 min waiting period was allowed before the first krypton-85 disappearance curve was recorded under control conditions.

For the measurement of the intrarenal distribution of blood flow, Kr^{85} dissolved in 0.2–0.5 ml of saline (0.85 g/100 ml) was injected rapidly through a double-barreled adapter into the renal artery catheter followed immediately by 0.2 ml of saline. The wash-out of the gas from the kidney during the control and experimental curves was monitored for 60 min using a scintillation probe with a sodium iodide crystal placed over the kidney. The detector was coupled to a scaler and a digital printer; the data were plotted on semilogarithmic graph paper. The multiexponential decay curves were analyzed graphically by the method originally described by Thorburn, Kopald, Herd, Hollenberg, O'Morchoe, and Barger (15). Under normal conditions, four different components are found by graphical analysis of the curves. These represent the blood flow rates of the cortex, the outer medulla, the inner medulla, and the perirenal and hilar fat. The blood flow rates may be calculated from the slopes of the component lines

$$F = \frac{k \times \gamma \times 100}{\rho}$$

where F is the flow rate in ml/100 g per min, k is the slope of the line, γ the partition coefficient for Kr^{85} between tissue and blood (1.0), and ρ the specific gravity of the tissue. The percentages of radioactivity entering into each region were determined from the zero time intercepts.

All the curves in the different phases of the experiment were recorded from the same kidney; the other kidney was used only at the end of the experiment for radioautographic studies. Once the control Kr^{85} curve was obtained, the animals were heparinized and allowed to bleed freely into the reservoir until blood pressure began to decrease and then more slowly until the blood pressure fell to 50 mm Hg. In most animals, as previously reported, blood pressure was lowered to 50 mm Hg in 15–30 min, after a loss of 20-40% of blood volume. The reservoir was then adjusted intermittently to maintain the blood pressure at 50 mm Hg throughout the remainder of the hypotensive period. During the period in which blood pressure was stable at 50 mm Hg, the animals lost an additional 15–20% of the initial blood volume. A second Kr^{85} disappearance curve was recorded 60 min after the start of the hemorrhage, when bleeding had stopped and the blood pressure was stable. Approximately 3 hr after the start of the hemorrhage, the blood volume of the animal was restored in the following five different ways.

In group I, the animals were reinfused with their own shed blood within 15–20 min.

In group II, seven animals received a constant infusion of phenoxybenzamine (POB) (100 μg/min) into the catheter of the kidney in which the Kr^{85} curves were recorded, and four animals received 200 μg/min of POB intravenously. These infusions were started 15 min before the beginning of the hemorrhage, and they continued until the end of the experiment. To verify the adequacy of the adrenergic blockade obtained with POB, norepinephrine (1 or 2 mg) was injected intravenously in four dogs similarly prepared, either by the intrarenal or the intravenous infusion of POB, and no blood pressure changes were observed. As in the previous group, these dogs were reinfused with their own blood within the same period of time.

Group III animals were reinfused with 50% of the shed blood, and in addition, they received low molecular weight dextran (Rheomacrodex; 10 ml/kg of a 10 g/100 ml solution).

Group IV animals received only low molecular weight dextran (LMWD) (20 ml/kg of a 10 g/100 ml solution) within 15–20 min.

Group V animals received 20 ml/kg of a 6% dextran solution of a mean molecular weight of 80,000 during the same period of time as in the preceding group.

After the blood pressure was restored, which was approximately 3½ hr after the start of the hemorrhage, Kr^{85} curves were repeated one or more times.

At the end of the experiment, the same amount of Kr^{85} was injected into the renal artery catheters, and the two kidneys were removed simultaneously at predetermined times after the injection. The kidneys were then immediately frozen in a mixture of dry ice and acetone, and slices were prepared for radioautograms in order to localize anatomically the different components of the Kr^{85} curves as previously described (15).

RESULTS

In these experiments the Kr^{85} disappearance curves have been recorded for 60 min, but only the blood flow rates and the percentages of initial radioactivity derived from the first two components will be presented, for reasons previously discussed (16).

Tables I–V indicate that the control data for the cortex and the outer medulla, as calculated from the krypton disappearance curves, are comparable to those previously reported (11, 15, 16). The modifications of the intrarenal distribution of blood flow during hemorrhagic hypotension illustrated in Tables I–V are in agreement with the previously published results obtained by using these methods (11, 12). Indeed, in some experiments, a smaller proportion of the cortex (cortex A) had a normal blood flow rate during hemorrhagic hypotension as indicated by the reduced amount of activity penetrating the first rapid component. In other experiments, much of the Kr^{85} was distributed into regions of the cortex (cortex B) which were perfused at a rate so similar to the rate of the outer medulla that only a single blood flow rate was found for these two areas by graphical analysis.

Group I. The reinfusion of the shed blood into these animals restored the arterial blood pressure to values comparable to those observed during the control conditions (Table I). However, the cortical blood flow was

Table I

Summary of Blood Flow Rates (ml/100 g per min) and Initial Distribution of Radioactivity (% counts) in Renal Cortex and Outer Medulla before and during Hemorrhagic Hypotension and after Blood Reinfusion in Heparinized Dogs

