Acetylstrophanthidin-Induced Reflex Inhibition of Canine Renal Sympathetic Nerve Activity Mediated by Cardiac Receptors with Vagal Afferents

MARC D. THAMES

SUMMARY The present experiments were performed to determine whether digitalis-induced augmentation of cardiac receptor discharge could induce reflex reductions in renal sympathetic nerve activity. Intracoronary injection or epicardial application of acetylstrophanthidin (AS) in chloralose-anesthetized dogs caused large decreases in renal sympathetic nerve activity which were accompanied by modest decreases in heart rate and arterial pressure. Vagotomy prevented these reflex responses. Cholinergic blockade with atropine markedly attenuated the heart rate responses to AS but had little effect on the arterial pressure or renal nerve activity responses. Epicardial application of lidocaine blocked cardiac vagal afferents and the reflex responses to intracoronary AS. In sinoaortic denervated dogs, the relationships between doses of AS and mean arterial pressure, heart rate, and renal nerve activity responses were linear. Decreases in renal nerve activity were evoked by doses of AS which did not reflexly change heart rate or arterial pressure. These data show that AS can evoke reflex bradycardia, hypotension, and withdrawal of renal sympathetic nerve activity solely by augmenting the inhibitory influence of cardiac receptors with vagal afferents. This reflex effect may contribute to the changes in renal function and thus to the diuresis that occurs when heart failure is treated with digitalis. Circ Res 44: 8-15, 1979
in the ventricle, and because of potent cardiorenal reflex mechanisms, studies were performed to test the hypothesis that digitalis-induced changes in cardiac receptor discharge may induce reflex withdrawal of renal sympathetic nerve activity. Such a reflex effect could contribute to the successful treatment of congestive heart failure. The results reported below support this hypothesis.

Methods

Mongrel dogs weighing 15-22 kg were anesthetized with sodium thiopental (30 mg/kg) and α-chloralose (80 mg/kg). Supplemental doses of chloralose (10 mg/kg) were given hourly. Auffed endotracheal tube was inserted and the dogs were ventilated artificially with air supplemented with oxygen (2-3 liters/min) at a frequency of 12 cycles/min and a tidal volume determined from a nomogram based on body weight. Arterial P0₂, P0₂, and pH were measured at intervals, and the respiratory frequency was adjusted to maintain P0₂ at 30-40 mm Hg. Arterial P0₂ exceeded 100 mm Hg in all experiments. When necessary, sodium bicarbonate was given intravenously to maintain pH between 7.3 and 7.4. During the recording of renal sympathetic nerve activity, the dogs were given decamethonium bromide (0.3 mg/kg.) to prevent muscle movement. Body temperature was maintained above 37°C by external warming.

Surgical Procedures

A midline cervical incision was used to expose both vagus nerves for subsequent section. In five experiments the aortic nerves on each side were dissected free from the vagosympathetic trunk distal to the nodose ganglion and identified by recording afferent traffic. The aortic nerve was traced distally to its junction with the vagus or sympathetic nerve and sectioned (Edis and Shepherd, 1971). This procedure has been shown to abolish acutely the baroreflex and chemoreflex from the aortic arch, and the baroreflex from the major intrathoracic arteries (Mancia et al., 1973). The cervical sympathetic nerves were cut distal to the cranial cervical ganglion.

In 16 dogs the carotid bifurcations were exposed to permit carotid denervation prior to or during the course of the experiment. Carotid sinus denervation was carried out by sectioning the carotid sinus nerves and by stripping the adjacent vessels of all visible innervation. The carotid regions were considered denervated when bilateral carotid occlusion failed to change heart rate or arterial pressure.

