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Centers involved in the autonomic reflex reactions originating from stretching of the atria

(cardiac reflex/atrial receptor/reflex interaction)

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ABSTRACT **Stretching the atria in anesthetized dogs produces reflex changes in heart rate, and in cardiac and renal sympathetic nerve activity. Anemic decerebration, cord transection at C4-C5, and severance of vagal or sympathetic cardiac nerves was done to identify the pathways and centers essential for these reflexes. Stretching the right atrium produced an acceleration of the heart and a definite increase in sympathetic nerve activity. Left atrial-stretch caused biphasic responses: an initial sympathetic nerve inhibition and slower heartbeat followed by sympathetic excitation and heart acceleration. The afferents responsible were carried mainly by the vagi; efferent neural control of the heart was mostly sympathetic. The reflex inhibition observed was integrated chiefly at the medullary level, but supramedullary structures contributed to the augmentation in sympathetic activity and heart rate. When central connections between vagal afferent and sympathetic efferent pathways were separated by cord transection, atrial stretch caused a decrease in heart rate due to reflex action through the vagal loop. After the cord was sectioned, we found that some afferent impulses from the atria traveling in sympathetic nerves produced a slight reflex augmentation of sympathetic efferent activity, though insufficient to affect the heart rate. Somatosympathetic reflexes evoked in cardiac and renal sympathetic nerves by stimulation of various somatic afferent pathways were also affected by atrial stretch indicating central nervous system interactions. Reflex responses to right atrial stretch were superimposed on accelerations of myogenic origin.**

Since Bainbridge first discovered the phenomenon in 1915 (1), stretching the atria has been known to evoke reflex changes in heart rate, although reports of which reflex reactions are actually involved have been contradictory. In the last decade, cardiac reflexes have again attracted the attention of many physiologists and clinicians (2–5). Linden and his associates, using anesthetized dogs found that both left and right atrial stretch evoked acceleration of the heart, and that this acceleration is due solely to increased activity of cardiac sympathetic nerves (2). They also showed that the afferent pathways that evoke these reflexes are in the vagi, as originally stated by Bainbridge. Other investigators have reported that the heart rate is reduced by stretch of the left atrium (see refs. 3 and 6). It was also found that cardiac sympathetic nerves contained afferent tracts that could evoke reflex responses when the atria were stretched and it was claimed that the cardiac acceleration produced by stretching the atria was mainly mediated by sympathetic nerves and spinal reflex action (7).

In a previous study (8), in which balloons were inserted and then inflated in the atria to cause stretching or in which sensitive areas were directly stretched, we found that stretching the right atrium produced only an acceleration of the heart and an increase in cardiac sympathetic nerve discharges. Stretching the left atrium, on the other hand, produced an early deceleration followed by a longer-lasting cardiac acceleration concurrent with a decrease and then an increase in cardiac sympathetic activity. Stretching the atria produced similar changes in activity of other sympathetic nerve trunks, such as the renal nerves. It was also found that somatosympathetic reflexes evoked by various somatic afferent nerves were affected by atrial stretch (8).

Although there have been many morphological and physiological studies of atrial receptors and their afferent nerves (3, 9), the reflexes they evoke and the nerve centers involved have not been fully determined. The objective of the present study was to identify the centers, as well as the afferent and efferent pathways that are involved in reflex responses originating from the atria, and to analyze the individual roles of each.

METHODS

Twenty-four dogs of either sex weighing 9–13 kg were used. They were anesthetized initially by intravenous injection of thiopental sodium (Pentothal Sodium, 25–30 mg/kg), gradually replaced when needed by intravenously administered α-chloralose until a total dose of 70 mg/kg was given. The use of Pentothal Sodium in the beginning of surgery reduced the amount of chloralose necessary to maintain a good state of anesthetization (see ref. 10). In two experiments, pentobarbital sodium (Nembutal, 35 mg/kg) alone was used. Succinyl choline chloride (1 mg/kg) was given to relax muscles, whenever necessary. Because the recordings were done during open chest surgery, animals were kept under artificial respiration (ventilation rate, 31 per min) and the level of end expiratory CO_2 was maintained at 4–4.5%. Thus, the phrenic nerves maintained normal rhythmic activity. A greater ventilation rate produced a loss of rhythmic phrenic nerve activity indicative of hyperventilation. Stretch responses were evoked by methods described (8). Sympathetic responses in inferior cardiac and renal nerves were recorded on moving film and also on a polygraph through a "leaky integrator." Somatosympathetic reflexes elicited in these nerves by stimulation of T_1-intercostal, L_1, L_2-spinal, radial, and posterior tibial nerves were averaged as recorded (8 or 16 consecutive responses—Nicolett, 1070 series signal averager). Blood pressure from the femoral artery, the electrocardiogram (limb leads), heart rate (tachogram triggered by the electrocardiogram R wave), and integrated phrenic nerve discharges were all registered on a Grass polygraph.

