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Cardiovascular, Renal, and Humoral Effects of Applying Local Anesthetic to the Atria of Conscious Dogs[1] (41133)

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Abstract. We studied the reflex effects of an acute reduction of atrial receptor activity in conscious dogs. In order to accomplish this, dogs were prepared surgically with a pericardial pouch that enclosed either both atria or a single atrium. The experiments were performed after the animals had recovered from the operation. Atrial receptor activity was decreased by perfusing a local anesthetic, lidocaine, through the pericardial pouch. The effectiveness of this technique was documented in anesthetized dogs by recording atrial type B receptor activity from the cervical vagus. It is likely that some ventricular receptors also were blocked with this technique. In the conscious dog, perfusion of each type of pouch with lidocaine consistently produced decreases in urine flow and salt excretion, but these changes were usually modest and did not consistently achieve statistical significance. Hemodynamics were relatively little affected in these experiments, but aortic pressure and left atrial pressure did rise significantly when lidocaine was added to the pouch that enclosed both atria. Plasma renin activity increased significantly during lidocaine perfusion in each series of experiments. These data are consistent with the concept that atrial receptors are capable of reflexly influencing salt and water excretion and plasma renin activity. Further work is needed to determine the potential physiological significance of these reflexes during normal day-to-day activities.

The physiological importance of atrial receptors in the reflex regulation of renal function and the secretion of renin and vasopressin remains to be clarified (1–5). Investigation of reflex effects from atrial receptors is complicated by several factors: (A) the experimental interventions are rarely, if ever, limited to the atria (3, 5), (B) the reflex response to a change in atrial receptor activity depends somewhat upon the concurrent activity of other cardiovascular receptors (6, 7), and (C) the bulk of these experiments has been performed on anesthetized animals; it is known that anesthesia alters cardiovascular reflexes (8–10) and renal function (11, 12).

In an attempt to overcome the above difficulties, we earlier devised a technique which allowed us to selectively produce tamponade of the atria within a pericardial pouch that enclosed the atria only (13, 14). Atrial tamponade caused a reduction in sodium excretion and urine flow in conscious dogs and generally caused a decrease in atrial type B receptor discharge (4), but it also was found to produce mild alterations in systemic hemodynamics; moreover the renal response persisted after vagotomy and cardiac sympathectomy (15). Consequently the renal changes that occurred during atrial tamponade in the intact dog were not necessarily attributable to a reflex initiated by atrial receptors; they conceivably could have been elicited from other sites in the circulation.

In this paper we describe a method which enables us to produce marked decreases in atrial receptor activity by means of a local anesthetic applied directly to the epicardial surface of the conscious dog. The addition of a local anesthetic to the entire intrapericardial space has been used previously

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(e.g., (16)). Arndt and his colleagues (personal communication) recently completed a study which demonstrated that both myelinated and nonmyelinated cardiac vagal afferent fibers were blocked by infusing procaine into the pericardium. In our experiments, lidocaine was perfused through a pericardial pouch that enclosed either both atria or the right or left atrium individually. Moreover, the lidocaine was confined to the designated atrial surfaces by this technique. The effectiveness of this intervention was confirmed by demonstrating that atrial receptor activity was markedly diminished by the lidocaine. This approach has the advantage of enabling one to study the effects of a large decrease in atrial receptor activity in the conscious dog at a time when other hemodynamic variables remain reasonably constant. We hypothesized that a sharp decrease in atrial receptor activity should produce alterations in renal function, plasma renin activity, and plasma vasopressin concentration if atrial receptors play a role in the physiological regulation of these variables.

Materials and Methods. Mongrel bitches were prepared for these experiments during a preliminary operation. They were anesthetized with sodium pentobarbital, 25 mg/kg iv, and the fifth rib on the left side was removed during an aseptic thoracotomy. In some dogs the pericardium over the ventricles was cut away, and the free edge was then sewn to the atrioventricular groove as described previously (13). This produces a pericardial pouch that encloses both atria but not the ventricles. For convenience we call this a biatrial pouch. In other dogs selective right or left atrial pouches were constructed (Fig. 1). Leakage beneath the pulmonary artery was prevented in these pouches by sewing the underside of the pulmonary artery to the adjacent wall of the left atrium. The left atrial pouch was formed by suturing the edge of the trimmed pericardium to the lateral wall of the pulmonary artery and continuing the suture line along the atrioventricular groove to the medial aspect of the inferior vena cava at the heart border. The right atrial pouch was formed by suturing

