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Parasympathetic Effects on in Vivo Rat Heart Can Be Regulated Through an \( \alpha_1 \)-Adrenergic Receptor

Patricia A. McGrattan, Joan Heller Brown, and Oliver M. Brown

A prejunctional mechanism involving an \( \alpha_1 \)-adrenergic receptor may exert control on the release of acetylcholine from parasympathetic nerve endings in the heart. To test this hypothesis in vivo, rats were prepared for electrical stimulation of the vagus nerves. Blood pressures and heart rates were monitored, and the animals were treated with \( \alpha \)-agonists and \( \alpha \)-antagonists. The \( \alpha_1 \)-selective agonist phenylephrine significantly attenuated vagally induced bradycardia in a dose-dependent fashion (\( ED_{50} = 19 \mu g/kg \)). This is consistent with the hypothesis that there is \( \alpha \)-adrenergic inhibition of ACh release. In contrast, the \( \alpha_2 \)-selective agonist, BHT-920, caused no change in heart rate during vagal stimulation. The effects of phenylephrine to raise heart rate and blood pressure during vagal stimulation were blocked by the \( \alpha_2 \)-selective antagonist prazosin (\( ID_{50} \) approximately 1 \( \mu g/kg \)) but not by the \( \alpha_2 \)-selective antagonists yohimbine and rauwolscine. This further supports an \( \alpha_1 \) assignment to the prejunctional adrenergic receptor mechanism, which can regulate the release of acetylcholine from cardiac parasympathetic neurons. (Circulation Research 1987;60:465-471)

Materials and Methods

Animal Preparation

Male Sprague-Dawley rats (Taconic Farms, Germantown, N.Y.) weighing 220–280 g were used in all experiments. Rats were anesthetized with a combination of 300 mg/kg chloral hydrate (Merck and Co. Inc., West Point, Penn.) and 30 mg/kg sodium pentobarbital (Abbott Laboratories, North Chicago, Ill.). Following a midline cervical incision, the trachea was intubated, and the right jugular vein and the left carotid artery were cannulated. Both the right and left vagus nerves were exposed and suspended over stainless steel bipolar electrodes and cut rostral to the electrodes to prevent afferent and efferent vagal reflexes. The electrodes were connected to a stimulus isolation unit (Grass, Quincy, Mass., model S1U5) driven by a Grass (model S88) stimulator. The vagi were given electrical pulse train stimulation: twin 5 volt pulses 25 milliseconds apart and 0.5 milliseconds in duration were administered at a pulse rate (4–5 Hz) chosen to entrain the heart to a rate that was approximately 65–70% of the control (prestimulation) rate. With pulse train stimulation in this range of frequencies, sinoatrial nodal rhythm synchronized with the periodic bursts of vagal activity, allowing reproduction of the desired percent decrease in heart rate for each animal regardless of exact individual resting rate.

Blood pressure was monitored from the carotid artery cannula through a pressure transducer (Statham model P23AC, Hato Rey, Puerto Rico) and recorded throughout the experiment on a Grass (model 7D) polygraph. A lead II surface electrocardiogram was recorded continuously on the Grass polygraph, and heart rate was determined from the interval between successive P waves.
Drug Protocols

The \( \alpha_2 \)-selective agonist phenylephrine (PE) and the \( \alpha_2 \)-selective agonist BHT-920 were tested for their effect on heart rate and blood pressure when administered alone or during bilateral vagus nerve stimulation. Vagal stimulation was initiated 1 minute before the i.v. injection of agonist. PE was administered at several dose levels from 1-100 \( \mu \)g/kg, and BHT-920 was given in doses of 10 and 100 \( \mu \)g/kg. Three or four trials of vagal stimulation alone, agonist alone, and the combined treatments were made on each animal with a washout (recovery) period of at least 5 minutes between treatments.

The effects of PE on heart rate and blood pressure were challenged with the \( \alpha_2 \)-selective antagonist prazosin and the \( \alpha_2 \)-selective antagonists yohimbine and rauwolscine. The antagonists were administered 2 minutes before the initiation of vagal stimulation (thus, 3 minutes before the injection of PE).

In some animals, bradycardia was produced by administration of the muscarinic agonist bethanechol (2.5 mg/kg, i.p.) in place of vagal stimulation. In another group of animals, blood pressure was increased by the temporary occlusion of the abdominal aorta in place of PE administration.