In determining the locus of central control, we did anemic decerebrations by first tying off the basilar artery; this did not change the blood pressure, respiratory rate, or sympathetic discharges. Three to five hours later, decerebration was accomplished by occluding both carotid arteries. In order to determine the effectiveness of decerebration, we obtained an electrocorticogram from the parietal cortex with a monopolar lead. In only one of 12 dogs studied was the anemic decerebration incomplete as indicated by a depression, rather than abolition, of the electrocorticogram within 1 or 2 min after the carotid arteries were clamped. In two instances, completeness of the anemic decerebration was verified by failure of ink to reach the forebrain after injection into the heart.

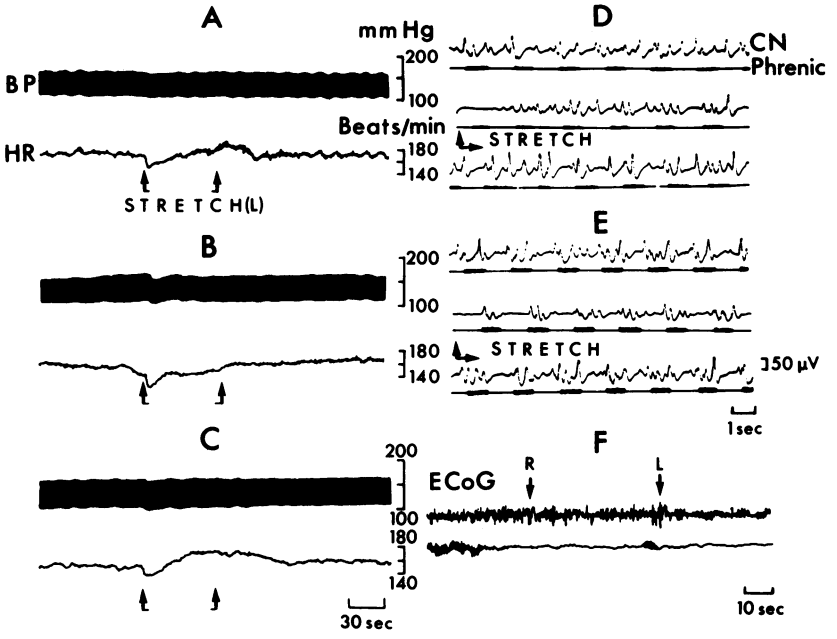

FIG. 1. Effects of anemic decerebration on responses evoked by stretching *left* atrium. (*A*) Changes in blood pressure and heart rate due to atrial stretch prior to decerebration. (*B*) Change in effects produced by the same atrial stretch after decerebration. (*C*) Response obtained 50 min after the unclamping of carotid arteries. (*D*) The activity recorded from cardiac sympathetic (CN) and phrenic nerves before decerebration. The top pair of tracings, control state; middle pair of tracings, during stretch; bottom pair of tracings, 40 sec after atrial stretch began, showing late augmentation of CN activity. (*E*) Similar recordings as *D*, but obtained during a state of decerebration. Amplification marker applies only to CN. (*F*) Changes in electrocorticogram (ECoG) recorded from the parietal lobe before and after the right, and then the left, carotid arteries (R↓ and L↓) were clamped. The basilar artery had been tied 5 hr earlier; the two tracings are continuous. Note differences in the time scales in *A–C*, *D–E*, and *F*.