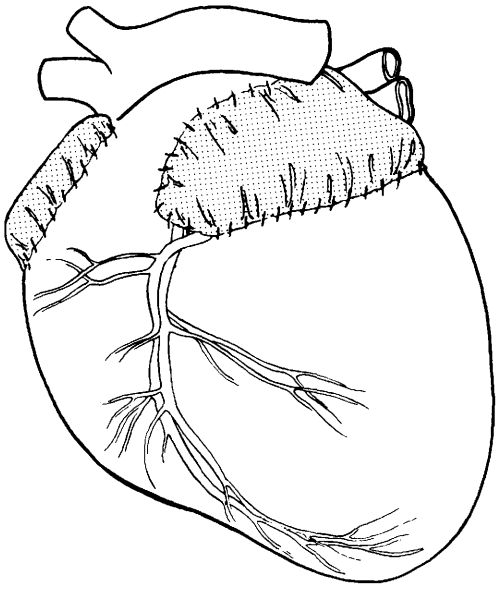

FIG. 1. Schematic view of a left atrial pouch and a small portion of a right atrial pouch as viewed through a left lateral thoracotomy.

the edge of pericardium over the right atrium to the atrioventricular groove, beginning at the lateral aspect of the superior vena cava as it enters the heart and continuing to the point where the atrioventricular groove was obscured by the right ventricular outflow tract; the suture line then was continued across the outflow tract and onto the adjoining lateral wall of the pulmonary artery.

Two catheters (3 mm i.d., not shown in Fig. 1) were placed at opposite ends of each pouch. Also, catheters were implanted in the descending aorta, superior vena cava, and left atrium (through a small tributary of a pulmonary vein) for subsequent hemodynamic monitoring. Two pacing electrodes were sewn to the ventricles. The catheters and pacing electrodes were brought through the skin behind the scapulas and protected with a nylon jacket. The dogs were treated with procaine penicillin, 500,000 U im daily, for 5 days postoperatively and were allowed to recover for a minimum of 1 week before the experiments were started.

We documented that intrapericardial

lidocaine effectively reduced atrial receptor discharge. We recorded atrial receptor activity from the cervical vagus of anesthetized dogs as described previously (17). In one test we perfused 15–30 ml of a 1% solution of lidocaine through a biatrial pouch either acutely or when sacrificing the experimental animals. Figure 2A illustrates one of these tests; the activity of an atrial type B receptor was completely abolished by the lidocaine. Receptor activity gradually returned after the lidocaine was washed out of the pouch with saline. Figure 2B shows a comparable experiment except that activity of a pulmonary inflation receptor appears on the right side of each panel. Lidocaine abolished the atrial type B activity but did not affect the activity of the pulmonary stretch receptor. A total of 18 atrial type B fibers was studied in this manner, and the activity of 17 was totally abolished by lidocaine; the other receptor was unaffected by lidocaine. Although the afferent impulses disappeared within 20–60 sec in some cases, others required as much as 8 min after lidocaine flushing before the activity disappeared. Time required for total disappearance of activity was not determined in all trials, but the average time appeared to be approximately 4 min. Time required for the initial return of activity in the fibers tested ranged from 3.5 to 29 min. Afferent impulses from nonmyelinated fibers were not recorded, but they doubtless were eliminated as well.

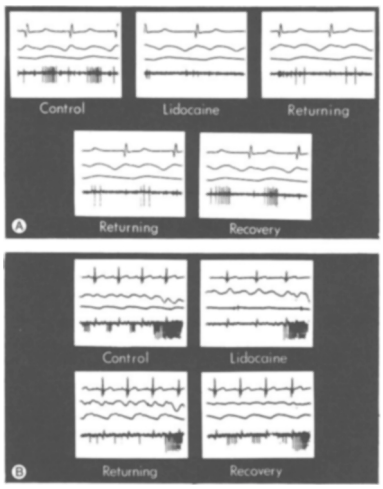

FIG. 2. Changes in atrial receptor activity induced by perfusing lidocaine through a biatrial pericardial pouch. From above downward are shown the electrocardiogram, right atrial pressure, aortic pressure, and electroneurogram recorded from the cervical vagus. (A) An atrial type B discharge pattern is seen in the control diagram. The discharge was abolished after the pouch was perfused with lidocaine. After flushing the pouch with saline, the type B firing pattern gradually returned. (B) A similar experiment in which a pulmonary stretch receptor (shown on the right in each panel) was recorded along with atrial type B activity.