Dog		Control			Hemorrhagic hypotension			After blood reinfusion 15–75 min‡			After blood reinfusion 85–145 min			After blood reinfusion 160–220 min		
		Cortex	Outer medulla	B.P.*	Cortex A	Outer medulla and Cortex B	B.P.	Cortex	Outer medulla	B.P.	Cortex	Outer medulla	B.P.	Cortex	Outer medulla	B.P.
1	Flow	830	100	125	755	142	50	770	140	130	695	197	125	830	220	120
	% counts	86	12		22	67		84	13		66	30		70	27	
2	Flow	690	111	125		91	50	600	220	120	740	230	120	520	130	85
	% counts	82	13			84		32	59		44	48		73	20	
3	Flow	830	160	120	920	143	50	695	180	130	695	150	120	1380	190	120
	% counts	79	18		70	22		79	17		56	42		35	60	
4	Flow	695	175	135		80	50	760	260	100	830	230	115	600	170	100
	% counts	83	14			88		33	63		68	28		61	34	
5	Flow	600	150	110	350	180	50	700	205	110				600	200	115
	% counts	81	17		20	71		62	35					54	57	
6	Flow	830	116	110		205	50	700	230	110				700	205	110
	% counts	90	8			93		70	27					40	57	
7	Flow			125		113	50	600	230	125						
	% counts					74		65	29							
8	Flow	761	135	130			50	690	209	125	740	201	120	770	185	120
	% counts	83	14					60	34		58	37		55	40	
9	Flow	600	104	120	520	170	50	830	167	110						
	% counts	84	14		25	68		64	33							
Flow (mean)		730	131	122	636	140	50	705	205§	118	740	202‖	120	770	186§	110
SEM		35	10	3	125	16		25	12	4	25	15	2	109	11	5
% counts (mean)		84	14		34§	71¶		61§	34¶		58¶	37¶		55¶	40¶	
SEM		1	1		12	8		6	6		4	4		5	6	

* Blood pressure.

‡ Time interval during which Kr^{85} curves were recorded.

§,‖,¶ Indicate that the *P* values from *t* test on paired observations are, respectively, <0.01, <0.02, and <0.001 in comparison with values obtained during the control curve.

not uniformly distributed as demonstrated by the radioautogram of a kidney removed immediately after krypton injection under these conditions (Fig. 1). This radioautogram, presented with the corresponding kidney slice, shows that some areas of the cortex are well filled with krypton indicating high flow rates within these regions, whereas other regions contain smaller amounts of radioactivity indicating much slower rates of blood flow or even complete ischemia. This nonuniform distribution of the cortical blood flow demonstrated by the radioautograms is corroborated by the results obtained from the krypton-85 disappearance curves. These data illustrate (Table I) that, although the cortical blood flow rates are comparable to control values, the percentages of initial radioactivity penetrating the cortex are significantly decreased at 15, 85, or 160 min after blood reinfusion.

Fig. 2 illustrates the radioautogram of a kidney removed 2 min after krypton-85 injection from an animal reinfused with its own shed blood in comparison to the radioautogram of a kidney removed at the same time under normal conditions. The radioactivity has already disappeared from the cortex and is localized within the region of the inner cortex and the outer medulla indicating that, under these conditions, the second component of the krypton curves corresponds to the blood flow rate of this region. The radioactivity has disappeared more rapidly from the inner cortex and outer medulla of the kidney removed after blood reinfusion, thus indicating a faster rate of blood flow in that region in comparison with control conditions. This finding is also supported by the data calculated from the Kr^{85} disappearance curves (Table I) which demonstrate a significant elevation of the juxtamedullary blood flow rate after blood reinfusion.

Radioautograms of kidneys removed 4 min after Kr injection (Fig. 3) also demonstrate that the radioactivity disappears more rapidly from the inner cortex

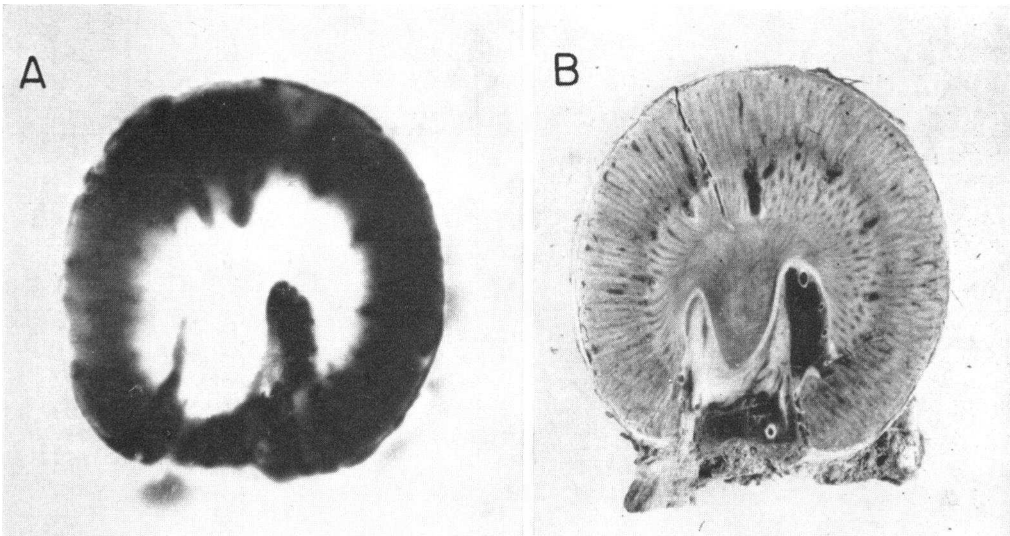

FIGURE 1 A: Radioautogram of a kidney removed immediately after intrarenal Kr^{85} injection from a dog reinfused with blood, showing the uneven distribution of the radioactivity.
B: Corresponding tissue slice.

and outer medulla after blood infusion in comparison with control conditions.

