Response of Type B Atrial Vagal Receptors to Changes in Wall Tension during Atrial Filling

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ABSTRACT

In anesthetized curarized cats with their chests open, we recorded the activity of type B right atrial stretch receptors, right atrial pressure, and instantaneous dimensional changes of the right atrium. The nervous activity was analyzed during alterations in atrial dynamics produced by acute volume loading of the right atrium under control conditions and during sympathetic and vagal stimulations. Our results demonstrated that the mean frequency of discharge in the burst was dependent on the absolute tension and the rate of change in tension developed in atrial muscles during filling. The responses of different receptors to changes in atrial dynamics were qualitatively similar but characteristic for each receptor studied. In some experiments nervous activity was recorded after the cats had been killed: static and dynamic changes in atrial tension were then produced by injecting blood into the right atrium. Under these conditions dynamic stimuli always activated the receptors at tensions below the threshold for static stimuli. During dynamic stimuli the instantaneous firing rate was always higher than it was during static stimuli applied at the same level of tension. This study indicates that the nervous activity of type B atrial vagal receptors is closely dependent on static and dynamic changes in atrial wall tension.

KEY WORDS
- sympathetic and vagal stimulations
- atrial pressure
- neural regulation
- atrial dimensions
- preload changes

The major obstacle to a direct evaluation of the functioning of atrial vagal (1) and sympathetic (2) mechanoreceptors has been the technical difficulty of recording their nervous activity simultaneously with instantaneous atrial dimensional changes. Recently, we have described the application of an ultrasound technique (3) to the measurement of a transverse diameter of the right atrium near the junction with the superior vena cava (4). Accordingly, in the present study, we analyzed the nervous activity of right atrial vagal receptors active during atrial filling, i.e., type B stretch receptors (5), in relation to right atrial pressure and right atrial dimensional changes. We found that the nervous activity was related to indexes of static and dynamic wall tension changes produced by volume loading of the right atrium under control conditions and during inotropic interventions.

Methods

The results were obtained in 15 experiments carried out on cats (2.5–4.0 kg) anesthetized with sodium pentobarbital (35 mg/kg, ip). In all of the cats the trachea was cannulated, and artificial respiration was used after the intravenous injection of a paralyzing dose of gallamine triethiodide (Sincarina, Farmitalia). The guidelines of the American Physiological Society regarding anesthetized curarized animals were observed. The respirator was adjusted to maintain arterial gases and pH (measured on an Astrup model RM1304 blood acid-base analyzer) within physiological limits. Polyethylene catheters were inserted into (1) a femoral artery, (2) the right atrium through the external jugular vein, and (3) a femoral vein. Right atrial and femoral arterial pressures were measured with Statham P23De strain gauges. The frequency responses of the catheter-manometer systems were flat (±5%) to 30 Hz (6).

The chest was opened bilaterally from the second to the fifth intercostal space, and the sternum was removed. A 2-cm incision was made in the pericardium to expose the right atrium. Two miniature piezoelectric crystals were sutured externally to the atrial myocardiun near the junction of the superior vena cava, as previously described (4). The sonomicrometer measured the transit time of ultrasounds between the two piezoelectric crystals at a sampling rate of 5,000/sec (3).

Afferent nervous activity was recorded, as previously described (7), from filaments isolated under a dissecting microscope from the right cervical vagus.
Right atrial pressure and diameter, femoral arterial pressure, the electrocardiogram (Grass P 511 preamplifier), and tracheal pressure were recorded on a multichannel ink-writing polygraph (Grass P 7). All of these variables and the nervous activity were recorded on a magnetic tape (Hewlett-Packard 3907 C). Five variables could also be photographed (Grass C 4 camera) from a slave cathode-ray tube arranged in parallel with a Tektronix 565 oscilloscope.

The right stellate ganglion and the cut peripheral end of the left vagus were dissected from the surrounding tissues and placed on bipolar electrodes connected to a Grass S 4 stimulator through isolation units (Grass SIU). The nerves were stimulated with rectangular pulses (10–20 v, 3–5 msec) at frequencies of 10–20 Hz. On occasion, norepinephrine (Noradrec, Recordati) (1–10 µg) and acetylcholine bromide (Pragmolina, Farmitalia) (1–10 µg) were injected intravenously.

