Reflex Diuresis during Tachycardia in the Dog

EVALUATION OF THE ROLE OF ATRIAL AND SINOAORTIC RECEPTORS

By Kenneth L. Goetz and Gary C. Bond

ABSTRACT
Renal function and systemic hemodynamics were studied during rapid atrial pacing in dogs with complete heart block and in control dogs with normal atrioventricular conduction. Rapid atrial pacing in dogs with complete heart block produced no significant change in urine flow, sodium excretion, or systemic hemodynamics. In contrast, rapid cardiac pacing in control dogs produced progressive increases in urine flow and sodium excretion and a decrease in arterial pulse pressure. Plasma antidiuretic hormone levels were not changed significantly by pacing in either group of dogs; likewise, mean atrial type B (volume) receptor discharge rate was not increased by pacing in either group. Rapid sequential atrioventricular pacing in three dogs with complete heart block did produce an increase in urine flow and sodium excretion, but rapid pacing of the atria alone in the same dogs did not cause a diuresis or a natriuresis. In other experiments on dogs with chronic sinoaortic denervation, rapid cardiac pacing caused no significant changes in urine flow or sodium excretion. Hence, the study provided no evidence to support the hypothesis that diuresis during tachycardia is elicited reflexly from atrial receptors. The data from dogs with sinoaortic denervation did suggest that receptors in the carotid sinus and the aortic arch participate in reflexly eliciting a diuresis during tachycardia.

KEY WORDS paroxysmal tachycardia volume receptors baroreceptors vasopressin natriuresis atrial pacing complete heart block

A diuresis frequently accompanies attacks of paroxysmal tachycardia (1-6). Although the etiology of the diuresis is unknown, several investigators have suggested that the increase in urine flow is elicited reflexly from atrial receptors (7, 8). According to the atrial receptor hypothesis of blood volume control (7), a reduction in the concentration of plasma antidiuretic hormone (ADH) and a subsequent diuresis should occur if atrial type B (volume) receptor activity is increased during tachycardia. Several studies on experimental animals have provided evidence compatible with this concept. Kilburn (9) reported preliminary data demonstrating that tachycardia induced in dogs by electrical stimulation of the atria produces a diuresis. He attributed the diuresis to reflex effects elicited by increases in atrial volume or atrial pulsation. Mersch and Arndt (8) reported that rapid cardiac pacing in cats brought about increases in atrial circumference and pressure—changes which possibly augment the activity of atrial volume receptors and lead to a reflex diuresis. Eliahou et al. (10) postulated that diuresis is elicited by increases in atrial pulsation rather than by increases in absolute atrial stretch.

One clinical observation, however, is difficult to reconcile with the concept that atrial receptors play an etiological role in the polyuria associated with tachycardia. It is known that particularly marked increases in left atrial pressure and volume occur during tachycardia in patients with mitral stenosis, yet this condition, even when mild, appears to prevent the diuretic response (1). In addition, the type of paroxysmal tachycardia most frequently accompanied by polyuria is paroxysmal atrial fibrillation (1, 2). We are unaware of any studies which suggest that atrial receptor activity is increased during atrial fibrillation; therefore, we believe that it would be premature to assign an etiological role to atrial receptors for the diuresis occurring during attacks of paroxysmal atrial fibrillation.

In view of the foregoing considerations, it appears that a reevaluation of the role of atrial
receptors in the diuresis accompanying tachycardia is warranted. Such a task is complicated by the widespread hemodynamic changes which normally occur during tachycardia. Changes in ventricular rate, arterial blood pressure, and other hemodynamic variables during tachycardia could independently produce part or all of any associated diuresis. Consequently, it seems to us that one logical approach to the problem is to produce a specific increase in atrial rate without altering other hemodynamic variables. Any change in renal function which occurs during the specific increase in atrial rate could then more appropriately be attributed to reflex effects from atrial receptors. Specific changes in atrial rate can be achieved by electrically pacing the atria during complete heart block (11). This paper describes studies of renal function during isolated rapid atrial pacing in dogs with complete heart block. The results are compared with those obtained during rapid cardiac pacing via the atria in control dogs with normal atrioventricular conduction. In addition, the effect of rapid cardiac pacing on renal function in dogs with denervated arterial baroreceptors was studied to determine whether elimination of these receptors alters the normal diuretic response to tachycardia.