The advantage of anemic decerebration was that its effects were reversible, provided the period of decerebration was short, not repeated, and a long recovery period allowed. Carotid sinus nerves were previously sectioned in these experiments so that clamping of the carotids did not affect results by changes in baroreceptor or chemoreceptor activity.

Spinal transection was done surgically at the level of C_4–C_5. The region was previously prepared for easy access after control reactions were recorded. Thus, both decerebration and spinal transection were performed without disturbing recordings of sympathetic activity. Whenever necessary, infusions of dextran–Ringer's solution were given temporarily to restore blood pressure after cord transaction.

RESULTS

Effects of Decerebration on Cardiac Reflexes. As reported previously (8) stretch of the *left* atrium caused a biphasic cardiac response. There was an initial reduction in heart rate; the sympathetic nerve activity was completely inhibited for a period of 4–5 sec, followed by a less marked but prolonged (20–30 sec) inhibition of both the tonic and reflex activity recorded from cardiac and renal nerves. After this inhibitory phase, a reverse reaction of longer (50–60 sec) duration occurred; the heart rate increased and augmented sympathetic nerve activity persisted for some 20–30 sec after termination of the stretch (Fig. 1*A* and *D*).

After control responses were recorded, we did anemic decerebration by clamping both common carotid arteries in dogs whose basilar artery had been tied several hours previously. The electrocorticogram showed nearly complete loss of activity within 60 sec (Fig. 1*F*). Although the heart rate and basal tonic activity of cardiac nerves were not changed much by this procedure, the same left atrial stretch now produced only a reduction in the rate and an initial inhibition in tonic activity without a late, subsequent excitatory phase. This deceleration also lasted longer than that observed during the control period (Fig. 1*B* and *E*). Somatosympathetic reflex action evoked by stimulation of T_1 afferent nerves was affected in the same manner as was the tonic activity. Renal nerve responses were practically the same as those of cardiac nerve responses; decerebration abolished the late augmentation of sympathetic nerve activity without affecting the initial inhibitory effects of left atrial stretch. After 10 min of decerebration, clamps on the carotid arteries were removed. The electrocorticogram gradually returned toward the control level, and regained approximately 80% of its original amplitude. As seen in Fig. 1*C*, 50 min after recovery, the reaction to left atrium stretch was similar to that of the control, i.e., the late acceleration of the heart rate and the late increase in sympathetic nerve activity reappeared, and the response to stretch again became biphasic.

Stretching the *right* atrium in intact animals generally evoked acceleration of the heart rate, and augmentation of sympathetic nerve activity (8). Decerebration often abolished or even reversed the response, and a slower heart rate associated with slight diminution in the tonic activity of the sympathetic nerves, occurred during stretching (Fig. 2*A* and *B*). Upon restitution of carotid flow almost complete recovery occurred, as the heart rate and tonic discharge in cardiac and renal sympathetics again showed the characteristic acceleration induced by stretch (Fig. 2*C*). Decerebration also abolished the facilitation of somatosympathetic reflex responses by right atrial stretch observed previously. The facilitatory actions reappeared after restoration of blood flow and apparent recovery of the cerebrum.

In those preparations in which stretch of the right atrium produced cardiac accelerations of combined reflex and myogenic origins, decerebration reduced the response by diminishing its reflex component but did not reverse it (Fig. 2*D–F*).

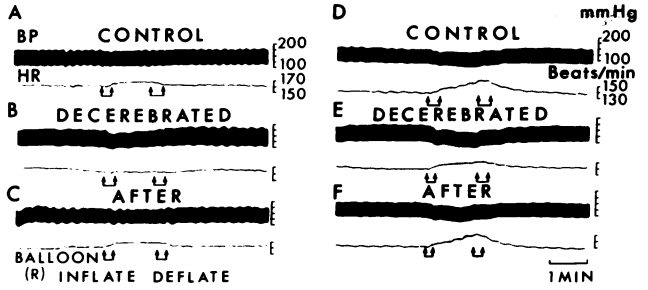

FIG. 2. Effect of decerebration on the reflex responses evoked by stretching the *right* atrium. (*A*) Changes in the blood pressure and the heart rate due to inflation of a balloon inserted into the sinoatrial region of the right atrium. Six milliliters of warm saline was introduced at the first point marked (↑—↑) and withdrawn 1 min later at the second point (↑—↑). (*B*) The same procedure as (*A*) was repeated after anemic decerebration. (*C*) Sixty minutes after unclamping the carotid arteries. (*D–F*) Similar series of experiment as *A–C* but from another dog.