Group II. Table II demonstrates that in animals which received phenoxybenzamine during the experiment, blood reinfusion restored the blood pressure to levels that are generally lower than control values, mostly in animals observed over a period of several hours. Essentially, the same modifications of the intrarenal distribution of blood flow were found in the animals of this group in comparison with the first group. The cortical blood flow rates are comparable to control conditions, and the percentages of initial radioactivity are significantly decreased as in the previous group. Fig. 4 illustrates the radioautograms of kidneys removed immediately after Kr injection into two different animals of this group, one kidney from a dog which received 100 μg/min of POB into the renal artery (Fig. 4A), and the other from a dog which received 200

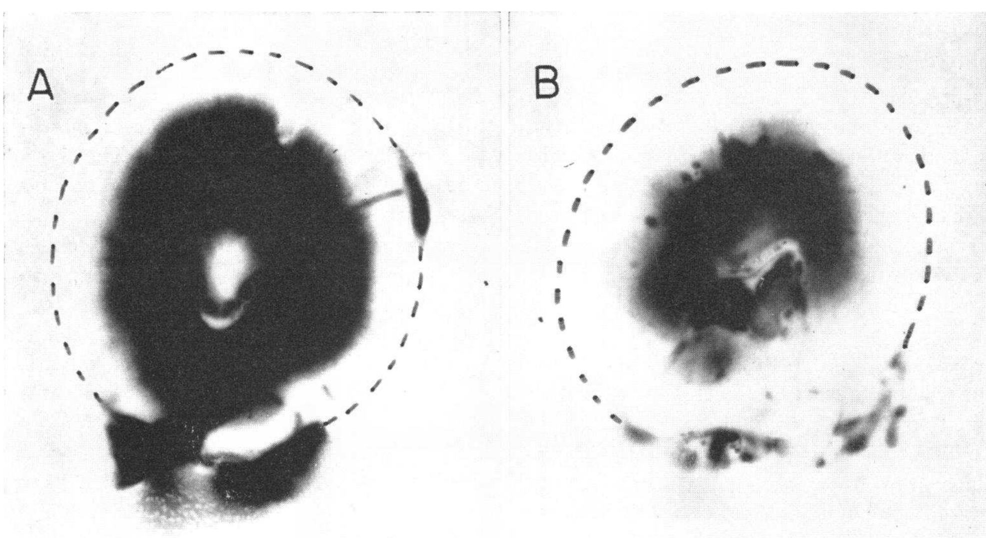

FIGURE 2 Radioautograms of kidneys removed 2 min after intrarenal Kr^{85} injection, showing that, in comparison with control conditions (A), the radioactivity disappears more rapidly from the inner cortex and outer medulla after blood reinfusion (B).

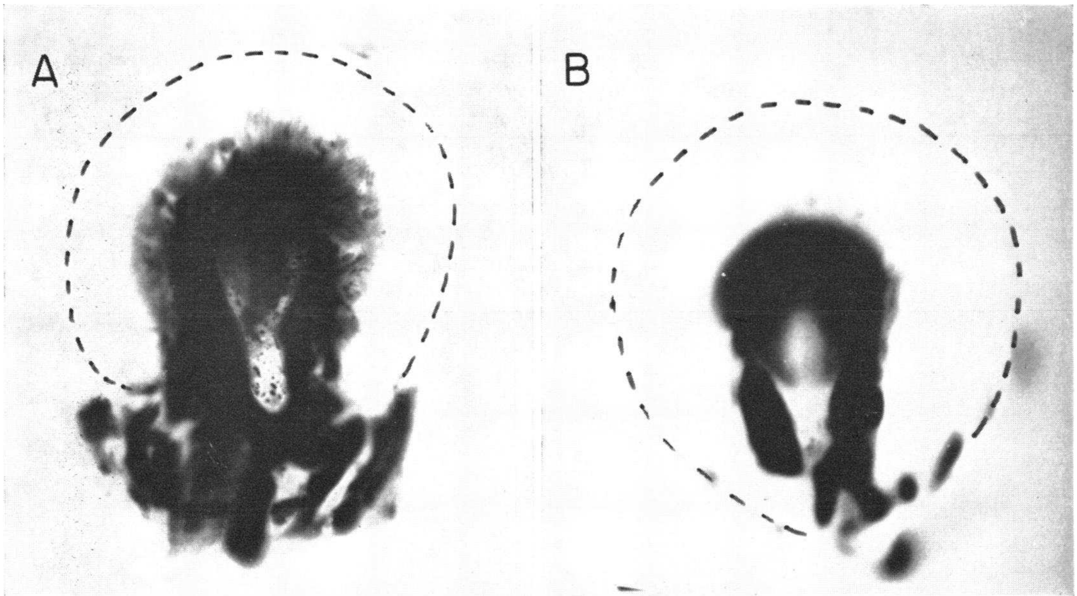

FIGURE 3 Radioautograms of kidneys removed 4 min after intrarenal Kr^{85} injection, showing that, in comparison with control conditions (A), the radioactivity disappears more rapidly for the inner cortex and outer medulla after blood reinfusion (B).

μg/min of POB intravenously (Fig. 4B). The uneven distribution of the radioactivity within the cortex, which in most occasions was less marked than in the preceding group (Fig. 4B), confirms the results obtained from the Kr^{85} curves for the cortical blood flow. As in the first group, the blood flow rate of the inner cortex and the outer medulla was increased after reinfusion. Nevertheless, in four dogs of this group (Nos. 10, 11, 19, 20) the blood flow rates and the percentages of initial radioactivity after blood reinfusion were comparable to control conditions, and the radioautograms showed a normal distribution of the radioactivity.

Group III. Table III illustrates the changes of the intrarenal distribution of blood flow in animals retransfused with 50% of the shed blood and LMWD (10 ml/kg of 10 g/100 ml solution). The modifications of the cortical blood flow were less pronounced than in the previous group as indicated by the comparable or even higher values of the blood flow rates and the slight, although significant, decrease in the percentage of initial radioactivity penetrating this region. However, the blood flow rates of the inner cortex and the outer medulla were significantly elevated under these conditions in comparison with control values. The radioautograms of kidneys removed immediately after Kr injection in these conditions showed only slight alterations in the cortical distribution of the radioactivity. On the other hand, radioautograms of kidneys removed 2 min after Kr injection, during the second component, demonstrated that the radioactivity disappears more rapidly from the inner cortex and the outer medulla after blood and LMWD infusion than under control conditions (Fig. 5).

