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The Effects of Cardiac Denervation on Renal Function (38820)

JOHN J. MULCAHY, W. PETER GEIS, AND RICHARD L. MALVIN

Department of Physiology, The University of Michigan, Ann Arbor, Michigan 48104 and Department of Physiology, Stritch School of Medicine, Maywood, Illinois 60153

The association of the kidneys with the heart in a negative feedback mechanism was established by Henry and his associates, when they showed that distention of the left atrium resulted in an increase in urine flow rate (1). Since that time various attempts have been made at studying renal function in preparations in which the nerves to the heart have been severed in order to uncover other possible neuroendocrine relationships between these two organs. These preparations have included vagotomy (2, 3), sympathectomy (4), regional neural ablation (5, 6), and cardiac transplantation (7, 8) However, none of these methods of cardiac denervation is complete and at the same time exclusively limited to the heart. Vagotomy or sympathectomy performed individually interrupts nerves to structures other than the heart and leaves some nerves to this organ intact. Regional neural ablation has also been shown to have both of these shortcomings (9, 10), while a small remnant of left atrial wall remains intact during the performance of cardiac transplantation (11).

Geis and his associates have developed a method of cardiac denervation in dogs which involves stripping the adventitia circumferentially from the aorta and pulmonary artery and incising and reanastomosing the free walls of both atria and the interatrial septum without the use of cardiopulmonary bypass (12). They had shown that after the performance of this two-stage procedure there is no response of myocardial contractile force or heart rate to stimulation of the vagus nerves and stellate ganglia. Thus, it appears that this is a preparation in which all efferent nerves to the heart have been severed and in which innervation of other structures is left intact. Although the extent of afferent denervation is unknown, it is reasonable in view of the demonstration of complete efferent denervation to conclude that the nerves from the heart have also been interrupted. We have used this preparation to study some of the renal responses to cardiac denervation.

Methods. In one series of experiments nine female mongrel dogs weighing between 15 kg and 30 kg were trained to stand quietly on a table. A permanent cystostomy cannula was placed in the bladder to facilitate the collection of urine. Cephalic and saphenous veins were used for infusion of solutions and sampling of blood. Control data assessing renal function were obtained without the use of anesthetics or sedatives. The two-stage denervation procedure as described by Geis *et al.* (12) was performed and the animals allowed 1 wk after the second stage to recover from the effects of surgery. Completeness of sympathetic and parasympathetic efferent denervation was assured by lack of chronotropic response to intravenous infusions of nitroglycerine (20 μg/kg) and phenylephrine (10 μg/kg). The same parameters were then evaluated under the same circumstances and the data before and after denervation were compared.

On the first day of testing after 16 hr of fasting with ad lib. access to water a priming solution containing 5 mg/kg *p*-aminohippuric acid (PAH) and 40 mg/kg creatinine was given. This was followed by a maintenance solution of PAH, 9.5 mg/ml, and creatinine, 37.5 mg/ml, infused at a rate of 0.4 ml/min. Two successive 20-min creatinine and PAH clearances were performed beginning 1 hr after administration of the priming solution. Renal blood flow (RBF) was estimated by the formula $c_{PAH}/(1\text{-Hct})$. The plasma volume estimated as 60 ml/kg was then expanded 25% at a rate of 50 cc/min with 3% dextran in 0.9% saline. In the pilot studies 6% dextran was used but was found to be more than two times hyper-

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oncotic. Two 20-min creatinine and PAH clearances were repeated beginning 10 min after expansion of the plasma volume. All blood samples were collected in heparinized syringes under sterile conditions and the formed elements resuspended in isotonic saline and reinfused into the animal.

Each animal was then placed on a low sodium diet, 5 meq/day, for 3 days, and food and water were withheld for 24 hr prior to testing. This low sodium diet was selected to permit accurate control of sodium uptake and assure that each animal was in a similar state of sodium balance when tested before and after denervation. On the morning of the fourth day, the dog was placed on the table and four 15-min urine samples were obtained, and the sodium and potassium content of each sample was determined. During the last control period a plasma sample was taken and analyzed for sodium and potassium concentrations. The plasma volume was then expanded 25% with 3% dextran in 0.9% saline at a rate of 50 ml/min. Collection of urine samples every 15 min was continued for 5 hr after plasma volume expansion. Thirty-seven minutes after dextran infusion another plasma sample for sodium and potassium concentration was obtained.

Creatinine was analyzed by the Jaffe reaction as described by Bonsnes and Taussky (13), and PAH according to the method of Smith *et al.* (14) Sodium and potassium concentrations were measured using a flame photometer.