Methods

Experiments were carried out on female mongrel dogs weighing an average of 13.2 kg. A thoracotomy with removal of the fourth right rib was performed aseptically at least 1 week before the experiments were conducted. In one group of dogs, complete heart block was produced by injecting formaldehyde into the bundle of His (12). Bipolar stainless steel electrodes were sewn to the right atrial appendage, and the pericardium was closed. The right phrenic nerve was carefully dissected free and displaced laterally to prevent possible diaphragmatic stimulation during atrial pacing. Catheters were inserted into the superior vena cava several centimeters above the right atrium and into the aorta via the right internal mammary artery. The catheters and Silastic-insulated electrode leads were passed through the chest wall and tunneled subcutaneously to the neck. The catheters were attached to a skin connector fitted with a rubber diaphragm (13). A group of control dogs was prepared in a similar manner except that heart block was not produced. All dogs were treated postoperatively for 5 days with procaine penicillin.

Experiments were conducted according to the following protocol. After a relatively constant urine flow was established, three control urine collections were made, and then rapid electrical pacing (5 msec, 6–9 V) of the atria or of the entire heart (in control dogs) was begun and continued for 1 hour. A 30-minute recovery period followed the pacing.

Urine was collected at 10-minute intervals through a self-retaining catheter. The bladder was flushed with air shortly before the end of each collection period. Creatinine clearance was used as an index of glomerular filtration rate. Dogs were given a priming dose of 20 mg creatinine/kg body weight and a maintenance dose of 0.75 mg/kg min⁻¹. The creatinine was dissolved in 5% glucose or 0.9% NaCl and infused at an average rate of 0.4 ml/min. Blood samples for creatinine analysis were withdrawn at the midpoints of each urine collection period. Creatinine determinations were made with a Technicon autoAnalyzer. Sodium concentrations were determined in duplicate by an IL model 143 flame photometer. Vena cava and arterial blood pressures were measured with Statham P23Db transducers which were zeroed at the spinocephalic processes of the vertebral column at T4–T5. Pressures, along with the electrocardiogram, were recorded on an Electronics-for-Medicine DR-8 recorder.

Blood samples for determination of plasma ADH concentration were withdrawn 5 minutes before rapid pacing started (control sample), 15 minutes after pacing was begun (pacing), and 30 minutes after pacing ended (recovery). Blood withdrawn was replaced by intravenous administration of an equal volume of warmed 6% dextran in normal saline. A 15–18-ml sample of plasma from each blood sample was extracted and concentrated to a final volume of 1.0 ml and then assayed for ADH in ethanol-anesthetized rats as described previously (14, 15).

Approximately half of the experiments were performed when the dogs were conscious, and the remainder were done when they were anesthetized with sodium pentobarbital (30 mg/kg, iv) or morphine sulfate (1 mg/kg, sc) followed by sodium pentobarbital (20 mg/kg, iv) or chloralose (80 mg/kg, iv). The chloralose was dissolved in polyethylene glycol (100 mg/ml). The response to pacing in anesthetized dogs was similar to that in conscious dogs; therefore, data from experiments with and without anesthesia were combined for presentation. The signed rank test of Wilcoxin (two-tailed) (16) was used for statistical evaluation. Data obtained during the pacing and the recovery periods were compared with the mean of values obtained during the three 10-minute control periods.

Sequential Atrioventricular Pacing.—In similar experiments, sequential atrioventricular pacing (90–110 msec atrioventricular delay) was produced in dogs with implanted bipolar electrodes on both the right atrium and the right ventricle. These results were compared with those obtained during pacing of the atria alone in the same dogs.

Recording of Vagal Afferent Impulses.—In four dogs with complete heart block and in six control dogs, additional experiments were performed to determine the response of atrial receptors to rapid pacing. Afferent atrial receptor impulses were recorded from fibers of the cervical vagus which were divided cephalad to the recording site. Neck dissection, oil pool formation, cervical vagal isolation, and desheathing were done under chloralose anesthesia according to the technique described by Sinclair (17). In control dogs, accepted
criteria (17) for identification of afferent type A and type B receptor activity were used. The discharge rate of atrial receptors was obtained by dividing the total number of impulses recorded during several complete ventricular cycles (during inspiration) by the corresponding time interval.

Identification of afferent impulses from atrial receptors in the presence of complete heart block has not been attempted so far as we know. We therefore established criteria which were used to identify impulses from atrial receptors in dogs with complete heart block. The criteria were established, in so far as possible, from the characteristics of type B impulses described for normal dogs (17).

In complete heart block, bursts of impulses from atrial receptors keep pace with atrial activity as reflected by the P waves of the electrocardiogram and the a waves of the central venous pressure tracing. Bursts of impulses from ventricular and aortic receptors, on the other hand, keep pace with the slower ventricular activity and thus are easily differentiated from atrial impulses. In these studies, atrial type B impulses were considered to be those which were recorded during each atrial diastole and which ended before atrial contraction as indicated by the recorded a wave; all type B impulses responded typically (17) to positive and negative pressures applied to the trachea. In addition, in some dogs, atrial type A receptor activity was identified. Type A impulses were considered to be those with atrial synchronicity which were recorded during or within 100 msec after the a wave.