Group IV. The reinfusion of LMWD alone (20 ml/kg of a 10 g/100 ml solution) restored the blood pressure to levels slightly but not significantly, lower than those observed under control conditions (Table IV). In contrast to the results obtained in the first three groups, the cortical and medullary blood flow rates and the percentages of initial radioactivity penetrating these regions were usually comparable with the values observed before the hemorrhage. Most of the radioautograms under these conditions were comparable with those of normal kidneys. Some of these dogs, however, were observed for a longer period of time after LMWD infusion, and they showed a slight drop in blood pressure secondary to a bleeding tendency. The radioautograms in these instances demonstrated (Fig. 6) that a narrow subcapsular zone of the cortex was vasoconstricted, since immediately after the krypton injection, no radioactivity was present in that area while the rest of the cortex was highly radioactive. The results of the Kr^{85} decay curves recorded in those conditions were not included in Table IV since they were highly abnormal and not representative because of the secondary drop in blood pressure.

Group V. Table V demonstrates that, after the reinfusion of 6% dextran (20 ml/kg) the percentage of radioactivity in the cortex is slightly but significantly

Table II

Summary of Blood Flow Rates (ml/100 g per min) and Initial Distribution of Radioactivity (% counts) in Renal Cortex and Outer Medulla before and during Hemorrhagic Hypotension and after Blood Reinfusion in Heparinized Dogs Protected with POB

Dog		Control			Hemorrhagic hypotension			After blood reinfusion								
								15–75 min‡			85–145 min			160–220 min		
		Cortex	Outer medulla	B.P.*	Cortex A	Outer medulla and Cortex B	B.P.	Cortex	Outer medulla	B.P.	Cortex	Outer medulla	B.P.	Cortex	Outer medulla	B.P.
10§	Flow	595	155	135		260	50	700	240	115	595	208	110	595	160	90
	% counts	80	17			93		57	39		62	33		80	18	
11	Flow	595	173	125		230	50	695	173	125	695	173	125	520	173	125
	% counts	76	21			95		86	11		80	17		80	15	
12	Flow	520	174	145	930	123	50	830	210	140	470	190	125	700	210	105
	% counts	76	20		24	68		34	59		29	55		26	61	
13	Flow	415	123	140		210	50	830	170	130			120‖			
	% counts	84	15			91		41	57							
14	Flow	600	130	110	520	200	50	700	190	110			90‖			
	% counts	85	13		49	49		53	43							
15	Flow	830	150	120	1040	116	50	520	150	120						
	% counts	85	12		25	64		63	35							
16	Flow	592	150	120			50	712	188	110	585	190	100	605	181	100
	% counts	81	16					55	40		57	35		62	31	
17¶	Flow	695	173	130		280	50	695	160	115						
	% counts	77	17			95		63	31							
18	Flow	695	113	140	520	143	50	465	155	125						
	% counts	81	16		63	30		52	42							
19	Flow	830	107	105	595	188	50	695	118	110						
	% counts	86	11		61	29		83	12							
20	Flow	1040	207	140		197	50	695	143	120						
	% counts	85	12			87		83	13							
Flow (mean)		673	150	128	721	195**	50	685	172**	120	586	190**	112‡‡	605	181	105§§
SEM		52	9	4	110	17		33	10	3	46	7	6	37	11	7
% counts (mean)		81	15		44‡‡	73‡‡		61‡‡	34‡‡		57**	35‡‡		62	31‖‖	
SEM		1	1		8	6		5	5		11	8		13	11	

* Blood pressure.
‡ Time interval during which Kr^{85} curves were recorded.
§ Dogs 10–16 received 100 μg/min of POB into the renal artery.
‖ Indicates that although the second post reinfusion curve was not recorded, the kidneys were removed only after that time interval.
¶ Dogs 17–20 received 200 μg/min of POB intravenously.
**,‡‡,§§,‖‖ Indicate that the P values from t test on paired observations are, respectively <0.05, <0.001, <0.01, and <0.02 in comparison with values obtained during the control curve.

reduced. The radioautogram in Fig. 7 confirms these slight modifications of the cortical blood flow distribution. As in the first three groups, the juxtamedullary blood flow rate was significantly elevated after dextran reinfusion (Table V). This finding was also confirmed by radioautographic studies which demonstrated that after dextran reinfusion the Kr^{85} disappeared more rapidly from the juxtamedullary region than under normal conditions.

DISCUSSION

The present experiments confirm that hemorrhagic hypotension produces important modifications of the intrarenal distribution of blood flow. Under these conditions, as described previously (11), an important diminution of the cortical blood flow was observed, accompanied by a preservation of the outer medullary blood flow. The reduction of the cortical blood flow is an agreement with the results obtained by other groups (10, 12, 13), but the preservation of the medullary blood flow rate, although confirmed by some investigators (12), remains a subject of controversy. Interestingly enough, when hemorrhagic hypotension is produced in animals which were not heparinized but to which heparin was added to the shed blood in the reservoir we regularly observed (in five experiments) that the cortex and outer medulla

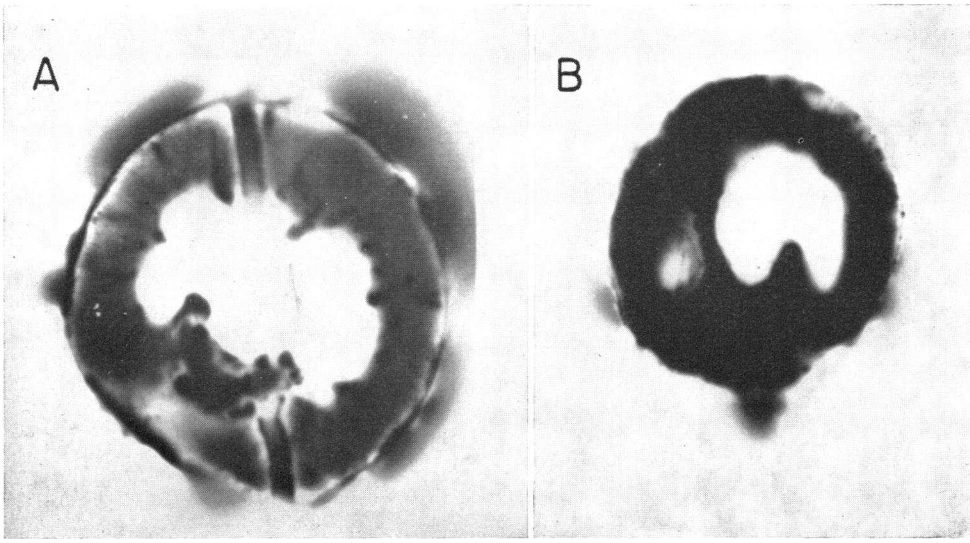

FIGURE 4 Radioautograms of kidneys removed immediately after intrarenal Kr^{85} injection from dogs reinfused with blood during POB infusion; 100 μg/min into the renal artery (A) and 200 μg/min intravenously (B). The radioactivity is unevenly distributed within the cortex.