We also documented the effectiveness of this technique with the individual right and left atrial pouches of experimental animals when they were sacrificed (Fig. 3). Perfusion of the right atrial pouch with lidocaine in this experiment eliminated the atrial receptor activity; recovery occurred after lidocaine was replaced with a saline perfusion. Perfusion of the left atrial pouch with lidocaine, however, did not affect the afferent activity of this fiber, thus indicating the selectiveness of the technique and, incidentally, localizing this particular receptor to the right atrium.

The animals were trained to rest quietly in an animal stand during the experiment. A self-retaining catheter was placed in the bladder; urine was collected at 10 min intervals and replaced with an equal amount of isotonic saline intravenously plus an additional 3 ml every 10 min to replace undetectable losses. A continuous perfusion of isotonic saline (about 2 ml/min) through one of the atrial pouches was started. Heart rate, aortic blood pressure,

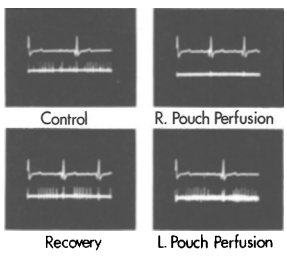

FIG. 3. Atrial receptor activity recorded during an experiment in which the dog was prepared with both right and left atrial pouches. See text for details of experiment.

left atrial pressure, and central venous pressure were recorded continually on an oscillographic recorder which was interfaced with a PDP-11/34 minicomputer (Digital Equipment Corporation, Maynard, Mass.) for on-line analysis. Each pressure tracing was sampled 100 times/sec, averaged each minute, and stored for later analysis. The program also provided a videographic display of the variables during the experiment. The graphic display was updated each minute.

The experiment began after urine flow had stabilized. It consisted of three periods (control, experimental, recovery) of 30 min each. Perfusion of the pouch with saline was continued throughout the control period. All solutions for pouch perfusion were kept at 37°. At the beginning of the experimental period, 20 ml of a solution containing 1% lidocaine was flushed through the atrial pouch. This was followed by a constant perfusion with 1% lidocaine at the same flow rate as the saline perfusion (2 ml/min). At the beginning of the recovery period, the lidocaine was flushed out with 20 ml of saline and then saline was used to perfuse the pouch during the remainder of the experiment. This perfusion technique obviated any problem with changes in intrapericardial pressure and thus avoided changes in systemic hemodynamics that might be caused by varying degrees of atrial tamponade.

Sodium and potassium concentrations in plasma and urine were determined with an IL Model 143 flame photometer; osmolality of plasma and urine was measured with a high precision Model 3R Advanced osmometer; and arterial pH, pO_2, and pCO_2 were measured with an IL Model 113 blood gas analyzer. Plasma renin activity was determined by radioimmunoassay with the method of Haber *et al.* (18) using antiserum and standards provided in a commercial kit (Clinical Assays, Inc.).

Plasma vasopressin was measured by radioimmunoassay using a modification of the method described by Robertson *et al.* (19). Synthetic 8-arginine vasopressin (AVP, 360 U/mg) was generously provided by Dr. Maurice Manning (Toledo, Ohio) and used for preparation of the radiolabel and the standards. Antiserum was produced by Skowsky *et al.* (20) and provided by the National Institute of Arthritis, Metabolic, and Digestive Diseases. The Skowsky antiserum is specific for 8-arginine vasopressin and 8-lysine vasopressin and has no cross-reactivity with 8-arginine vasotocin or oxytocin. Labeled AVP was prepared with carrier-free $Na^{125}I$ (New England Nuclear). The general method was described by Butt (21), who modified the Hunter and Greenwood method in an attempt to prevent any damage that chloramine-T might cause to the hormone by direct interaction in the iodination mixture.

The sensitivity of the assay ranged from 0.2 to 0.4 pg detectable in the 0.2 ml of plasma analyzed. The recovery of known amounts of AVP (3–10 pg/ml) during the acetone extraction ranged from 63 to 74% on repeated testing. Parallelism was demonstrated by making four serial dilutions of plasma samples. These yielded AVP concentrations which were parallel to the standard curve. AVP (40 pg) was converted to an immunologically unreactive form following 30 min of incubation with rat liver (19).