Experiments after Sinoaortic Denervation.—Experiments were performed to determine whether carotid and aortic arch receptors participate in eliciting an increase in urine flow during tachycardia. Aortic arch baroreceptors and chemoreceptors were denervated selectively (to be referred to as sinoaortic denervation) through a midline neck incision under sodium pentobarbital anesthesia by the technique of Edis and Shepherd (18). This technique requires the use of a dissecting microscope to identify the aortic nerve as it separates from the vagus just below the nodose ganglion. In each dog in this group, additional evidence as to the identity of the aortic nerve was produced by eliciting typical heart rate changes in response to electrical stimulation of the central end of the cut nerve (18). Carotid baroreceptors and chemoreceptors were denervated by cutting the sinus nerve, stripping the adventitia from the carotid sinus and the proximal portion of the occipital artery, and painting the entire area with 8% phenol. Catheters were placed in a branch of the femoral artery and a tributary of a femoral vein, taken subcutaneously to the neck, and connected to skin connectors (13). This operation was performed aseptically, and the dogs were allowed to recover for 5–8 days. In each dog used in these studies, effective elimination of arterial baroreceptors was confirmed by the absence of reflex bradycardia following intravenous injection of phenylephrine (0.3–0.4 mg). Similarly, chemoreceptor denervation was demonstrated by the lack of a pressor response to the injection of sodium cyanide (0.2 mg/kg). The presence of intact cardiopulmonary afferents in the vagus was demonstrated in each dog by the typical von Bezold response which was evoked by intravenous injection of veratridine (10–50 μg).

Immediately after sinoaortic denervation, each dog had tachycardia and severe hypertension (systolic pressure 200–230 mm Hg and diastolic pressure 140–170 mm Hg). Most dogs were treated with phenoxybenzamine (0.5–1.0 mg/kg) and propranolol (2–4 mg) immediately after the postoperative blood pressure was recorded, but they received no medication other than penicillin after that time. Blood pressures in each dog were at normotensive levels when they were measured in the resting, conscious state within 1–3 days after baroreceptor denervation, but pressures were extremely labile. Startling a dog with a loud noise, for example, could cause a marked rapid increase in blood pressure, i.e., to 200/140, with no associated cardiac slowing. Blood pressures stabilized when the dogs were anesthetized.

Experiments with the dogs subjected to sinoaortic denervation were performed with general anesthesia according to the same protocol as that described for the control dogs. Rapid cardiac pacing in this group was accomplished through previously implanted atrial electrodes in three dogs and through a no. 7 French unipolar electrode catheter in five dogs. The electrode catheter was introduced through a femoral vein and positioned in the right atrium with electrocardiographic monitoring.

**Results**

A summary of the hemodynamic data recorded from dogs with complete heart block appears in Figure 1. Note that ventricular rate, mean arterial pressure, mean arterial blood pressure, and central venous pressure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>AR (bts/min)</td>
<td>150</td>
</tr>
<tr>
<td>VR (bts/min)</td>
<td>100</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>90</td>
</tr>
<tr>
<td>S-D (mm Hg)</td>
<td>70</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>60</td>
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![Figure 1](http://circres.ahajournals.org/)
blood pressure, pulse pressure, and central venous pressure were not changed significantly during the period of rapid atrial pacing.

Figure 2 summarizes the hemodynamic data recorded from the control dogs. Rapid cardiac pacing in these dogs with normal atrioventricular conduction produced a significant decrease in pulse pressure. Although mean arterial blood pressure increased slightly, the increase was not statistically significant. Central venous pressure was not changed significantly.

Rapid electrical pacing of the atria for 60 minutes produced no significant changes in measured renal function in the dogs with complete heart block (Fig. 3). Rapid cardiac pacing in control dogs, however, did produce significant increases in urine flow, sodium excretion, and creatinine clearance (Fig. 3). Mean urine flow and sodium excretion during the control period were somewhat higher in the group with heart block, but the type of response obtained was not dependent on this difference. A similar response was obtained in a preliminary study (19) with 30-minute periods of pacing, even though in that study mean control urine flow and sodium excretion in the control dogs were higher than they were in the dogs with complete heart block.