Slow (10–50 ml at approximately 0.5 ml/sec) and fast (3 ml at approximately 2 ml/sec) injections of saline, bleeding, and inferior vena cava occlusion were performed to change right atrial volume under control conditions and during isotropic interventions. Data were collected from cats having a systolic blood pressure above 100 mm Hg.

BEATING HEART

In the beating heart the analysis of the neural activity, the diameter, and the pressure changes was performed only during the expiratory pause of the respiratory cycle. We calculated: (1) the number of spikes per burst (n), (2) the duration of the burst (dB), (3) the mean frequency of discharge in the burst (n = 1/dB), and (4) the average discharge rate (n x heart rate/60).

The intramycocardial tension was estimated on the basis of Laplace’s law for a thin-walled structure, T = PR, where P is the pressure and R is the radius of the right atrium at the junction with the superior vena cava. The mean rate of change in tension, ΔT/Δt, and the mean absolute tension, T, were calculated as follows (Fig. 1):

\[ ΔT/Δt = (T_{max} - T_0)/Δt \text{ dynes/cm sec}^{-1} \times 10^9, \tag{1} \]

\[ T = (T_0 + T_{max})/2 \text{ dynes/cm} \times 10^9, \tag{2} \]

where \(T_{max}\) = maximum atrial pressure \(P_{max}\) times one-half of the maximum atrial diameter \(L_{max}\), \(T_0\) = pressure at the foot of the v wave \(P_0\) times one-half of the minimum diameter \(L_0\), and \(Δt\) = duration of atrial filling (period of lengthening or phase 1 of atrial diameter changes) (4). The responsiveness of the receptors was mainly analyzed using the mean impulse frequency per burst rather than the instantaneous impulse frequency to avoid possible erroneous calculations involved in the determination of small differences between interspike intervals. This type of analysis has been shown to be reliable for studying receptor responses to sinusoidal stretches (8). Because of similar limitations we calculated the mean rate of change in tension rather than the instantaneous maximum rate of change in tension. As an index of static stimuli we used the mean tension \(T\) instead of the maximum tension \(T_{max}\) which is reached when receptor activity has already subsided.

NONBEATING HEART

In six experiments the recording of nervous activity was maintained after the cats had been killed by bleeding and asphyxia. This method was used to avoid excessive dilatation of the atrium and thereby overstretching of the receptors. Under these conditions the transducing properties of slowly adapting atrial mechanoreceptors are unmodified for at least 20 minutes, and their activity is not increased by tissue anoxia (5, 7).

While we recorded the activity of a single unit, tension was altered by injecting and withdrawing blood. The static component of the receptor discharge was studied by correlating the instantaneous frequency of firing with different levels of static pressure and diameter length. The dynamic response of the receptors (instantaneous frequency of discharge vs. the rate of change of tension) was analyzed during the injection of a constant volume of blood at different rates starting from the same initial

\[ \text{FIGURE 1} \]

Analog recording illustrating the relationships between right atrial pressure (RAP), right atrial diameter (RAD), and nervous activity of a type B right atrial receptor. \(P_0\) and \(L_0\) = pressure and length immediately prior to atrial filling, \(P_{max}\) and \(L_{max}\) = maximum pressure and length at the end of filling, dB = duration of the burst, \(Δt\) = duration of atrial filling.

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pressure and diameter. In all of these experiments the volume of fluid injected and the changes in diameter were linearly related, suggesting that the diameter measurement during the heart cycle reflects changes in atrial volume.

LOCATION OF THE RECEPTORS

In the beating heart the receptors responsible for the afferent neural activity were located in the right atrium by using the maneuvers suggested by Paintal (1). After each receptor had been studied, the cat was killed and the sensory endings were located by probing the internal and external surfaces of the opened atrium (9).