The intraassay reproducibility was determined in a single assay by triplicate analysis of 14 aliquots of a single plasma sample. The mean concentration of AVP was 2.6 ± 0.4 pg/ml (mean ± SD), and the coefficient of variation was 16%, a value comparable to that reported by Robertson *et al.* (19) for plasma concentrations in the same range. The interassay reproducibility was determined by performing 10 separate assays over 11 months on a large pool of dog plasma. The mean AVP concentration of the plasma was 3.9 ± 0.7 pg/ml for an overall interassay variability of 19%, a value comparable to those reported by others (19, 22).

Statistical analysis of all data was performed by the PDP-11/34. Within each group of animals, comparison of each variable with its own control value was made by means of a one-way analysis of variance for repeated measures on the same factor (23). The Newman–Keul test then was used to obtain the P value. Comparison of

mean values between different groups of animals was accomplished by Student's t test. P values of <0.05 were considered to denote statistical significance. Data in all figures and tables are expressed as means ± SEM.

Results. Perfusion of the pericardial pouch with lidocaine produced similar directional responses in the three types of experiments, but the magnitude of the responses varied and did not always reach statistical significance. The hemodynamic effects of perfusing lidocaine through a biatrial pouch are shown in Fig. 4. Significant increases in aortic and left atrial pressure were elicited by the lidocaine. The heart was paced in these experiments in order to prevent changes in heart rate. Renal responses occurring during these experiments are shown in Fig. 5. There were progressive decreases in urine flow, sodium excretion, and potassium excretion during lidocaine perfusion, but only the change in urine flow reached statistical significance. Urine osmolality tended to rise during the period of lidocaine perfusion, and this increase reached statistical significance in the first 10 min of the recovery period. Plasma osmolality and free water reabsorption were unchanged during the experiment. Plasma renin activity increased significantly in response to the lidocaine and returned to control levels in the recovery period, but plasma vasopressin levels were unchanged (Table I).

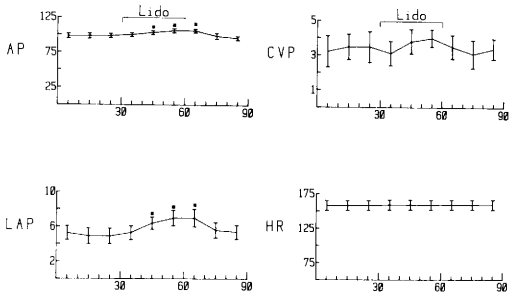

FIG. 4. Hemodynamic effects of perfusing lidocaine through a biatrial pouch in nine experiments on eight conscious dogs. AP, LAP, and CVP denote aortic, left atrial, and central venous pressures (mm Hg), respectively. HR denotes heart rate in beats per minute. Asterisks mark changes which are significantly different from control values at the $P < 0.05$ level.

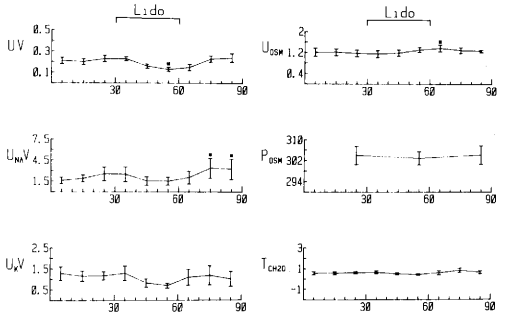

FIG. 5. Renal effects of perfusing lidocaine through a biatrial pouch on renal function in nine experiments on eight conscious dogs. Abbreviations used are UV = urinary volume (ml/min), $U_{Na}V$ = sodium excretion (μeq/min/kg), U_KV = potassium excretion (μeq/min/kg), U_{Osm} = urine osmolality (Osm/kg H_2O), P_{Osm} = plasma osmolality (mOsm/kg H_2O), and T_{CH_2O} = free water reabsorption (ml/min).