TABLE III

Summary of Blood Flow Rates (ml/100 g per min) and Initial Distribution of Radioactivity (% counts) in Renal Cortex and Outer Medulla before and during Hemorrhagic Hypotension and after Blood and LMWD‡ Reinfusion in Heparinized Dogs*

Dog		Control			Hemorrhagic hypotension			After blood and LMWD reinfusion 15–75 min		
		Cortex	Outer medulla	B.P.*	Cortex A	Outer medulla and Cortex B	B.P.	Cortex	Outer medulla	B.P.
21	Flow	520	130	125	830	190	50	640	180	115
	% counts	82	15		16	76		72	24	
22	Flow	600	138	125	520	147	50	1050	270	130
	% counts	85	12		18	70		81	18	
23	Flow	490	100	115	460	160	50	640	220	115
	% counts	83	14		49	47		65	32	
24	Flow	350	106	125	416	148	50	755	173	115
	% counts	84	12		57	37		82	14	
25	Flow	595	115	125	555	165	50	830	207	125
	% counts	90	5		21	72		81	16	
26	Flow	555	126	95	595	188	50	830	250	105
	% counts	87	10		66	29		62	34	
27	Flow	595	116	95	765	197	50	695	138	75
	% counts	89	8		60	36		80	14	
28	Flow	695	110	105		218	50	765	154	115
	% counts	87	9			91		66	26	
Flow (mean)		550	117	114	592	176¶	50	775¶	199¶	112
SEM		36	5	5	58	9		47	16	6
% counts (mean)		86	11		41¶	57¶		73¶	22¶	
SEM		1	1		8	8		3	3	

* Reinfusion of 50% of the shed blood.

‡ Low molecular weight dextran (10 ml/kg of a 10% solution).

§ Blood pressure.

|| Time interval during which Kr^{85} curve was recorded.

¶ Indicates that the *P* value from *t* test on paired observations is <0.001, in comparison with values obtained during the control curve.

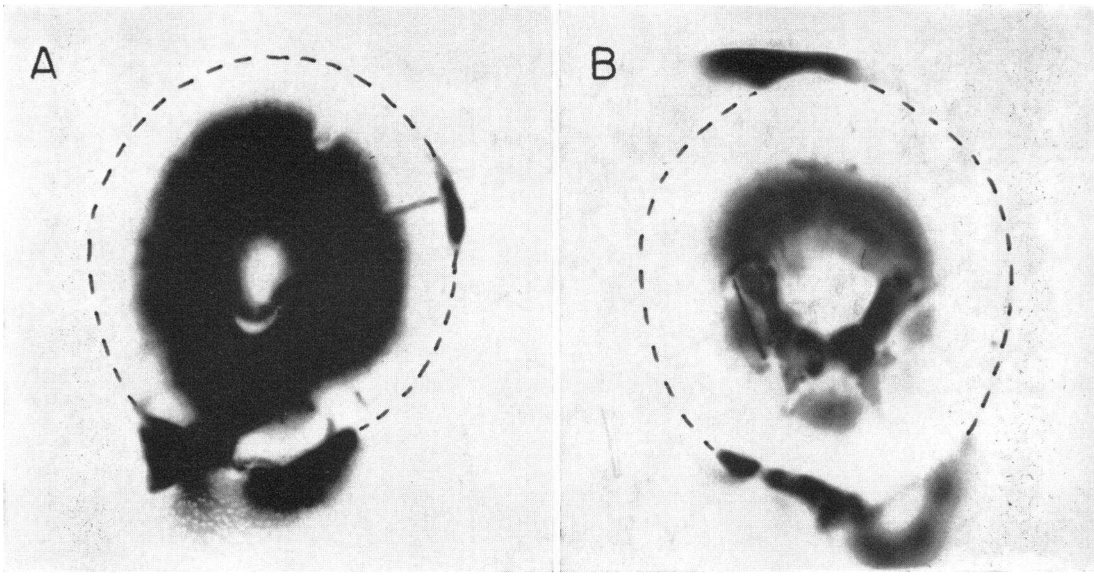

FIGURE 5 Radioautograms of kidneys removed 2 min after intrarenal Kr^{85} injection, showing that, in comparison with control conditions (A), the radioactivity disappears more rapidly from the inner cortex and outer medulla after blood and LMWD reinfusion (B).

were perfused at a much slower rate in comparison with control conditions (Table VI).

When the blood volume and the arterial blood pressure are restored by reinfusion of the shed blood after hemorrhagic hypotension, several investigators (6–9, 13) have reported that the renal resistance remained above control levels and that the total renal blood flow was reduced. The diminution of the outer cortical blood flow observed in the present experiments readily explains the increased renal resistance and the decreased renal blood flow while, in contrast, the blood flow rate of the inner cortex and the outer medulla is increased. Kramer (10) also suggested that during the postinfusion period, the blood flow through the cortex only partly recovers, although his results for the medullary blood flow differ from those of the present investigation. Aukland and Wolgast (13) also noticed in dogs that the reinfusion of blood after 2–3 hr of hypotension did not restore the total renal blood flow to values which were comparable with those of the control conditions. Using the hydrogen desaturation technique, they noticed on many occasions that the outer medullary hydrogen clearance was at a higher level after reinfusion. This finding would suggest that the cortical blood flow was reduced and would account for the reduced total renal blood flow as found in the present experiments.