Results

BEATING HEART

The neural activity of 15 type B right atrial receptors was studied in relation to right atrial pressure and right atrial diameter. Nine receptors were located near the junction of the superior vena cava with the right atrium, four near the junction of the inferior vena cava, and two in the lateral wall of the atrium.

The relationships between the spontaneous activity of these receptors and the \( v \) wave of right atrial pressure were similar to those previously reported (5, 9, 10). With respect to right atrial diameter (4), receptor activity under control conditions was initiated with little or no phase lag during atrial lengthening (phase 1). The end of the burst of neural activity preceded or coincided with the end-diastolic diameter. The peak frequency of receptor activity could not be consistently related to the slope of either the diameter or the pressure tracing. Occasionally, when the rate of increase in one variable was clearly constant, the peak frequency could be related to an abrupt increase in the other variable. For instance, in Figure 2 the mean rate of lengthening is constant and the peak frequency of receptor activity coincides with an increase in the slope of filling pressure. Consequently, in this case, the peak frequency of discharge corresponded to a rapid increase in tension.

Under control conditions, none of the receptors

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**FIGURE 2**

Effects of preload changes. Tracings in a and b represent, from top to bottom: the electrocardiogram, right atrial pressure (RAP), right atrial diameter (RAD), and nervous recording of a type B right atrial receptor. a: Injection of 3 ml of warm saline starting at the arrow. b: Inferior vena cava occlusion. c: Mean frequency of discharge in the burst (impulses/sec) vs. mean rate of change of tension (\( \Delta T/\Delta t \) dynes/cm \( \times 10^6 \)). d: Mean frequency of discharge in the burst (impulses/sec) vs. mean absolute tension (\( T \) dynes/cm \( \times 10^6 \)). In c and d, the open symbols indicate data obtained from the records shown in a and b; the solid symbols indicate data obtained from additional trials on the same receptor.
studied were active during passive atrial shortening (phase 2), diastasis (phase 3), active atrial shortening (phase 4), or movements of the atrioventricular valves (phase 5) (4).

The average control values of neural activity, the mean rate of change in tension \( \Delta T/\Delta t \), the mean tension \( \bar{T} \), the duration of filling, and the heart rate are shown in Table 1.

**Acute Preload Changes.**—In Figure 2 the frequency of discharge of the receptor, the number of spikes per burst, the duration of the burst, \( \Delta T/\Delta t \), and the \( \bar{T} \) increased during injection of saline (Fig. 2a) and decreased during inferior vena cava occlusion (Fig. 2b). Heart rate and duration of atrial filling were constant under both conditions. When the mean frequency of discharge in the burst was plotted versus \( \Delta T/\Delta t \) and \( \bar{T} \), we obtained the two curves shown in Figure 2c and d. The neural activity of this receptor reached a plateau at a frequency of about 110 impulses/sec. Although the slope of the curves and the maximum frequency of discharge were characteristic for each receptor studied, similar curvilinear relationships with both \( \Delta T/\Delta t \) and \( \bar{T} \) were always observed during acute volume changes.

It should also be mentioned that impulse frequency was also related to the amplitude of stretch \( \Delta T \). During acute volume loading \( \Delta t \) was constant and therefore the amplitude of stretch was proportional to \( \Delta T/\Delta t \) (Fig. 2e).

**Inotropic Interventions.**—Compared to the control condition (Fig. 3a), norepinephrine injection (or electrical stimulation of the right inferior cardiac nerve) decreased atrial diastolic pressure, right atrial diameter (both end-diastolic and end-systolic diameters [4]), and, consequently, \( \bar{T} \) and increased \( \Delta T/\Delta t \) (Fig. 3b). The number of spikes per burst, the duration of the burst, and the average discharge rate were decreased (Table 1). Electrical stimulation of the left vagus (or acetylcholine injection) increased right atrial pressure, right atrial diameter (both end-diastolic and end-systolic diameters [4]), and \( \bar{T} \) and decreased \( \Delta T/\Delta t \) (Fig. 3c). The number of spikes per burst, the duration of the burst, and the average discharge rate were increased (Table 1). However, the mean frequency of discharge in the burst was only slightly modified by either intervention (Table 1).