In a second series of 14 dogs weighing between 13 and 15 kg, polyethylene catheters were permanently implanted in the femoral artery and in the right atrium via the azygous vein. Both catheters were brought out through the skin on the back of the animal. In seven dogs mean arterial pressure and central venous pressure were measured using a polygraph while the dogs were awake and at rest. The other seven dogs were subjected to the two-stage denervation procedure and allowed to recover from the effects of surgery. Mean arterial pressure and central venous pressure were measured in the same way under the same conditions as in the control group. Following these measurements, the dogs were anesthetized with chloralase (70 mg/kg), the trachea was intubated, and the tube connected to a positive-pressure respirator. The chest was opened, a flow probe was placed on the ascending aorta and cardiac output was measured. All measurements were made after a 16-hr fast.

Results. Of the nine dogs in the first series from which preoperative data were obtained, seven survived the two-stage denervation procedure. Each of the parameters was evaluated in at least five dogs and all dogs appeared to be in good health when tested. Table I summarizes the renal hemodynamic observations. Glomerular filtration rate (GFR) and RBF during the control period before and after denervation were compared using the paired *t* test. No statistically significant difference was found in either GFR or RBF as a result of cardiac denervation. Filtration fraction showed little variation in either of the control periods or after plasma volume expansion, and dogs with denervated hearts maintained their ability to increase GFR after acute plasma volume expansion.

In Table II are the data relating to concentrations of Na and K in plasma before and after denervation and before and after volume expansion. It is apparent that no significant changes were found as a result of either procedure.

Figures 1 and 2 show the time courses of changes in the $U_{Na}V$ and U_KV resulting from volume expansion. Urinary excretion of Na was comparable during the control period in both groups of dogs. However, after volume expansion the dogs with denervated hearts showed a significantly greater natriuresis than normal dogs. The data for U_KV are somewhat more difficult to interpret as U_KV was slightly higher during both the control and post expansion periods in the denervated dogs.

In the second group of experiments in which the data were not paired, all dogs in both the control group and the group with denervated hearts showed a central venous pressure between 0 and 2 cm H_2O. Table III compares the cardiac output and mean arterial pressure for both of these groups. Since the animals were approximately the same size (13–15 kg), correction for body weight was not done. None of these three

TABLE I. RENAL HEMODYNAMICS BEFORE AND AFTER CARDIAC DENERVATION. EACH VALUE REPRESENTS THE MEAN ± SEM. $N = 5$ IN EACH GROUP. COMPARISONS WERE MADE USING STUDENT'S t TEST APPLIED TO PAIRED DATA.

	Control				After volume expansion			
	Innervated	Denervated	Δ	P	Innervated	Denervated	Δ	P
GFR (ml/min)	85 ± 8	85 ± 7	0	N.S.	92 ± 7	97 ± 8	+5	N.S.
RPF (ml/min)	290 ± 32	315 ± 50	+25	N.S.	305 ± 34	325 ± 40	+20	N.S.
FF (%)	30 ± 1	29 ± 2	−1.0	N.S.	31 ± 2	31 ± 1	0	N.S.
RBF (ml/min)	482 ± 50	504 ± 75	+22	N.S.	458 ± 48	472 ± 57	+14	N.S.

TABLE II. CONCENTRATION OF Na AND K IN PLASMA BEFORE AND AFTER DENERVATION. EACH VALUE REPRESENTS THE MEAN ± SEM. $N = 7$ IN EACH GROUP. COMPARISONS WERE MADE USING STUDENT'S t TEST APPLIED TO PAIRED DATA.

	Control			After volume expansion		
	Innervated	Denervated	P	Innervated	Denervated	P
Na (meq/liter)	143 ± 1	141 ± 2	N.S.	141 ± 1	142 ± 2	N.S.
K (meq/liter)	4.1 ± 0.1	4.5 ± 0.3	N.S.	3.9 ± 0.2	4.1 ± 0.3	N.S.

parameters of cardiovascular hemodynamics was significantly altered by cardiac denervation.

Discussion. It is evident that cardiac denervation had no demonstrable effect on resting values for any of the cardiovascular or renal parameters measured in these experiments. The striking feature noted is the augmented natriuresis seen after plasma volume expansion in dogs with denervated hearts. An increase in GFR or in the concentration of Na in plasma would increase the filtered load of sodium and favor increased excretion. However, neither GFR nor concentration of Na showed a significant difference when normal dogs and dogs with denervated hearts were compared after plasma volume expansion.

A depressed aldosterone level is associated with a decrease in distal tubular sodium reabsorption as well as potassium retention. The kaluresis seen after plasma volume expansion in dogs with denervated heart suggests that a reduction in aldosterone secretion is not the main stimulus for the increase in sodium excretion. In addition, the time course of the natriuresis is so rapid as to suggest that a decrease in the circulating level of aldosterone is not responsible. This evidence is suggestive but not conclusive as plasma aldosterone levels were not directly measured. In recent years a number of physical and compositional factors have been found to influence sodium excretion. Included among these are blood volume, mean arterial pressure, interstitial fluid volume, renal venous pressure, plasma sodium concentration, and renal blood flow