These results also suggest that the decreased vascular resistance of the inner cortex and the outer medulla observed during hemorrhagic hypotension (11) may persist for some time following the restoration of the arterial blood pressure by blood reinfusion. The increased blood flow rate of that region after reinfusion is well documented by the Kr^{85} disappearance curves and the radioautograms which clearly demonstrate that the radioactivity disappears more rapidly from the inner cortex and the outer medulla in comparison with control conditions (Figs. 2–3).

A few possibilities have been explored in order to elucidate the mechanisms responsible for the redistribution of the intrarenal blood flow under these conditions. The increased renal resistance during hemorrhagic hypotension is accompanied by elevated blood levels of catecholamines (17), and their persistance in the blood after reinfusion (8) could explain the modifications of the renal circulation (16). Similarly, an increased sympathetic activity as suggested by McGiff (8) may also explain the redistribution of the intrarenal blood flow (18).

POB did not abolish the modifications of the intrarenal distribution of blood flow produced by hemorrhagic hypotension, and the cortical vasoconstriction persisted after blood reinfusion, although to a lesser extent. In some experiments (dogs Nos. 10, 11, 19, 20) the blood flow rates after blood reinfusion were comparable with control values, and the radioautograms showed a normal distribution of the radioactivity within the cortex, whereas in most experiments the circulatory changes were comparable with those observed in the absence of POB infusion (Table II, Fig. 4). These results suggest that the changes in the intrarenal blood flow distri-

TABLE IV

Summary of Blood Flow Rates (ml/100 g per min) and Initial Distribution of Radioactivity (% counts) in Renal Cortex and Outer Medulla before and during Hemorrhagic Hypotension and after LMWD Infusion in Heparinized Dogs*

		Control			Hemorrhagic hypotension			After LMWD infusion								
								15–75 min			85–145 min			160–220 min		
Dog		Cortex	Outer medulla	B.P.‡	Cortex A	Outer medulla and Cortex B	B.P.	Cortex	Outer medulla	B.P.	Cortex	Outer medulla	B.P.	Cortex	Outer medulla	B.P.
29	Flow	520	123	110	240	91	50	470	123	95	520	130	120	485	138	105
	% counts	88	9		33	55		67	28		86	12		84	13	
30	Flow	470	95	130			50	600	140	120	700	118	130	465	120	120
	% counts	83	15					82	16		87	12		81	17	
31	Flow	490	150	140		87	50	520	190	130	380	105	100			
	% counts	77	21			93		81	16		91	5				
32	Flow	600	122	140	520	100	50	415	140	115	415	94	130	320	130	120
	% counts	82	14		10	77		85	15		85	12		59	37	
33	Flow	460	116	125		97	50	700	130	90	380	102	95	415	110	90
	% counts	87	12			92		83	15		78	19		78	19	
34	Flow	600	100	115		140	50	840	230	90						
	% counts	92	7			94		82	16							
35	Flow			120		110	50	830	200	140						
	% counts					43		80	12							
36	Flow			120		166	50	830	140	100						
	% counts					93		91	7							
37	Flow	640	104	105	460	110	50	600	134	115						
	% counts	92	7		85	11		82	16							
38	Flow	540	120	130			50	645	158	115						
	% counts	85	12					81	16							
Flow (mean)		540	116	124	406	113	50	645	159‖	111	479	110	115	421	124	109
SEM		24	6	4	85	10		49	11	5	61	6	7	37	6	7
% counts (mean)		86	12		43¶	70**		81	16		85	12		76	21	
SEM		2	2		22	11		2	2		2	2		6	5	

* Low molecular weight dextran (20 ml/kg of a 10% solution).
‡ Blood pressure.
§ Time interval during which Kr^{85} curves were recorded.
‖,¶,** Indicate that the *P* values from *t* test on paired observations are, respectively, <0.02, <0.05, and <0.001 in comparison with values obtained during the control curve.

bution are not due to circulating catecholamines or to increased sympathetic activity, since in animals similarly prepared the intravenous injection of large amounts of norepinephrine (1 and 2 mg) did not affect the blood pressure, demonstrating a good adrenergic blockade. Other factors which are not influenced by POB could be responsible for the circulatory changes. Indeed, the cortical vasoconstriction may be explained by the rise in angiotensin blood level stimulated by hemorrhage (19), since the action of angiotensin on the kidney is not prevented by POB (personal observation).

Mechanical factors, such as the occlusion of the arterioles by thrombosis or the aggregation of red cells in the smaller vessels of the cortex, might be responsible for the circulatory changes observed in the kidney after prolonged hypotension. Indeed, aggregation of red cells and marked reduction of blood flow in small vessels have been demonstrated in animals subjected to shock (20). Anatomical damage to the kidney was also observed under those conditions. In the present experiments, a direct visualization of the small vessels of the cortex was obviously impossible, and no direct evidence for the presence of aggregation of red cells in the capillaries either during shock or after blood transfusion could be obtained. However, histologic sections of kidneys removed from dogs several hours after blood reinfusion with or without POB protection demonstrated occasional thrombosis of small arterioles of the cortex (Fig. 8). These anatomical alterations correlate well with the radioautograms and the Kr^{85} decay curves which demonstrated that limited areas of the cortex had a reduced rate of blood flow or were completely ischemic, whereas the rest of the cortex was well perfused.