Through a left thoracotomy the pericardium was opened and the margins of the pericardium were attached to the thoracotomy margins to fashion a cradle for the heart. This allowed the application of AS to the surface of the left ventricle and containment of the normal saline (sodium chloride, 140 mEq/liter) with potassium chloride (4 mEq/liter) added to wash out the drug. In other studies, the left atrial appendage was retracted, and a 27-gauge needle connected to a PE20 catheter was passed through the wall of the circumflex coronary artery for intracoronary drug injection. Catheter and needle patency were maintained by infusing heparinized 5% dextrose in water (0.25 ml/min). In most experiments, the needle was passed into the circumflex coronary artery without the vessel having to be exposed by pericoronary dissection.

The left flank was opened between the iliac crest and the costovertebral angle and the left renal artery then was exposed.

Recording of Nerve Activity

A small branch of the renal sympathetic nerve was cut distally and dissected free from the renal artery and surrounding connective tissue. The nerve sheath was removed, and the nerve was covered with mineral oil and placed on bipolar platinum electrodes to record sympathetic efferent nerve activity. Traffic was recorded from the intact nerve or, in some instances, from thin filaments obtained from the nerve. The signal was amplified by a Grass band-pass amplifier (P511) with the high frequency cutoff at 300-3000 Hz and the low frequency cutoff at 30 Hz. The output of the amplifier was viewed with a Tektronix oscilloscope. The output of the amplifier also was fed into a loudspeaker and into a Beckman resetting integrator whose reset interval was a function of the recorded activity (Lais et al., 1974). The values for nerve activity are reported in Hz and represent the average discharge frequency over 30-60 seconds during the control period, over 10-30 seconds of the peak change which followed AS administration, and (when applicable) over 30-60 seconds following recovery.

Hemodynamic Measurements

Arterial pressure was measured through a cannula in the right femoral artery connected to a Statham P23Db transducer. Mean arterial pressure was obtained by electrical averaging. Heart rate was measured with a cardiotachometer preamplifier which was triggered by the arterial pressure wave. In nine experiments, mean left atrial pressure was measured using a left atrial cannula passed through the appendage and connected to a Statham P23Db transducer.

Protocols for AS Administration

Epicardial Administration

AS (75-125 μg in 1 ml of 3% ethanol in saline) was applied to the surface of the left ventricle in 10 dogs. This dose range has been shown previously to activate receptors in the left ventricle of the dog when applied to the epicardium (Sleight et al., 1969). The epicardial route of administration was used in our initial experiments because it minimized systemic absorption and because it permitted the demonstration of reversibility by washout of the
AS. In preliminary experiments in this laboratory, it was found that the influence of epicardial AS on heart rate, arterial pressure, and renal nerve activity persisted for up to 15 minutes. Sleight et al. (1969) showed that the influence of epicardial AS on heart rate and arterial pressure persisted for up to 12 minutes. Therefore, 2-4 minutes after epicardial administration of AS, the drug was washed out (over 2 minutes) by three or four successive washings with 10-15 ml of normal saline which had been warmed to body temperature. The dogs then were vagotomized and the protocol was repeated. To determine whether the carotid baroreceptors were modifying the responses to epicardial AS, the carotid sinuses were denervated in five experiments and were left undisturbed in five experiments. In two dogs, AS was applied to the epicardium before and after cholinergic blockade with atropine (0.5 mg/kg, iv).

**Intracoronary Administration**

In six dogs with sinoaortic baroreceptors intact, a dose of 60-100 μg of AS was injected over a 3-second period into the circumflex coronary artery. The AS was injected through a small catheter (PE20) connected to a 27-gauge needle which was passed through the wall of the artery. The injection was repeated after section of the aortic depressor and vagal nerves and again after carotid sinus denervation. One of these six dogs was treated with atropine (0.5 mg/kg, iv) before the protocol to block cholinergic responses was started. In three experiments, the effect of 3 ml of 1% lidocaine applied to the surface of the left ventricle was determined while the lidocaine subsequently was washed from the epicardium and pericardial cradle.

**Intracoronary Administration in Dogs with Sinoaortic Deafferentation; Dose vs. Response**

In five dogs with sinoaortic deafferentation, dose vs. response relationships were determined by injecting two (one dog) or three (four dogs) different doses (range 10-100 μg) of AS into the circumflex coronary artery. An interval of 30-60 minutes was permitted between injections to minimize persistent effects of previously administered drug. After the vagi was sectioned 100 μg of AS was again injected by the intracoronary route.