This finding suggests that receptor activity is dependent on both \( \bar{T} \) and \( \Delta T/\Delta t \), since these variables are affected in opposite directions by positive and negative inotropic interventions compared to the control condition (Table 1).

On occasion, unlike the control condition, sym-

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**TABLE 1**

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<thead>
<tr>
<th>Neural and Hemodynamic Effects of Inotropic Interventions in Relation to Control Conditions</th>
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<tr>
<td><strong>Spikes per burst (n)</strong></td>
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<tr>
<td>Duration of the burst (msec)</td>
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<td>Frequency of discharge (impulses/sec)</td>
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<td>Average discharge rate (impulses/sec)</td>
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<td>Rate of change of tension (dyne/cm sec⁻¹ × 10⁹)</td>
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<td>Mean tension (dyne/cm × 10⁹)</td>
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<td>Duration of filling (msec)</td>
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<td>Heart rate (beats/min)</td>
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All control values are means ± se. Values for sympathetic and parasympathetic interventions are the mean differences ± se from control and numbers in parentheses are percent changes from control values. Significance was determined using a paired t-test. \( P < 0.05 \) = not significant.

\* \( P < 0.001 \).

\† \( P < 0.01 \).

\‡ \( P < 0.05 \).

_Circulation Research, Vol. 36, June 1975_
pathetic stimulation caused four receptors to display one or two action potentials during atrial systole after the peak of the a wave, usually in correspondence with end-systolic diameter. The response has been observed by others but not yet explained (11–14).

Patterns of Response of the Receptors during Changes of $\bar{T}$ and $\Delta T/\Delta t$.—Seven receptors were studied by producing atrial volume changes during sympathetic and vagal interventions. The activity of three receptors was better related to $\Delta T/\Delta t$ than to $\bar{T}$ (Fig. 4A and B), although the discharge of two other receptors was better related to $\bar{T}$ than to $\Delta T/\Delta t$ (Fig. 4D and E). Two receptors displayed similar relationships with both $\Delta T/\Delta t$ and $\bar{T}$. A given pattern of response was characteristic and repeatable for each receptor. Different responses probably were not the result of changes in atrial muscle properties, since the relationships between $\Delta T/\Delta t$ and $\bar{T}$ were similar in all of the experiments (Fig. 4C and F).

Relationships between Frequency and Duration of the Discharge: The Number of Spikes per Burst.—During volume loading performed under control conditions, near-linear relationships between frequency and burst duration were observed in all of the experiments (Fig. 5). As shown in Figure 2, progressive increases in preload, from the lowest level obtained with inferior vena cava occlusion to the maximum level obtained during infusion, decreased the latency for the onset of the neural discharge with respect to lengthening and

Circulation Research, Vol. 36, June 1975
extended the burst duration until the time when end-diastolic diameter was achieved.

The relationship between frequency and burst duration was shifted to the left by sympathetic nerve stimulation and to the right by vagal stimulation (Fig. 5). The broken lines in Figure 5 connect bursts with the same number of spikes. It is evident that bursts with the same number of impulses have a shorter duration and a higher frequency during sympathetic stimulation; the opposite is true during vagal stimulation.

Nonbeating Heart

Six receptors were studied: five were located at the junction of the superior vena cava with the right atrium and one in the lateral wall of the atrium.

Static Discharge.—At the end of bleeding (60–100 ml), only one receptor was spontaneously active, discharging at a very low firing rate. The other receptors started firing during a slow infusion of saline at a given tension that was characteristic for each receptor. Above the threshold the instantaneous frequency of discharge of all of the receptors increased in relation to increasing static levels of pressure and diameter (Fig. 6a–c). During such infusions the atria and the ventricles occasionally began to contract weakly (5). The relationship between nervous discharge and static tension is shown in Figure 6e.