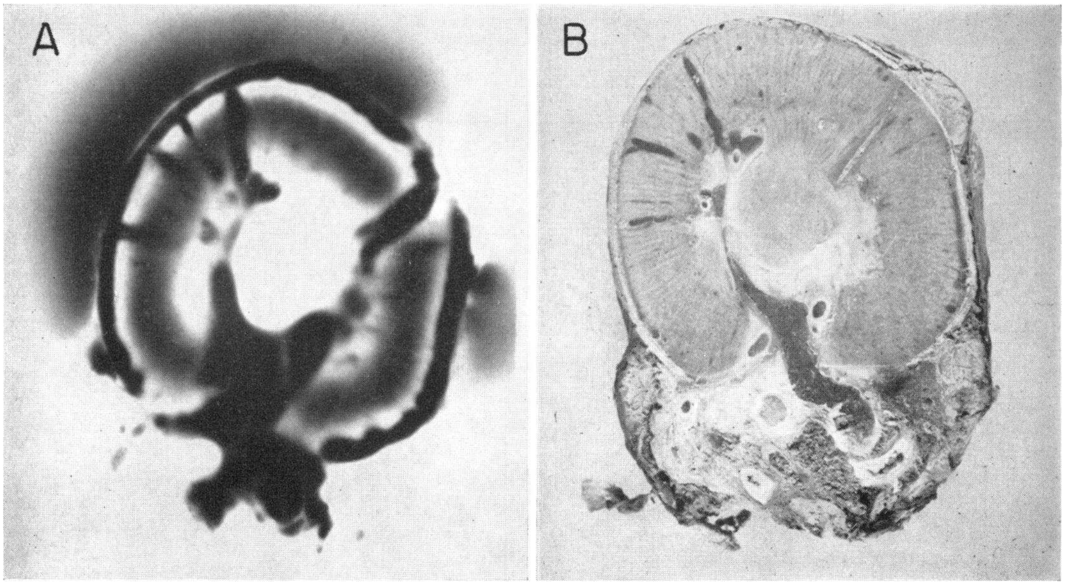

FIGURE 6 Radioautogram of a kidney removed from a dog reinfused with LMWD, demonstrating that, immediately after intrarenal Kr^{85} injection, no radioactivity is present in the subcapsular zone of the cortex.
B: Corresponding tissue slice.

TABLE V

Summary of Blood Flow Rates (ml/100 g per min) and Initial Distribution of Radioactivity (% counts) in Renal Cortex and Outer Medulla before and during Hemorrhagic Hypotension and after 6% Dextran Reinfusion in Heparinized Dogs*

					Hemorrhagic hypotension			After 6% dextran reinfusion		
		Control				Outer medulla and		15–75 min		
Dog		Cortex	Outer medulla	B.P.§	Cortex A	Cortex B	B.P.	Cortex	Outer medulla	B.P.
39	Flow	554	99	110	277	96	50	640	180	110
	% counts	88	8		57	25		75	20	
40	Flow	695	115	110		97	50	830	180	100
	% counts	84	11			95		85	11	
41	Flow	695	118	110	519	143	50	831	244	100
	% counts	89	9		72	24		57	38	
42	Flow	695	112	140		143	50	595	195	115
	% counts	90	7			91		78	19	
Flow (mean)		660	111	118		120	50	724	200‖	106
SEM		35	4	8		13		62	15	4
% counts (mean)		88	9			59		74¶	22¶	
SEM		1	1			20		6	6	

* 20 ml/kg.
‡ Time interval during which Kr^{85} curve was recorded.
§ Blood pressure.
‖,¶ Indicate that the P values from t test on paired observations are, respectively, <0.001 and <0.05 in comparison with values obtained from the control curve.

It has been well documented by many authors (21–24) that LMWD may reduce the intravascular cellular aggregation and increase the velocity of the microvascular flow. Moreover, it has been shown that the infusion of LMWD to animals subjected to shock may counteract the flow changes and prevent the damage to the kidney (20). The results obtained from the present experiments with dogs reinfused with LMWD, either alone or with blood, support those findings. When the animals were retransfused with a mixture of blood and LMWD the anomalies of the cortical circulation were less marked, but the blood flow rate of the inner cortex and the outer medulla was still markedly increased in comparison with control values as demonstrated by the Kr^{85} curves and the radioautograms. The hematocrit of these dogs dropped by 25–30%, and the viscosity of their blood probably decreased simultaneously which would account for the improvement of the renal circulation as reported for other vascular beds (23). The histologic sections of these kidneys demonstrated that the anomalies observed in the preceding group were still present but to a lesser degree as fewer instances of thrombosis were noticed.

The alterations of the cortical and medullary circulation practically disappeared when LMWD alone was infused and a further drop of the hematocrit was precipitated. These results are compatible with the observations of Gelin, Brunius, Fritjofsson, and Lewis (25) who, using the Xe^{133} method, demonstrated that LMWD could increase the renal blood flow and the urine flow in the dog, despite maintained hypotension. Among other considerations, the lowering of the blood viscosity (26) and the antithrombotic effect of LMWD may preserve a high velocity of the microvascular flow under those conditions. The intravascular thromboses observed in the preceding groups were never observed on the histologic section of kidneys from animals reinfused with LMWD. On the contrary, in most instances, the vessels appeared dilated. The histologic findings indicate that mechanical intravascular phenomenom may partly explain the renal circulatory changes observed in the cortex after blood reinfusion but do not offer any better explanation for the different results observed when LMWD or dextran were reinfused, since no anatomical lesions were noticed after dextran infusion.

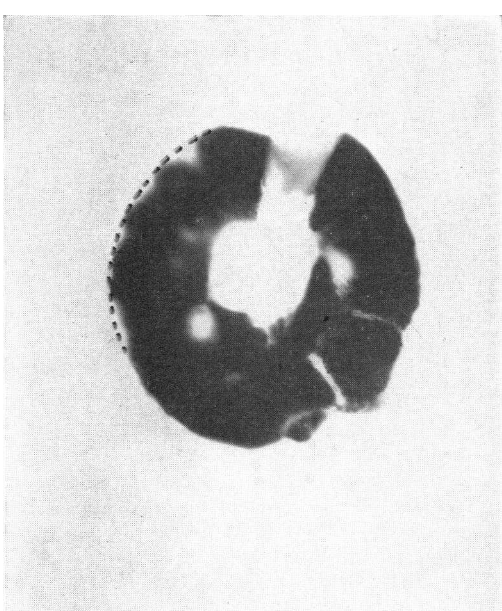

FIGURE 7 Radioautogram of a kidney removed from a dog reinfused with 6% dextran immediately after Kr^{85} injection, showing a slight patchiness of the cortex due to altered outer cortical blood flow.