**Data Analysis**

Responses of arterial pressure, heart rate, left atrial pressure, and renal nerve activity to administration of AS were measured. The observations were summed to obtain mean and standard error for each group. The statistical significance of the difference in means was evaluated by Student's t-test for paired observations (Steel and Torrie, 1960). The level of significance was taken as 0.05.

**Results**

**Epicardial Administration of AS**

Application of AS [range 75-125 μg, mean dose (±SE) 108 ± 5 μg] to the epicardial surface of the left ventricle resulted in significant decreases in mean arterial pressure, heart rate, and renal nerve activity (Table 1). These changes were significant for the five dogs with carotid sinuses denervated, and for the combined data for all 10 dogs. Only the decreases in renal nerve activity were statistically significant in the five dogs with carotid sinus innervation intact. Table 1 also shows that after washing out the drug all measured variables returned to values that were not different from control. Left atrial pressure did not change significantly from control in three experiments.

The latent period between drug application and the first evidence of response (in any measured variable) ranged from 6 to 17 seconds with a mean latency of 10.7 ± 1.2 seconds. The mean latencies for change in mean arterial pressure, heart rate, and renal nerve activity were similar.

In two dogs the heart rate decreased by 22 and 18 beats/min following epicardial application of AS. After cholinergic blockade with atropine, epicardial AS caused decreases in heart rate in these two dogs of 8 and 5 beats/min, respectively. The blood pressure responses were modestly reduced, but renal nerve activity changes were not affected by atropine.

Application of vehicle to the left ventricle did not change any measured variable. After vagotomy, epicardial AS caused no significant change in any measured variable, although there was a tendency toward an increase in heart rate and arterial pressure (Table 1).

**Intracoronary AS**

Injection of AS [range 60-100 μg, mean dose (±SE) 81 ± 6 μg] into the circumflex coronary artery in six dogs with baroreceptors intact resulted in significant decreases in arterial pressure, heart rate, and renal nerve activity (Fig. 1). The latent periods between intracoronary injection and the first evidence of response were similar to those observed following epicardial application. The maximum changes in these variables usually occurred during the first 60 seconds after injection. Left atrial pressure was measured in three of these six experiments and was not changed by AS injection. Since the drug could not be washed out as was done following epicardial administration, we followed the time course of the effects evoked by intracoronary AS. Figure 2 shows the renal nerve electroneurograms from one experiment with the arterial pressures and heart rates measured at the time each recording was obtained. Intracoronary AS (60 μg) resulted in marked reduction of renal nerve activity along with
cardiac slowing and hypotension. Fifteen minutes after AS injection, the cardioinhibitory and vaso-depressor effects were still apparent, and renal nerve activity was about 50% of control. Not until 23 minutes after AS injection did all measured variables return to control.

In three experiments the reflex responses to intracoronary AS were reversed by the application of

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Combined data

| Mean            | 129 | 139 | 125  |
| SE              | 9   | 8   | 8    |

MAP = mean arterial pressure (mm Hg); HR = heart rate (beats/min); RSNA = renal sympathetic nerve activity (Hz); C = control; AS = acetylstrophanthin; R = recovery values obtained after AS washout.

* P < 0.05.
3 ml of 1% lidocaine to the epicardial surface of the left ventricle. Figure 3 shows the renal electroneurograms from one of these experiments with the arterial pressures and heart rates measured at the time each recording was obtained. Intracoronary AS (75 µg) resulted in marked decreases in renal nerve activity, heart rate, and arterial pressure, which persisted until the lidocaine was applied to the epicardial surface of the left ventricle. Within 4 seconds of lidocaine administration, all measured variables were returning toward control. In these three experiments, heart rate returned to control after lidocaine application. Vagotomy caused a further increase in heart rate. Thus, the vagal efferent innervation of the sinus node probably was not interrupted by the lidocaine.