Dynamic Discharge.—With the exception of the receptor that was spontaneously discharging at the end of bleeding (located around the superior vena cava), the tension at which the receptors were activated by a dynamic stimulus was always lower than the tension required to make the same receptors active during a static stimulus. In Figure 6a–c the periods of static tension were interrupted by spontaneous weak atrial and ventricular contractions. Atrial contractions (marked by downward arrows) were characterized by an increase in pressure, a decrease in diameter, and a cessation of the nervous discharge. Upward arrows signal brief rises in pressure and length due to a backflow of blood through the atrioventricular valves during weak ventricular contractions. The instantaneous frequency of discharge of the receptors during these periods was always higher than it was for the

*Circulation Research, Vol. 36, June 1975*
RECORDATI, LOMBARDI, BISHOP, MALLIANI

corresponding levels of static tension (Fig. 6e). Moreover, it can be seen that above a certain level of tension the frequency of discharge was the same for static and dynamic stimuli (Fig. 6d and e). Figure 6f shows the relationship between right atrial pressure and right atrial diameter in this experiment.

In three experiments the dynamic stimuli were produced by injecting the same amount of saline into the right atrium at different speeds: for the same level of tension, the instantaneous frequency of discharge of the receptor was higher for a higher rate of change in tension.

Discussion

The type B receptors described by Paintal have been shown to be slowly adapting stretch receptors that respond to pulsatile changes in atrial filling (1, 5, 10). The dynamics of atrial muscle during filling are characterized, however, by the amplitude, velocity, and duration of stretch at any given length (4). For these reasons, we studied the discharge of type B atrial receptors together with atrial pressure and instantaneous atrial dimensions under different hemodynamic conditions.

The impulse frequency in the burst was used as an index of the responsiveness of the receptors to the mechanical stimuli on the basis of the generally accepted relationships between stimulus strength, generator potential and impulse frequency (15). The impulse frequency was related either to diameter changes or to the calculated tension; the results we obtained were similar in both cases. However, we preferred to use tension for the following reasons: (1) When the rate of lengthening was constant, the instantaneous frequency of discharge in the burst was related to changes in the slope of the pressure curve (p wave) (Fig. 2). (2) The activity of isolated and in situ muscle spindles, crustacean stretch receptors, and Golgi tendon organs is more closely correlated with tension than it is with muscle length (15, 16). It is reasonable to assume that atrial receptor endings and atrial tissue also possess viscoelastic properties; thus, their responses to dynamic stimuli should be frequency dependent (16).

The mean frequency of discharge in the burst of all of the receptors was related to $T$ and $\Delta T/\Delta t$ (Figs. 2 and 4). The sensitivity of the receptors to static and dynamic components of the mechanical stimulus was confirmed in the nonbeating heart by analyzing the response of the receptors (in terms of instantaneous frequency of discharge) to different levels of static stretch and to dynamic stretches performed at different rates and different diameters. The results imply that type B atrial receptors respond not only to the amplitude but also to the velocity and the mean level of atrial filling. The sensitivity of the receptors to amplitude, velocity, and level of stretch could not be quantitatively evaluated, since, in the beating heart, it is difficult to maintain two of these variables constant while the third is altered. For the same reason it was also impossible to evaluate whether stiffness changes occurred in atrial muscles and whether they influenced receptor activity.

During the cardiac cycle, the maximum duration of the activity of the receptors is established by the period of atrial filling (Figs. 1–3 and Table 1). However, when the filling time is constant, changes in the magnitude of the stimulus alter the time relationship between the appearance and the cessation of the burst and the phase of lengthening (Fig. 2). Therefore, the duration of the burst depends on the duration of atrial filling, the static and dynamic tension developed in atrial muscles during filling, and the threshold of the receptor. As a
Responses to static and dynamic stimuli of a single receptor. Tracings are the same as they are in Figure 1. Neural recordings were obtained after the cat had been killed. a-d: Pressure and length were increased by slowly infusing the right atrium. During the infusion, atria and ventricles began to contract weakly. Downward arrows indicate atrial contractions; upward arrows indicate ventricular contractions. e: The instantaneous frequency of discharge of the receptor (impulses/sec) increased almost linearly (static) with the increase in static atrial tension (T dynes/cm > 10^4). The brief increases in pressure and length produced by the backflow of blood during ventricular contractions were taken as dynamic stimuli. The instantaneous frequency of discharge during these periods was higher than it was for corresponding levels of static tension (dynamic). The static and dynamic responses matched at elevated tensions (a and e). Note in a, b, and c that during atrial active shortening the receptor ceased firing. f: Atrial pressure-length relationship.