Perfusion of the right atrial pouch with lidocaine did not produce significant changes in the hemodynamic variables that were monitored (Fig. 6). Again, the heart was paced to prevent changes in heart rate. Renal responses in this series consisted of a decrease in urine flow and potassium excretion (Fig. 7), both of which reached significance in the final period of lidocaine perfusion. Urinary sodium excretion followed a comparable pattern, but the change did not reach statistical significance. Urine osmolality was increased significantly in the final collection period during lidocaine perfusion and in the first two collections in the recovery period; plasma osmolality and free water absorption were unchanged throughout. Plasma renin activity was increased by applying the local anesthetic to the right atrial pouch, and this increase was still evident in the sample taken 25 min into the recovery period; plasma vasopressin was unchanged (Table I).

Experiments with the left atrial pouch produced relatively little change in the hemodynamic variables measured (Fig. 8). It was not necessary to pace the heart in these experiments because the lidocaine did not have access to the sinoatrial node. The spontaneous heart rate was quite constant throughout the experiment. Although there were no significant changes in urine flow or sodium excretion during lidocaine perfu-

TABLE I. EFFECT OF PERFUSING POUCHES WITH LIDOCAINE ON PLASMA RENIN ACTIVITY AND PLASMA VASOPRESSIN CONCENTRATION

	PRA (ng AI/ml/hr)"				AVP (pg/ml)"			
Pouch	*n*	Control	Lidocaine	Recovery	*n*	Control	Lidocaine	Recovery
Biatrial	9	1.42 ± 0.40	2.16 ± 0.38*	1.64 ± 0.38	6	4.0 ± 0.7	3.8 ± 0.6	3.2 ± 0.4
Right atrial	10	1.34 ± 0.38	2.46 ± 0.77*	2.84 ± 0.86*	9	5.1 ± 0.7	5.5 ± 0.6	6.4 ± 1.5
Left atrial	10	1.01 ± 0.23	1.57 ± 0.41*	1.51 ± 0.35*	8	5.2 ± 0.5	4.4 ± 0.3	4.4 ± 0.3

" All values determined from plasma drawn 5 min before the end of each respective period.
*$P < 0.05$ vs control.

sion (Fig. 9), these variables did decline during the experimental period and return toward control values during the recovery period. The only significant change induced by lidocaine was an increase in plasma renin activity; this increase persisted during the recovery period; plasma vasopressin levels did not change (Table I).

The concentration of lidocaine in the serum in these experiments was measured (Bioscience Laboratories) in order to estimate the amount of lidocaine absorbed into the blood stream. After 25 min of lidocaine perfusion through the biatrial pouches, serum lidocaine levels were 7.2 ± 0.8 μg/ml; in right atrial pouch experiments, 4.3 ± 0.8 μg/ml; and in left atrial pouch experiments, 1.1 ± 0.4 μg/ml. To assess whether these lidocaine concentrations might in themselves alter renin or vasopressin levels, we tested the effects of intravenously infused lidocaine in four conscious dogs. An iv bolus of lidocaine (1–3 mg/kg) was followed by 60 min of iv infusion at 1–4 mg/min. Mean plasma lidocaine values after 25 min were 5.8 ± 0.8 μg/ml (range 1.5 to 8.1 μg/ml) and, after 55 min, 7.7 ± 0.8 μg/ml (range 2.4 to 10.2 μg/ml). Plasma renin activity and vasopressin concentration were unchanged by intravenous lidocaine administration as indicated in Table II. The heart was paced in these experiments and remained constant at 148 ± 8 bpm throughout the 90 min period. Renal function and systemic hemodynamics were not changed significantly during the experiments, but left atrial pressure did rise progressively from a control value of 4.5 ± 0.8 to 7.2 ± 1.8 mm Hg during the final 10-min period of lidocaine administration. This conceivably could have been caused by a direct depressant effect of lidocaine on the myocardium (24). Three other animals served as time controls and stood in the stand for 90 min without receiving lidocaine. Humoral and hemodynamic measurements were comparable to those obtained from the dogs receiving lidocaine iv except that left atrial pressure did not rise at any time during the experiment.

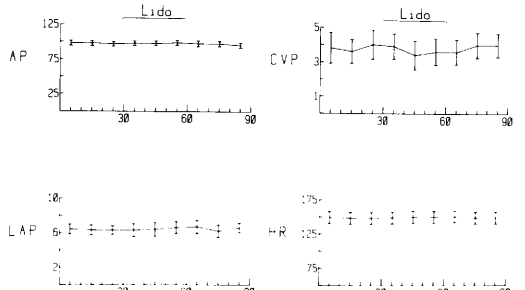

FIG. 6. Hemodynamic effects of perfusing a right atrial pouch with lidocaine in 10 experiments on nine conscious dogs. Abbreviations and units are the same as in Fig. 4.