In one experiment the dog was treated with atropine before the protocol was begun, to block cholinergically mediated responses. After atropine, intracoronary AS (60 µg) decreased mean arterial pressure from 105 to 80 mm Hg, heart rate from 160 to 138 beats/min and renal nerve activity from 18 to 11 Hz.

Intracoronary injection of vehicle in four dogs did not change any measured variable. Vagotomy prevented the bradycardia, hypotension, and the decrease in renal nerve activity which previously had been seen following intracoronary AS. However, there was a tendency toward a rise in arterial pressure and a decrease in nerve activity (Fig. 1). After denervation of both carotid sinus regions, intracoronary AS resulted in a significant increase in arterial pressure and a tendency toward an increase in renal nerve activity (Fig. 1).

Intracoronary AS; Dose vs. Response

The relationship between dose and response for intracoronary AS was determined in five dogs with sinoaortic deafferentation. The buffer nerves were sectioned so that the evoked responses could not be modified by the arterial baroreceptors. Figure 4 shows the responses as a function of dose of AS (µg/kg) injected into the circumflex coronary artery. Linear regression analysis of the data indicates that the relationships between doses and responses are linear. The regression equations and r values for the heart rate, arterial pressure, and renal nerve activity, respectively are: Y = 27.9 (log10X) + 4.1, r = 0.85; Y = 60.6 (log10X) + 6.8, r = 0.78; and Y = 83.0 (log10X) + 42.4, r = 0.71. It should be noted that the threshold dose for decreases in renal nerve activity due to AS was 30 µg/kg.
activity was approximately one-third of the threshold dose for decreases in heart rate or arterial pressure. In three experiments, injection of low doses of AS (0.5-0.7 μg/kg) caused small increases in arterial pressure. This increase in arterial pressure did not mediate the reduction in renal nerve activity, because the dogs were sinoaortic denervated. In addition, in the dogs with sinoaortic denervation in which AS induced the largest increase in arterial pressure (15 mm Hg) and a 27% reduction in renal nerve activity, raising and lowering arterial pressure by more than 20 mm Hg (with phenylephrine, and nitroglycerin, respectively) did not change renal nerve activity.

Intracoronary AS in three dogs with sinoaortic denervation caused small transient changes in left atrial pressure (from 3.0 to 2.5, from 2.5 to 3.0, and from 3.2 to 2.7 mm Hg, respectively).

**Effect of AS in Dogs after Vagotomy and Carotid Sinus Denervation**

In 16 of the 21 experiments, AS was applied to the epicardium of the left ventricle (five experiments) or given by intracoronary injection (11 experiments) after vagotomy and denervation of the carotid sinus regions. This resulted in increases in arterial pressure (122.6 ± 6.1 to 147.5 ± 7.3 mm Hg), in heart rate (179.8 ± 6.4 to 185 ± 7.3 beats/min), and in renal nerve activity (24.9 ± 4.6 to 28.8 ± 5.8 Hz). The increases in arterial pressure and renal nerve activity in these 16 experiments were significant.

**Arrhythmias Following Administration of AS**

Prior to vagotomy, ventricular arrhythmias were observed in three of 11 dogs following intracoronary injection, and in one of 10 dogs after epicardial administration of AS. One dog developed ventricular bigeminy, and the other two exhibited occasional unifocal premature ventricular beats. No episodes of ventricular tachycardia were observed. After vagotomy, 10 of these 21 dogs had premature ventricular beats following AS administration.

**Discussion**

These data show that AS can reflexly reduce renal sympathetic efferent nerve activity via cardiac vagal afferent pathways. This was so whether the AS was applied to the epicardial surface of the heart or injected into the circumflex coronary artery. Moreover, large decreases in renal nerve activity were observed even when blood pressure and heart rate changes were quite modest.