**TABLE 1**

<table>
<thead>
<tr>
<th></th>
<th>Control (units/ml)</th>
<th>Pacing (units/ml)</th>
<th>Recovery (units/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(mean ± SE)</td>
<td>(mean ± SE)</td>
<td>(mean ± SE)</td>
</tr>
<tr>
<td>Heart block</td>
<td>1.9 ± 0.1</td>
<td>2.5 ± 0.1</td>
<td>2.1 ± 0.1</td>
</tr>
<tr>
<td>Control</td>
<td>1.6 ± 0.05</td>
<td>1.2 ± 0.3</td>
<td>1.3 ± 0.3</td>
</tr>
</tbody>
</table>

Values are means ± SE. Pacing values were obtained from samples drawn after 15 minutes of continuous atrial pacing in dogs with complete heart block or after 15 minutes of continuous cardiac pacing in control dogs. S = number of experiments.

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The concentration of ADH in plasma samples obtained during the period of pacing did not differ significantly from control values in either group of dogs (Table 1).

A representative tracing of atrial type B activity recorded from a dog with complete heart block is shown in Figure 4, and a comparable tracing from a control dog appears in Figure 5. In each group of dogs, the number of type B impulses recorded during each atrial diastole generally decreased as pacing rates increased. As a result, the mean number of type B impulses recorded per second decreased with each increment in pacing rate in both groups of dogs, but the decrease was statistically significant only in the group with heart block (Fig. 6). In addition, atrial type A receptor activity...
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Responses (means ± se) of atrial type B receptor discharge rate during pacing in four dogs with complete heart block and six control dogs. B Imps/sec = type B receptor discharge rate. Pacing rates were increased above control rate (C) in increments of 30 beats/min (C + 30, C + 60, and C + 90). R = recovery rate. n = number of fibers studied. An asterisk above a bar indicates that P < 0.05.

was detected in five vagal fibers of dogs with complete heart block and in three vagal fibers of control dogs. The mean number of type A impulses per second increased in each group of dogs during pacing; the maximum mean increase was 57% in dogs with heart block and 20% in control dogs, thus tending to confirm the results of Arndt et al. (20) who demonstrated that atrial type A receptor activity increases as heart rate increases.

In three additional anesthetized dogs with complete heart block, sequential atrioventricular pacing produced an increase in urine flow and sodium excretion, but after a recovery period (40–50 minutes) pacing of the atria alone was without effect on these same variables (Fig. 7).

Rapid cardiac pacing did not produce significant alterations in urine flow, sodium excretion, or glomerular filtration in dogs with chronic sinoaortic denervation (Fig. 8). Hemodynamics recorded during these experiments are summarized in Figure 9. Note that the arterial blood pressure of these dogs with sinoaortic denervation was not at hypertensive levels when studied 5–8 days after denervation (Fig. 9).

Discussion

This study does not support the hypothesis that diuresis during tachycardia is elicited reflexly from atrial receptors. Rapid atrial pacing in dogs with
Summary of hemodynamic data recorded during rapid cardiac pacing in eight dogs with sinoaortic denervation. Abbreviations are the same as in Figures 1 and 2. A star above a data point indicates that $P < 0.001$, an open box indicates that $P < 0.01$, and an asterisk indicates that $P < 0.05$ (t-test).

Complete heart block did not elicit a diuresis, but rapid cardiac pacing in control dogs elicited a diuresis and a natriuresis. The possibility that dogs with complete heart block might be incapable of developing a significant diuresis was eliminated by the experiments demonstrating that sequential atrioventricular pacing produced a brisk diuresis. However, rapid atrial pacing alone was ineffective in the same dogs. Thus something more than isolated rapid atrial action is required to produce a diuresis in the dog.

It is worth emphasizing that the discharge rate of type B receptors was not increased in either control dogs or dogs with complete heart block. According to the atrial receptor hypothesis of fluid volume control, an increase in type B discharge rate is necessary to produce a reflex diuresis from these receptors. An increase in atrial type B discharge rate conceivably could occur at very high cardiac rates which reduce cardiac output and increase atrial pressure and atrial dimensions (8). It is clear from our results, however, that such extreme hemodynamic derangements are not required to elicit a diuresis during tachycardia.

The demonstration that sinoaortic denervation eliminated the diuresis suggests that receptors in the carotid sinus and aortic arch areas participate in eliciting a diuresis reflexly during tachycardia. A similar view was reached by Gilmore (21), who suggested that the diuresis, to a large degree, was caused by the reflex withdrawal of renal sympathetic vasoconstrictor nerve discharge.

Finally, we wish to emphasize that this study was designed specifically to study possible involvement of atrial receptors in the production of polyuria associated with tachycardia. Although the data provide no evidence for atrial receptor involvement in this situation, it does not necessarily follow that atrial receptors are of no importance in the regulation of body fluid volume. On the contrary, other evidence suggests that atrial receptors may play a role in body fluid economy (7, 14, 22, 23).

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References


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