Several recent studies have shown that stimulation of the carotid sinus baroreceptors exerts a reflex, negative inotropic effect upon ventricular performance.1-4 Since it was generally accepted that the vagus nerves do not directly influence the ventricular myocardium,5-8 it was assumed that the efferent fibers of the carotid-ventricular reflex traversed sympathetic pathways exclusively. In many1-3 or all4 of the experiments in these previous studies, the cervical vagus nerves were transected to preclude alterations in cardiac frequency, atrial performance, and atrio-ventricular conduction.

According to recent studies,9-13 however, the assumption that the parasympathetic division of the autonomic nervous system does not directly affect the ventricles is unwarranted. Efferent vagal stimulation has been shown to depress ventricular performance.9-11 Furthermore, the vagi have been shown to mediate a depressant influence upon the left ventricle in response to carotid chemoreceptor stimulation.12-13 Since it is well established that the cardiac vagal centers are also activated by carotid sinus baroreceptor stimulation,14 it was decided to determine whether the baroreceptor reflex affected myocardial performance via parasympathetic pathways to the ventricles. Complicating effects due to parasympathetic alterations of heart rate, atrial performance, or atrio-ventricular conduction were controlled rigorously by employing the paced, isovolumetric left ventricle preparation.

Methods

Experimental dogs were anesthetized with an intramuscular injection of morphine sulfate (2 mg/kg), followed 30 min later by an intravenous infusion of urethane (400 mg/kg) and chloralose (40 mg/kg). Donor dogs, which were bled to fill the perfusion system, were anesthetized with thiamylal (Surital) sodium (12.5 mg/kg). The isolated carotid sinus and isovolumetric left ventricle preparations were made essentially as described previously.3-12 The cephalic and coronary vascular beds were perfused at a constant pressure (near 100 mm Hg) from an elevated overflow reservoir which was connected to a cannula in the proximal segment of the ligated left subclavian artery. The descending thoracic aorta was ligated beyond the origin of this artery. The pulmonary hili were securely ligated. The elevated reservoir was filled with blood from a rotating-disc oxygenator by means of a roller pump. Blood was returned to the oxygenator from cannulas in the superior vena cava and in the right atrium and ventricle. Left ventricular performance was assessed by measuring the pressure within a balloon (filled with a constant volume of saline) inserted into the ventricular cavity. A catheter was inserted along with the balloon to remove Thesbian drainage. The heart was paced at a constant rate well in excess of the spontaneous rate by means of electrodes attached in parallel to the right atrial appendage and right ventricle; both electrodes were referred to a common electrical ground.

A second reservoir of arterial blood was situated at a hydrostatic level approximately 150 mm Hg above the level of the dog, and was connected by rubber tubing to the isolated carotid sinus. During most of the experiment, this tubing was clamped. In half the experiments, while the
tubing was occluded, the residual collateral flow to the sinus (1 or 2 ml/min) was drained back to the oxygenator, keeping pressure within the sinus at or slightly below atmospheric pressure. To produce sudden pressure elevations in the carotid sinus, the clamp was released, usually for 30 sec.

Results

SYMPATHETIC BLOCKADE WITH BRETYLIUM TOSYLANTE

Four experiments were done to verify the blocking properties of bretylium tosylate at the sympathetic neuroeffector junctions in this preparation, and to determine the proper dosage. A representative experiment is illustrated in figure 1. At A and B, the left stellate ganglion was stimulated with square wave pulses of 10 v, 5 msec, at frequencies of 10 and 15 sec⁻¹, respectively. Left ventricular systolic pressure (LVSP) increased to above 160 mm Hg from a control level of 55 to 60 mm Hg. During stimulation of the cardiac segment of the cut left cervical vagus nerve (at C), LVSP decreased to approximately half its control value. At arrow 1, bretylium tosylate (10 mg) was injected into the blood at the venous end of the oxygenator, and after a delay time of about 40 sec, LVSP increased from 52 mm Hg to a maximum value of 90 mm Hg. Subsequent vagal stimulation (at D) elicited depression of LVSP of about the same relative magnitude as at C, before bretylium. Stellate ganglion stimulation (at E), however, evoked an attenuated response. After a second dose of 10 mg bretylium (arrow 2), the effects of similar stimulation of the stellate ganglion became progressively less pronounced (F, G, H, and I). After a final dose of 10 mg bretylium, the response to stellate ganglion stimulation (at J) was negligible, whereas the ventricular response to vagal stimulation (at K) resembled the previous responses. In three other experiments of this series, similar results were obtained.

BARORECEPTOR REFLEXES BEFORE AND AFTER BLOCKADE

Figure 2 displays an experiment in which pressure within the isolated carotid sinus was suddenly elevated to 144 mm Hg from a control level of 68 mm Hg (upper left panel). This elicited a reduction of LVSP of 9 to 12 mm Hg. After a few control observations had been made, 30 mg bretylium were added to the blood passing into the venous end of the oxygenator.
Effects of sudden elevations of pressure in the isolated carotid sinus upon left ventricular pressure in the paced, isovolumetric left ventricle preparation. While the upper right tracing was being recorded, 30 mg bretylium tosylate were added to blood passing into the venous end of the oxygenator. The lower left panel was recorded 20 min after bretylium was administered. Atropine sulfate (4.0 mg) was added to the blood in the oxygenator while the lower central panel was being recorded. The lower right panel was recorded 5 min later. The two pressure tracings at the right were registered at a faster paper speed to display the configuration of the left ventricular pressure pulses.