The experiments employing epicardial administration indicate that the reflex effects of the AS can be reversed by washing out the drug. These results from dogs with intact vs. denervated carotid sinuses (Table 1) suggest that the carotid baroreceptors may have exerted a modest modulating influence on the reflex responses that resulted from the epicardial administration of AS. The presence of intact carotid baroreceptors may account in part for the more modest decreases in heart rate and arterial pressure, but not in renal nerve activity observed in those experiments.

When AS was injected by the intracoronary route, larger reflex effects were evoked ($P < 0.05$) than when larger doses of the drug were applied to the epicardium. One possible explanation for this difference is that intracoronary AS could reach receptors throughout the left ventricular wall, whereas epicardial AS would influence receptors primarily on or near the surface of the heart. Another explanation for this apparent difference may be due to the fact that when AS was given by the intracoronary route it was distributed primarily to the inferoposterior left ventricle. In contrast, when the drug was dripped on the surface of the left ventricle, its largest effect probably was on cardiac receptors in the anterolateral left ventricle. Recent studies from this laboratory using nicotine and verapamil have demonstrated a preferential distribution of inhibitory cardiac receptors with vagal afferents to the inferoposterior left ventricle of the dog (Walker et al., 1978).

The dose vs. response studies in dogs with sinoaortic denervation indicate a 3-fold difference in the threshold dose for changes in renal nerve activity as opposed to the hypotensive and bradycardic responses. Although we did not record changes in neural activity in sympathetic efferent nerves to other parts of the circulation, the absence of evidence for generalized sympathetic withdrawal (i.e., no cardiac slowing or hypotension) when renal nerve activity was clearly decreased suggests a differential rather than uniform reflex response in vasomotor output to different vascular beds and to the heart (Abboud et al., 1976). This observation also is consistent with results of previous studies which indicate that the principal peripheral vascu-
lar reflex effects mediated through changes in cardiopulmonary input are reflected most prominently in the kidney, with lesser changes in skeletal muscle, in contrast to the sinoaortic baroreceptors, for which the reverse appears true (Mancia et al., 1976; Öberg and Thorén, 1973).

In the present experiments it is difficult to be certain of the relative concentration of drug to which the sensory endings were exposed, and thus to be able to relate this concentration to doses of the drug that are used clinically. The fact that ventricular arrhythmias were seen in only four of 21 experiments, and that neither ventricular tachycardia nor fibrillation was observed, suggests that most doses of AS used did not result in locally toxic levels.

When AS was injected by the intracoronary route, the evoked reflex effects were seen to persist for periods greater than 20 minutes. Application of lidocaine to the epicardial surface of the heart reversed the AS-induced changes in heart rate, arterial pressure, and renal nerve activity. Our results further suggest that the heart rate responses to epicardial lidocaine were not due to blockade of the parasympathetic innervation of the sinus node, because lidocaine returned heart rate only to control levels, and vagotomy caused further increases in heart rate. This interpretation is consistent with the results of other investigators who used procaine to block the reflex effects mediated by left ventricular receptors without affecting the vagal afferent innervation of the sinus node (Sleight et al., 1969; Thorén, 1973).

The three experiments in which atropine was administered indicate that the AS-induced bradycardia is mediated in part through sympathetic withdrawal as has been previously reported (Melville, 1952). In addition, these experiments indicate that the contribution of the bradycardia to the hypotensive response to AS is modest, and that AS-induced changes in renal nerve activity are not directly dependent on decreases in heart rate.

The increases in arterial pressure and in renal nerve activity following intracoronary injection of AS in vagotomized sinoaortic denervated dogs may have been due to activation of cardiac sympathetic afferents (Peterson and Brown, 1971). The responses were too rapid to suggest that these effects were mediated through direct central nervous system effects of the drug (Garan et al., 1974). Although part of the increase in arterial pressure seen following vagotomy may have been due to augmented vasomotor output, it also is possible that this increase was due to increases in contractility and, possibly, to direct vasoconstrictor effects of the AS.