Consequence, alterations in atrial filling can be signaled through variations in the instantaneous frequency and duration of the discharge.

Frequency per burst and burst duration were linearly related only during preload changes performed under control conditions (Fig. 5). These relationships (as were the relationships between \( \bar{T} \) and \( \Delta T/\Delta t \)) were shifted to the left by sympathetic and to the right by vagal interventions. Therefore, for the same burst duration (or for the same mean level of stretch) the impulse frequency was always higher during sympathetic stimulation than it was during control conditions. The opposite occurred during vagal interventions. It can be concluded that type B receptors, as indicated by the changes in their frequency of discharge, are sensitive to the dynamic component of stretch, which, for any given level of atrial filling, may be modulated by the sympathetic and parasympathetic outflows to the heart. On the other hand, the number of impulses per burst seems to be more affected by the absolute level of static tension (17-19), the amplitude of stretch (1, 10, 19), and the duration of the stimulus (19) than it is by the dynamic component of the stretch. Similarly, the average discharge rate (Table 1) is more closely related to the level of atrial distention than it is to the frequency of stimulation (19-21).

Changes in heart rate affect the duration of atrial filling without altering right atrial dimensions (4). In the present study, however, the contribution of changes in heart rate with respect to inotropic interventions was not determined.

The relationships of impulse frequency with \( \bar{T} \) and \( \Delta T/\Delta t \) were characteristic for each receptor studied (Fig. 4). This finding suggests that receptors may differ in their sensitivity to static and dynamic stimuli. These differences do not necessarily imply the existence of two kinds of type B receptors. They may depend on several factors such...
as the distribution of the sensory endings (22, 23), the distribution of the distending forces, and the working range of the receptors (19). Other mechanoreceptors detecting both position and velocity, for instance, are known to lose their ability to detect position at a high velocity of stimulation (24).

No relationships were found between the pattern of activity and the location of the endings (superior vena cava, inferior vena cava, or lateral wall). However, it should be mentioned that it is difficult to exactly evaluate the distention or the forces acting at each receptor site by measuring a single dimension in a complex geometrical structure. This limitation may also account for the inability to identify the mechanical stimuli responsible for the occasional activation of the receptors at the end of systole during sympathetic stimulation.

In the nonbeating heart, below the threshold for static stretch type B atrial receptors can be activated by a dynamic stretch. Above the static threshold the continuous firing ceases during active muscle shortening. This phenomenon may explain why these receptors are normally active only during atrial filling, and a maintained stretch may explain their continuous discharge during acute circulatory failure when cardiac chambers are markedly distended (7, 25).

Arndt et al. (19) in a recent study on atrial mechanoreceptors in the cat during sinusoidal stretches of atrial strips in situ demonstrated that both type B and type A receptors are sensitive to static and dynamic components of stretch. Under their experimental conditions, dynamic sensitivity was present in the high-frequency range and with large stimulus amplitude. In our experiments, most of the receptors displayed their peak frequency of discharge before the end of atrial lengthening, thus showing a clear dynamic sensitivity in a low-frequency range of stimulation. These responses of type B receptors to dynamic stimuli in the beating atrium and in atrial strips may be dependent on differences in the mechanics of the wall elements carrying the receptors.

In the beating heart the dynamics of atrial walls may be altered by sympathetic and vagal interventions. Vagal stimulation, for instance, decreases the dynamic component of stretch for any given level of atrial filling. In view of these findings, the recent report that type B receptors in the dog are mainly sensitive to the static component of the stimulus, their frequency of discharge being maximum at the end of atrial filling (17), may thus be explained on the basis of the high vagal tone that influences cardiac function in the dog.

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