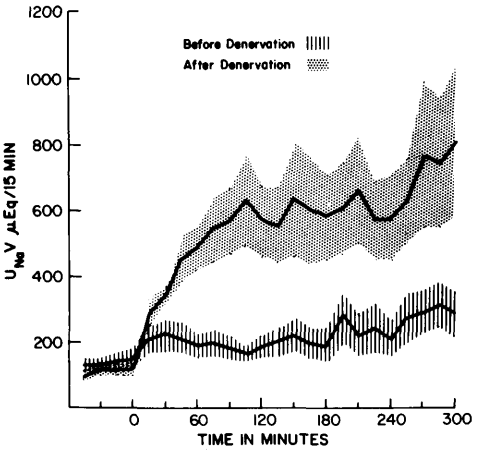

FIG. 1. The effect of cardiac denervation on urinary sodium excretion rate, $n = 7$. The mean of each of the 15-min samples is plotted and the shaded areas represent the SEM. Plasma volume was rapidly expanded at time = 0. The total urinary sodium content for the 5 hr after plasma volume expansion for each dog was compared before and after denervation using Student's t test applied to paired data, $P < 0.05$.

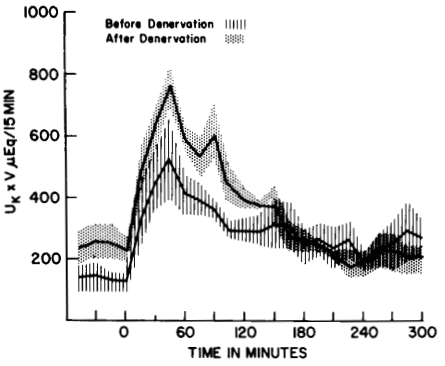

FIG. 2. The effect of cardiac denervation on urinary potassium excretion rate, $n = 5$. The mean of each of the 15-min samples is plotted, and the shaded areas represent the SEM. Plasma volume was rapidly expanded at time = 0. The total urinary potassium content for the 5 hr after plasma volume expansion for each dog was compared before and after denervation using Student's t test applied to paired data, $P < 0.05$.

TABLE III. MEAN ARTERIAL PRESSURE (MM HG) AND CARDIAC OUTPUT (ML/MIN) IN A CONTROL GROUP OF DOGS COMPARED WITH A GROUP OF DOGS WITH DENERVATED HEARTS. EACH OF THE VALUES REPRESENTS THE MEAN ± SEM. $N = 7$ IN EACH GROUP.

	Control group	Group with denervated hearts	P
M.A.P.	114 ± 12	118 ± 8	N.S.
C.O.	1650 ± 116	1546 ± 148	N.S.

which directly affect sodium excretion, while hematocrit, renal vascular resistance, and filtration fraction influence the excretion of this ion inversely (15–19). It has been shown that after this method of cardiac denervation the blood volume is elevated and hematocrit reduced, the latter due partly to blood loss during surgery (20). In the same study, intersititial fluid volume was unchanged after denervation, and we have seen that mean arterial pressure, renal venous pressure (central venous pressure), plasma sodium concentration, renal blood flow, renal vascular resistance (MAP/RBF), and filtration fraction show no significant difference when normal dogs and dogs with denervated hearts are compared in the resting state. Although the plasma volume was expanded to the same degree after denervation as before, the control plasma volume being greater after the two-stage operative procedure, may account for the augmented natriuresis seen with infusion of the dextran–saline solution.

Another possible explanation for the increase in urinary sodium might involve interruption of afferents from an intracardiac receptor responding to changes in vascular volume. Evidence for this has been provided by Goetz and his co-workers who changed atrial transmural pressure by regulating the fluid content of a previously created pericardial pouch (21). They found that a reduction of mean atrial transmural pressure of 4–8 mm Hg caused a significant drop in sodium excretion and urine flow without changing cardiac output or mean arterial pressure. They concluded that changes in atrial transmural pressure unaccompanied by hemodynamic changes elsewhere were capable of influencing sodium excretion. Although it is not clear why interruption of these receptors by cardiac denervation should lead to an exaggerated response to volume expansion, it is consistent with the hypothesis that cardiac afferents do play a role in the regulation of salt and water balance.

Summary. Assessment of certain parameters of renal function were carried out before and 1 wk after total denervation of the heart by a method which leaves nerves to other organs intact. No changes in mean blood pressure, central venous pressure, cardiac output, GFR, or RPF were noted after cardiac denervation. $U_{Na}V$ after a low sodium diet was similar during a control period before and after denervation, but in response to expansion of the plasma volume a 3-fold greater natriuresis was seen in the denervated group. Alterations in the filtered load of sodium, the secretion of aldosterone, or most of the recently described physical and compositional factors known to influence sodium excretion cannot adequately explain this natriuresis. Expansion of an already augmented plasma volume after denervation or the possibility of a natriuretic or antinatriuretic factor with afferents interrupted in the process of cardiac denervation must be considered as etiologic factors.

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