In all three experiments in which bretylium and atropine were employed in the same sequence and dosage as in that depicted in figure 2, elevation of intrasinusal pressure to 150 mm Hg for 1 min evoked a mean depression of LVSP of 10.2% under control conditions. Twenty min after bretylium, rises of intrasinusal pressure of equivalent magnitude and duration elicited a mean reduction of LVSP of 7.4%. In all experiments, the responses were completely abolished by atropine.

Five other experiments were performed which were similar to the three just described, except that the vagi were blocked reversibly by cooling. The cervical vagi were placed in hollow, metal, trough-like devices, through which brine was circulated at −5° to −20°C to block the vagi, or at +40°C to restore conduction. Figure 3 depicts a representative experiment. In panels A and B, the responses to
elevation of intrasinusal pressure and to bretylium tosylate resemble those already described in relation to figure 2. The black bars at the top of the tracings represent sudden elevations of intrasinusal pressure to 160 mm Hg from control levels of 0 mm Hg. Twenty minutes after giving bretylium, elevation of intrasinusal pressure (first two black bars in segment D, fig. 3) evoked a 9.4% decrease in LVSP, compared to a 13.0% decrease before bretylium (segment A). Cooling the vagi (left arrow, segment D) caused an increase in LVSP, and blocked the effects of raising intrasinusal pressure. Rewarming the vagi (right arrow) diminished LVSP, and the reflex ventricular response to elevation of intrasinusal pressure reappeared, although it was somewhat attenuated in comparison to the response observed before cooling the vagi.

In the five experiments of this type, the mean depression of LVSP evoked by raising intrasinusal pressure during the control period amounted to 9.1 ± 1.3% (SE) (fig. 4). Twenty min after bretylium, the mean reduction of LVSP was 6.4 ± 0.8%, a response which was 70% as great as that observed prior to bretylium. During vagal cooling, a slight response was observed in one experiment, and no response was detectable in the other four experiments. After rewarming, the diminution of LVSP elicited by baroreceptor stimulation amounted to 5.8 ± 0.9%.

**Discussion**

For the entire series of experiments in *Circulation Research, Vol. XVIII, January 1966*
which the carotid sinus baroreceptors were stimulated by sudden elevations of intrasinusal pressure, the depression of LVSP was 9.5 ± 0.8% (SE) of the control value prior to the administration of bretylium tosylate, and 6.8 ± 0.9% after bretylium. Complete sympathetic blockade was assured by the absence of any detectable response when the vagus nerves were blocked by atropine or by cooling. Hence, the efferent pathways eliciting depression of left ventricular performance during carotid sinus baroreceptor stimulation must include both divisions of the autonomic nervous system.

After blockade by bretylium, the response was 71% as great as that observed prior to blockade. It is probable, therefore, that under the conditions of the present study, the predominant effect was mediated by parasympathetic fibers. This assertion cannot be made with any certainty, however, since the autonomic tuning might be reset by bretylium in such a manner that parasympathetic responsiveness would be greater after administration of this agent. Certainly, the relative roles played by the two divisions of the autonomic nervous system would vary depending upon the dose and type of anesthetic used and upon other experimental conditions (such as the extent of surgical manipulations and the perfusion pressure at the aortic arch and at the other, nonisolated carotid sinus). Therefore, the results of these experiments permit no predictions concerning the relative roles of the sympathetic and parasympathetic systems in the intact, unanesthetized organism.

The augmentation of LVSP after atropine and during vagal cooling, which is evident in figures 2 and 3, was observed consistently. This enhancement of LVSP is an indication of the magnitude of the tonic depressant effect exerted by the vagus nerves under the conditions of these experiments. The effect of atropine cannot be attributed in part to central nervous system stimulation, since the cardiac sympathetic fibers had previously been blocked by bretylium. Restoration of a tonic parasympathetic influence on the ventricle is evident upon rewarming the vagi (fig. 3).

The enhancement of ventricular performance by bretylium tosylate, which is evident in figures 1, 2, and 3, has been reported previously. It has been attributed to a direct stimulatory effect upon the myocardium and also to a release of myocardial catecholamines.

Summary

In innervated, isovolumetric left ventricle preparations, sudden elevations of pressure in the isolated carotid sinus elicited a 9.5% depression of left ventricular systolic pressure (LVSP). After blockade of sympathetic neuroeffector junctions by bretylium tosylate, equivalent intrasinusal pressure changes evoked a 6.8% reduction of LVSP. This response could be completely abolished by atropine sulfate or by cooling the cervical vagi. Therefore, under the conditions of the present experiments, the vagus nerves mediated a significant fraction of the reflex depression of ventricular performance induced by carotid sinus baroreceptor stimulation. An appreciable elevation of LVSP was produced by atropine and by vagal cooling after blockade of sympathetic junctions. This enhancement of ventricular performance is an indication of a tonic negative inotropic influence of the vagus nerves upon the ventricular myocardium.

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