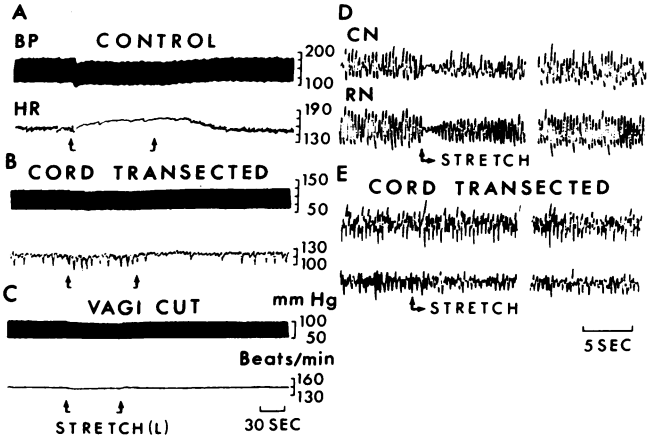

FIG. 3. Effects of cord transection on the reflex response due to stretching the *left* atrium. (*A–C*). The blood pressure and heart rate changes caused by atrial stretch before (*A*), after cord transection at C_4 (*B*), and after both vagi were subsequently severed (*C*). (*D–E*) Records obtained by using an integrator to average the changes in activity of cardiac (CN) and renal (RN) sympathetic nerves resulting from atrial stretch before (*D*) and after cord transection (*E*); (*A*) and (*D*), (*B*) and (*E*) were recorded simultaneously. In (*E*), the amplification was increased to two and one-half times that in (*D*). Records after the break in (*D*) and (*E*) were taken 5 sec after the end of atrial stretch.

Sympathetic nerve activity was not altered by atrial stretching after decerebration, and after complete denervation of these hearts a stretch-induced myogenic acceleration was still present, supporting our conclusions.

Table 1 shows the maximum changes in heart rate produced by stretching the atria, expressed as the percentage above or below basal rates, and the effect of decerebration. The results shown are the average changes obtained in 14 to 16 tests taken from four to five individual experiments. Table 1 again shows that decerebration reduced the degree of cardiac acceleration produced initially or ultimately by stretching both the left and right atria. It was found that this reduction in acceleration after decerebration was mainly due to a loss of the augmentation in sympathetic activity normally evoked by atrial stretch.

Reflex Action after Separation of Vagal and Sympathetic Loops by Spinal Transection. Although autonomic nerves are efferent pathways by definition, the vagi and cardiac sympathetic nerves anatomically contain afferent nerves from the atria. Afferent fibers in the vagi have been thought to be the major ones involved in the cardiac reflexes induced by atrial distensions (2, 8), but there is also evidence of a contribution by afferent fibers in sympathetic nerves (11). When a spinal cord section is made at the level of C_4 or C_5, signals from vagal afferent fibers can neither activate sympathetic efferent nor can afferent fibers of the sympathetic trunks affect the vagi. Thus, reflex actions initiated from the atria must depend on a vago-vagal loop through the medulla or an independent sympathosympathetic loop involving only the cord.

Table 1. Effects of decerebration on changes in heart rate produced by stretching the atria

Atrium stretched	Phase	% Change: Control/ intact	Decerebrated	After recovery
Left	Early	−10.3% (16)	−9.6% (14)	−8.4% (16)
	Late	+8.3	+1.4	+8.3
Right*	Early and late	+23.1%*(15)	+8.8%*(14)	+13.6%*(15)

Percent change in heart rate (beats/min) over basal rate was calculated from the minimal level of inhibition and the maximal level of acceleration that occurred during the first 30 sec after beginning atrial stretch (early phase), and in the succeeding 30 sec and shortly after ending stretch (late phase). The basal values represent the mean heart rate during 60-sec periods before atrial stretch. Values from a number of tests (shown in parentheses) were pooled. Four dogs were used to study left atrial stretch, and five dogs were used to study right atrial stretch.