TABLE VI

Summary of Blood Flow Rates (ml/100g per min) and Initial Distribution of Radioactivity (% counts) in Renal Cortex and Outer Medulla before and during Hemorrhagic Hypotension in Nonheparizined Dogs

Dog		Control			Hemorrhagic hypotension	
		Cortex	Outer medulla	B.P.	Outer medulla and Cortex A and B	B.P.
41	Flow	520	138	120	64	50
	% counts	81	14		58	
42	Flow	595	189	140	51	50
	% counts	76	22		56	
43	Flow	520	122	140	82	50
	% counts	85	12		63	
44	Flow	690	198	115	60	50
	% counts	75	22		55	
45	Flow	520	149	125	109	50
	% counts	85	12		49	

The narrow subcapsular cortical zone of ischemia in response to a slight drop in blood pressure after LMWD infusion was also observed during hemorrhagic hypotension (11) and after angiotensin infusion (27); this area corresponds to the aglomerular zone of the cortex which appears to react more intensively to vasoactive stimuli.

In summary, these results suggest that the increased renal vascular resistance observed after blood reinfusion which followed hemorrhagic hypotension may be explained by a reduction of the cortical blood flow rate. On the other hand, it appears that the decreased vascular resistance of the inner cortex and outer medulla observed during hemorrhagic hypotension may persist

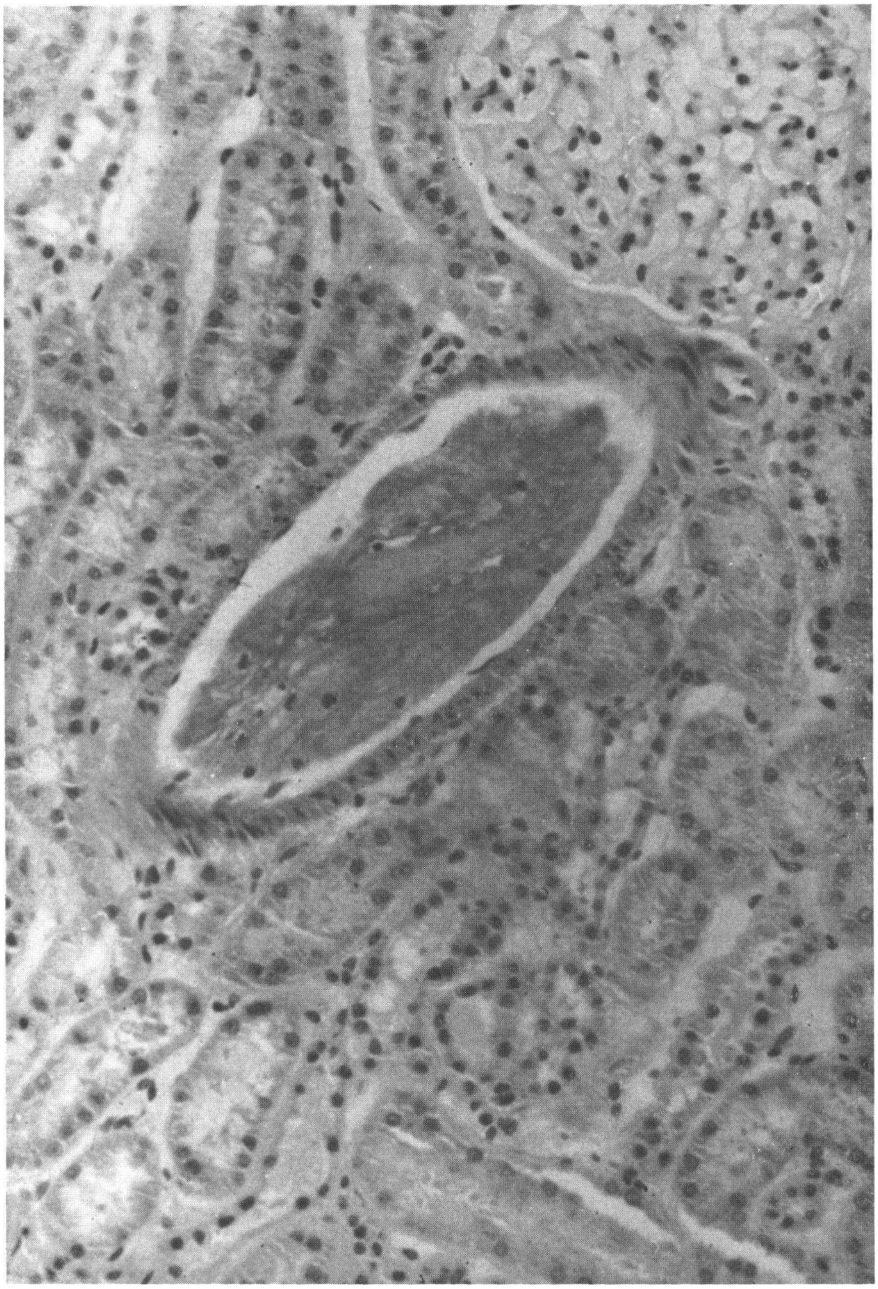

FIGURE 8 Photograph of a histology section from the kidney of a dog receiving POB and reinfused with his own shed blood showing a recent arteriolar thrombosis.

for some time after the restoration of the arterial blood pressure by retransfusion.

ACKNOWLEDGMENTS

We wish to express our appreciation to Mr. Andre Grenier and Albert Dupuis for their assistance and to Mr. Gerard Gagnon, Mrs. Lorraine Dagenais, and Miss Bernadette Joly for the preparation of the illustrations and the manuscript. The collaboration of Dr. L. P. LeGresley in the preparation and interpretation of the histologic sections is also appreciated.

This work was supported by grants of the Medical Research Council of Canada and the Quebec Heart Foundation.

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