The responses to intracoronary and to epicardial AS are similar to the Bezold-Jarisch response elicited by intracoronary injection of nicotine or veratridine (Sleight et al., 1969). The latent periods I observed were a few seconds longer than those reported for Veratrum alkaloids. The striking structural similarities between digitalis and Veratrum alkaloids may be the basis for their similar effects on sensory endings.

The similarity between the reflex responses to AS and to Veratrum alkaloids is further supported by a previous study (Thames, 1977), in which it was shown that activation of ventricular receptors with vagal afferents by intracoronary injection of cryptenamine, a Veratrum alkaloid, resulted in bradycardia, hypotension, and marked suppression of renin secretion. Renal blood flow did not change after cryptenamine injection.

I did not systematically investigate the changes in renal blood flow or in renin release that result from intracoronary AS. However, in two preliminary experiments (data not shown), intracoronary injection of ouabain caused bradycardia, hypotension, no change in renal blood flow, and a decrease in renin release. The method used for the measurement of plasma renin activity has been described previously (Thames et al., 1978).

Sleight and colleagues (1969) demonstrated that epicardial application of AS (100 μg) increased the frequency of discharge of 14 of 26 receptors with nonmyelinated vagal afferents (C-fibers). When compared to the effects of nicotine, the influence of AS on the discharge of C-fibers was slower in onset, had a more prolonged effect, and activated a smaller proportion of endings (Sleight et al., 1969). In addition to stimulating these endings directly, AS may increase their discharge by sensitizing them to their natural stimulus (Quest and Gillis, 1974), or by causing local increases in contractility which could increase the discharge of these endings (Thorén, 1977). Because of the short latencies observed between AS administration and the evoked reflex responses, it is likely that the augmented discharge of ventricular receptors was, in the present experiments, due primarily to a direct effect of the AS on these sensory endings. Although it is not known that the effects I observed were mediated exclusively by cardiac vagal C-fibers, there is evidence to support this view (Thorén et al., 1976; Öberg and Thorén, 1973; Sleight et al., 1969).

When digitalis is given intravenously to normal dogs, the vasoconstrictor effects of the drug cause an increase in peripheral resistance and in arterial pressure, and thus result in arterial baroreceptor-mediated bradycardia (McRitchie and Vatner, 1976). However, this may not be the mechanism for the cardiac slowing following the administration of digitalis during cardiac failure. When digitalis is given to patients with heart failure, generalized vasodilation, rather than vasoconstriction, usually is observed (Mason and Braunwald, 1964). The present study suggests that augmented input from cardiac receptors may contribute both to the vasodilation and to the bradycardia. Previous studies support this view (Sleight et al., 1969; Gillis et al., 1975).

Greenberg et al. (1973) and Zucker and colleagues (1977) have shown that atrial receptors with mye-
linated vagal afferents have reduced sensitivity in heart failure. This decreased sensitivity appears related both to decreases in atrial compliance and to structural alterations in the receptor endings (Zucker et al., 1977). These authors have suggested that reduced activity from atrial receptors may contribute to the renal compensatory mechanisms observed in heart failure (Greenberg et al., 1973; Zucker et al., 1977). It is not known whether receptors other than those in the atria have reduced sensitivity in heart failure. Further, it is not clear that atrial receptors with myelinated afferents are the cardiac source for an inhibitory influence on the vasomotor output to the kidney (Brennan et al., 1971). If, however, one assumes that the sensitivity of the receptors which are the principal cardiac source of renal vasomotor inhibition is reduced in heart failure, then this might be the situation in which the reflex effects of digitalis would be greatest, since baseline renal nerve activity would be high, whereas baseline cardiac receptor input would be decreased.

In conclusion, the present study shows that AS, a digitalis preparation, can evoke reflex reductions in renal sympathetic nerve activity mediated through cardiac receptors with vagal afferents. This effect is apparent even at low doses of the drug which do not reflexly influence heart rate or arterial pressure. The concentration of AS to which the receptors were exposed probably was not toxic. It thus can be suggested that similar cardiac receptor-mediated reflex effects on the kidney may be activated when digitalis is administered to patients in congestive heart failure.

Acknowledgments

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