* This acceleration was due in part to the myogenic response.

As seen in Fig. 3, a typical response produced by stretching the left atrium (Fig. 3*A*) was greatly altered after cord transection. The heart rate showed a greater fluctuation and the same atrial stretch used in Fig. 3*A* evoked only a mild deceleration of the heart rate (Fig. 3*B*). This slower rate was mainly due to the action of afferent and efferent pathways in the vagus nerves, because cutting the vagi completely abolished this response (Fig. 3*C*). Recording responses from the sympathetic nerves after sectioning the cord showed that tonic activity had been greatly reduced, an occurrence also indicated by the decrease in systemic blood pressure. Stretching the atrium caused no change or a slight augmentation of tonic activity in the cardiac and renal nerves; the maximum change observed was much less than that seen before cord transection (Fig. 3*D* and *E*; also note that magnification in Fig. 3*E* is two and a half times greater than in Fig. 3*D*). A similar diminution in response to right atrial stretch occurred after cord section.

Fig. 4*A* shows that the somatosympathetic reflex responses evoked in cardiac and renal nerves by T_1-intercostal nerve stimulation possessed two potentials which were both supraspinal reflexes (12), judging from their latencies (50 msec and 150 msec in cardiac nerve; 70 and 180 msec in renal nerve). There is also an indication of a spinal reflex because the cardiac nerve shows an early though quite small deflection with a latency of 20 msec. Stretching the *right* atrium markedly augmented supraspinal responses in both nerves (Fig. 4*A*, middle pair of traces). After spinal cord transection at C_4, T_1-intercostal nerve stimulation evoked a potential having a latency of 20 msec but only in the cardiac nerves because such stimuli in spinal preparations evoke reflexes largely confined to efferent pathways from or close to the cord segment of stimulus entry (13). The same atrial stretch as before evoked a marked increase in this efferent response (Fig. 4*B*, the middle tracing). Thus,

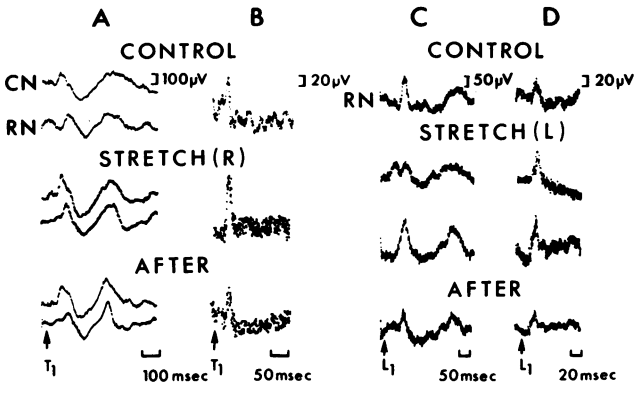

FIG. 4. Effects of atrium stretch on somatosympathetic reflexes before and after cord transection. (*A*) Reflexes in cardiac (CN) and renal nerves (RN) evoked by T_1 stimulation before, during, and after stretch of the *right* atrium. (*B*) After cord transection at C_4, only the spinal reflex was recorded from CN in response to T_1 stimulation. (*C*) and (*D*) are from another experiment in which *left* atrial stretch was used, and recordings were from renal nerve. Between (*C*) and (*D*) the cord was transected at C_5. Thus, (*D*) shows only the spinal reflex. The four tracings in both (*C*) and(*D*) are: control, the beginning of atrial stretch, later during stretch, and after atrial stretch. All tracings are the average of eight consecutive responses evoked every 3.5 sec.

there definitely is a spinal component to the atrial reflex and summation of reflexes can occur within the cord.