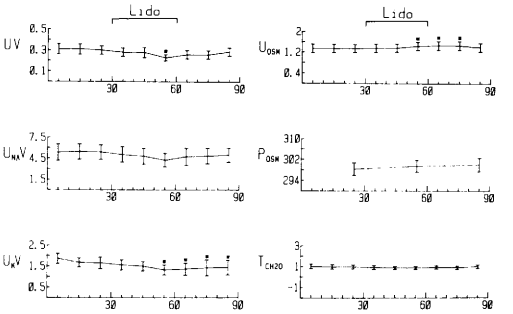

FIG. 7. Renal effects of perfusing a right atrial pouch with lidocaine in 10 experiments on nine dogs. Abbreviations and units are the same as in Fig. 5.

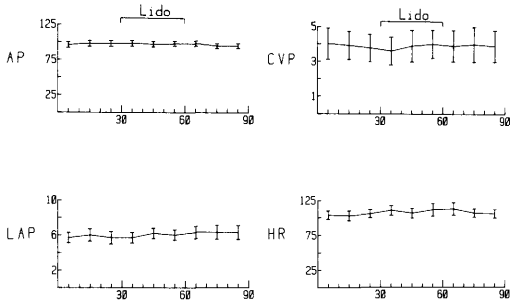

FIG. 8. Hemodynamic effects of perfusing a left atrial pouch in 10 experiments on eight conscious dogs. Abbreviations and units the same as in Fig. 4.

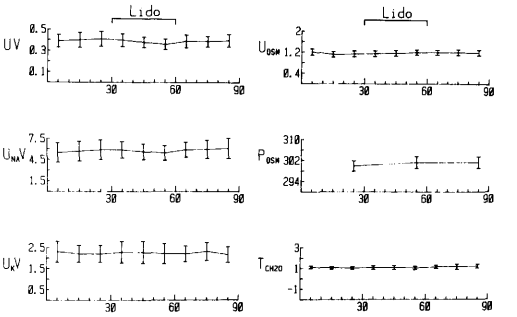

FIG. 9. Renal effects of perfusing lidocaine through a left atrial pouch in 10 experiments on eight conscious dogs. Abbreviations and units are the same as in Fig. 5.

Discussion. The aim of this investigation was to test whether an acute reduction in atrial receptor activity in the conscious dog produces changes in renal function, plasma renin activity, and plasma vasopressin concentration. The major advantage of our experimental method lies in its capacity to produce a substantial decrease in atrial receptor activity in the conscious dog. Although the results did not always achieve statistical significance, the addition of lidocaine to the atrial epicardial surface consistently produced decreases in urine flow and sodium and potassium excretion as well as increases in plasma renin activity. These results are compatible with the view, first proposed by Henry *et al.* (25), that the heart contains receptors which can reflexly influence renal function.

Although it was not possible to monitor atrial receptor activity in the conscious dog, our recordings of atrial receptor discharge from the vagal nerve of anesthetized dogs did document that lidocaine sharply reduced afferent neural activity arising from atrial receptors. It seems reasonable to assume that a similar reduction in atrial receptor activity occurred during the period of lidocaine perfusion in the conscious dog. We also obtained evidence indicating that the effects of lidocaine were limited to the heart by demonstrating that vagal afferent impulses from pulmonary stretch receptors were not blocked during the period of lidocaine perfusion. Finally, the elevation of plasma lidocaine levels induced by intravenous administration of the anesthetic did not produce changes in renal function or plasma renin activity.