Fig. 4*C* shows the effect of *left* atrium stretch in an intact preparation. The somatosympathetic reflex response evoked in a renal nerve by an L_1 spinal nerve stimulation was first inhibited then augmented by atrial stretch (Fig. 4*C*, the middle two tracings) just as tonic activity was affected (Fig. 3*D*). Spinal cord transection at C_4 abolished the late reflex (latency, 70 msec) but a spinal reflex with a latency of 15–20 msec became apparent (Fig. 4*D*). Stretching the left atrium after cord transection markedly augmented the response without an initial inhibition (Fig. 4*D*, two middle tracings), and indicated that spinal reflexes evoked by atrial stretch acting through sympathetic nerves only excite the heart. This same stimulus also evoked a reflex through the vagovagal pathway that dominated the reflex and caused the heart rate to decrease (Fig. 3*B*). Thus, the somatosympathetic reflex, evoked by stimulation of T_1-intercostal or L_1 spinal nerves after cord transection, was clearly augmented by stretching either the left or right atrium even though cardiac slowing was occurring due to the more powerful action of the vagus loop.

Effects of Severing the Vagi or Sympathetic Nerves on Cardiac Reflexes. When sympathetic nerves to the heart were severed by crushing both stellate ganglia in intact dogs the heart rate was, as expected, greatly reduced. The effect of atrial stretch on the heart rate was abolished as found for cord transection. Recordings from the renal nerve showed, however, that the neural response to stretch was only slightly altered by sectioning the cardiac sympathetic nerves, indicating that afferent pathways from the atrium which pass through sympathetic nerves do not significantly contribute to the reflex response of sympathetic efferent nerves.

The importance of vagal afferent pathways was indicated by the loss of or great reduction in reflex response of the heart rate and sympathetic system to stretch, when these nerves were severed or blocked by cooling, as reported (8). However, in a few instances, only acceleration of the heart rate was produced in response to stretching the left atrium after the vagi had been severed, and in such cases afferent pathways in the cardiac sympathetic nerves produced excitatory reflexes by acting solely through the sympathetic efferent pathways. The magnitudes of such sympathetic loop responses were greater in animals with intact than in animals with severed spinal cords due to participation of supraspinal centers.

The loss of either vagus or sympathetic efferent nerve control results not only in changes of the basic heart rate but also in large fluctuations of rate that are synchronous with phrenic nerve discharges. This indicates that efferent control from both nerves is necessary to maintain a stable heart rate.

DISCUSSION

From results presented in this study the following conclusions have been drawn concerning regulation of heart rate by reflexes originating from the atria. Afferent impulses evoked by stretching the right atrium are mainly carried by fibers in the vagi and produce augmentation of activities in both vagus and sympathetic nerves. The major effect on the heart is through the cardiac sympathetic efferent fibers and the action of vagal efferent fibers is masked; thus, an acceleration of the heart rate results. Stretching the left atrium, however, produces an initially strong inhibition of sympathetic nerve activity caused reflexly by impulses in vagal afferent nerves that dominate any effects from afferent fibers in sympathetic nerves. This inhibitory phase is followed by an augmented sympathetic nerve activity that reaches its peak 30–50 sec after the beginning of the stretch stimulus. The response of the heart to left atrial stretch is thus biphasic. Vagus efferent fibers are also excited by stretching the left atrium, of acting reciprocally with the sympathetics initially and thus probably contributing to the early slowing. This activity continues, but does not suffice to prevent the late acceleration caused by an augmented sympathetic activity.

Supramedullary structures exert an influence on the medullary and spinal neurons that mediate sympathetic and vagal efferent activity. Decerebration reduces reflex responses of sympathetic nerves to atrial stretch and this results in a diminution of cardiac acceleration. The role of afferent fibers included in cardiac sympathetic nerves is to produce reflex excitation of sympathetic efferent fibers, though their role is revealed only when vagal afferent fibers are inactivated.

The conclusion that vagal afferent and sympathetic efferent fibers play the major role in atrial stretch-induced cardiac reflexes agrees well with findings by others (2). However, our study indicates the existence of a biphasic response in sympathetic neuronal discharges and in the heart rate caused by stretching the left atrium. We also wish to emphasize the presence of a myogenic contribution to the accelerator response initiated by stretching the right atrium (8, 14). These two findings must partly explain the basis for the previously mentioned conflicting results reported by various investigators (2, 3, 6).

Although it is generally believed that the vagus and the sympathetic nerves act reciprocally in control of the heart, our finding indicates that simultaneous excitation of both sympathetic and vagal efferent neurons can also occur in reflex action. A more detailed study of the relationship between vagal and sympathetic nerve action on the heart during atrial stretch will be reported elsewhere (15).

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