Since several cardiac nerves pass through the areas enclosed by the atrial pouches, it is likely that the lidocaine blocked afferent activity from myelinated and nonmyelinated fibers from ventricular receptors as well as from atrial receptors. It has been suggested that some ventricular receptors may have a volume-regulating reflex function (26) and may reflexly inhibit renin secretion in the anesthetized dog (27). Consequently a decrease in ventricular receptor activity could have contributed to the changes observed in our experiments. It was expected that local anesthesia would affect efferent neural pathways as well; the demonstration that lidocaine increased the heart rate of unpaced animals when it had

TABLE II. EFFECT OF INTRAVENOUS LIDOCAINE INFUSION ON PLASMA RENIN ACTIVITY AND PLASMA VASOPRESSIN CONCENTRATION

	n	Control	Lido (25 min)	Lido (55 min)	Recovery (25 min)
Renin (ng AI/ml/hr)	4	1.95 ± 0.09	1.81 ± 0.11	1.89 ± 0.20	1.60 ± 0.27
AVP (pg/ml)	3	4.6 ± 1.5	3.9 ± 1.2	4.4 ± 1.4	3.5 ± 0.8

access to the sinoatrial node is consistent with this line of reasoning. The heart of the resting animal was presumably largely under vagal influences, and the elimination of efferent neural activity thus led to an increase in heart rate.

The right and left atrial pouches were employed to investigate whether different reflex effects might be elicited from the two sides of the heart. We demonstrated that right and left atrial receptors could be blocked selectively with this technique; the distribution of cardiac nerves (28) within each pouch implies that the blockade of ventricular afferent fibers would be predominantly on the side perfused by lidocaine; i.e., relatively good separation of effects from the right and left heart could be achieved. No obvious differences in reflex responses were observed, but the renal response was weaker in the left atrial pouch experiments.

One can only speculate regarding the importance of these reflex effects under normal living conditions. Our recordings of atrial receptor activity in anesthetized dogs demonstrated that atrial receptor discharge was totally eliminated in 17 out of 18 fibers tested during perfusion of the pericardial pouch with lidocaine. Clearly, a decrease in atrial receptor activity of this magnitude in our experiments on conscious dogs would reflect a dramatic change, probably larger than would occur under all but strong pathophysiologic stresses. In light of this consideration, the decreases in urine flow and sodium and potassium excretion that averaged 20% or less would appear to be quite modest. The decreases did not consistently reach statistical significance, and those observed in the left atrial pouch experiments never achieved significance. These considerations suggest that the observed reflex effects may be of little consequence under ordinary circumstances. Another possibility, which has been discussed previously (29), is that atrial receptors may exert relatively little tonic influence on these variables. Thus a decrease in cardiac receptor activity would produce little or no reflex change. On the other hand, an increase in atrial receptor activity might produce a greater response (29). It has been demonstrated that an increase in left atrial pressure induced by obstructing flow through the mitral valve causes a diuresis and natriuresis in the conscious dog (30, 31), and this response is presumed to be caused by a reflex from left atrial receptors. The above explanation also may account for the rather unexpected observation that plasma vasopressin levels did not increase during the period of lidocaine perfusion. It generally is agreed that an increase in atrial receptor activity elicited by inflating a balloon in the left atrium causes a decrease in circulating vasopressin, at least in the anesthetized dog (e.g., (32)).

The most consistent response detected during the period of lidocaine perfusion was the rise in plasma renin activity. Significant increases in plasma renin activity occurred in response to perfusing lidocaine through the right atrial, left atrial, and biatrial pericardial pouches. These data are consistent with the conclusion of others that atrial receptors have the capability to inhibit renin secretion (33, 34). It is possible that a reduction in ventricular receptor activity may have contributed to the rise in renin activity; Thames (27) has reported data and suggested that ventricular receptors may exert a tonic inhibitory influence on renin secretion.

Cardiac receptors may exert a reflex inhibitory influence on the vasomotor center (1). Hemodynamic changes recorded in our biatrial pouch experiments were consistent with this concept; aortic pressure increased significantly during the last two periods of lidocaine perfusion and remained elevated in the first recovery period before returning to control values. The increase in left atrial pressure that occurred simultaneously with the increase in arterial pressure may have reflected the increasing ventricular afterload. The rise in aortic pressure was not elicited, however, when lidocaine was perfused through the individual right or left atrial pouches, presumably because the alteration in afferent traffic was insufficient to evoke reflex changes in arterial pressure.

In summary, these results are compatible with the view that cardiac receptors have

the capacity to reflexly alter renal function, renin secretion, and vasomotor center activity in the conscious dog. The renal response was relatively modest and did not consistently reach levels of statistical significance even though atrial receptor activity presumably decreased substantially; we suggest that assumptions regarding the physiological relevance of this response should be made with some caution.

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