Drugs

BHT-920 was generously provided by Boehringer Ingelheim KG (Ingelheim am Rhein, Germany), prazosin HCl was the kind gift of Pfizer Inc. (Groton, Conn.), and phenylephrine HCl (PE) was provided by Winthrop Labs (New York, N.Y.). Yohimbine HCl was purchased from Sigma (St. Louis, Mo.), rauwolscine HCl from Atomergic Chemetals (Plainview, N.Y.), and bethanechol chloride from Merck Sharp & Dohme (West Point, Penn.). All drugs were dissolved in physiologic saline solution except prazosin HCl, which was dissolved in dimethylsulfoxide and diluted with saline to a final concentration of dimethylsulfoxide not greater than 10%; this vehicle solution had no effect on the measured properties. All drugs were administered by i.v. injection unless otherwise noted.

Calculations and Statistics

Heart rate and mean arterial blood pressure were determined during the following treatment periods: 1) control conditions, 2) agonist administration alone, 3) vagal stimulation alone, and 4) agonist administration during vagal stimulation (these periods were repeated in the case of pretreatment with antagonist). The values from 3 or 4 trials of each treatment period were averaged for each animal. The data reported here are the maximal treatment-induced changes from control values, which were seen at 10 seconds after agonist administration for blood pressure (mm Hg, mean ± SEM) and at 60 seconds for heart rate (bpm, mean ± SEM). Where appropriate, blood pressure and heart rate data from each treatment group were compared by two-way analysis of variance (ANOVA) and orthogonal comparisons. 13

Results

The resting heart rate for the rats in these studies was 433 ± 5 beats per minute. This rate is elevated compared to that in control rats because cutting the cervical vagus nerves releases the heart from central parasympathetic control. Electric stimulation of the vagus nerves was adjusted to effect a 35-40% decrease in heart rate (a decrease of 150-170 bpm). This bradycardia was maintained for 150 seconds, the entire period of vagal stimulation. A slight decrease in blood pressure accompanied the bradycardia. Figure 1 shows the effects of vagal stimulation on heart rate (lower panel) and blood pressure (upper panel). Also shown in Figure 1 are the heart rate and blood pressure responses to the \( \alpha_2 \)-selective agonist PE. Note that since afferent and efferent vagal fibers were severed, reflex responses to vagal stimulation or PE injection were not observed for blood pressure or heart rate, respectively. When injected alone, PE (25 \( \mu \)g/kg) increased blood pressure dramatically, from 80 to 148 mm Hg, but had no effect on heart rate. However, when PE was administered during vagal stimulation, not only did blood pressure increase, but there was also a significant attenuation of the vagally induced bradycardia (the maximum increase in heart rate being 47 bpm). This observation is consistent with the hypothesis that activation of \( \alpha_2 \)-receptors decreases the release of ACh from parasympathetic neurons. The maximum increase in blood pressure occurred at 10 seconds after PE administration, and the maximum change in heart
rate was observed at 60 seconds. ANOVA treatment of the heart rate data from 45–150 seconds in Figure 1 indicated that the heart rate resulting from PE administration during vagal stimulation was significantly higher than from vagal stimulation alone \((p < 0.05, F_{1, 50} = 6.94)\). The effect of PE to increase blood pressure was also highly significant \((p << 0.001, F_{1, 50} = 176)\).

Both blood pressure and heart rate responses to PE were dose dependent, as shown in Figure 2. Curves were fitted by eye to the data points, which represent the changes in blood pressure (upper panel) and heart rate (lower panel) with increasing doses of PE during vagal stimulation. The blood pressure changes were plotted for 10 seconds post-PE injection, and the heart rate changes were plotted for 60 seconds post-PE — the maximum response times for each (see Figure 1). The ED\(_{50}\) for the increase in blood pressure was 8 \(\mu g/kg\), and the ED\(_{50}\) for the increase in heart rate was 19 \(\mu g/kg\).

Several \(\alpha\)-antagonists were used to characterize the heart rate and blood pressure effects of PE during stimulation of the vagus nerves. Figure 3 shows the results of treatment with prazosin, an \(\alpha_1\)-selective antagonist, and rauwolscine, an \(\alpha_2\)-selective antagonist. When injected alone, 50 \(\mu g/kg\) of prazosin had little effect on heart rate but decreased blood pressure as expected. Initiation of vagal stimulation in the presence of prazosin still produced a bradycardia. However, injection of PE subsequent to prazosin resulted in no change in blood pressure or heart rate. Rauwolscine injected alone (50 \(\mu g/kg\)) had no effect on heart rate and caused little decrease in blood pressure. Vagal stimulation following rauwolscine administration resulted in the characteristic pronounced decrease in heart rate and a small decrease in blood pressure. Injection of PE subsequent to rauwolscine resulted in an increase in blood pressure and a marked attenuation of the vagal bradycardia, as seen in the absence of antagonist. The observation that the ability of PE to raise blood pressure and to attenuate vagal bradycardia is blocked by prazosin, but not by rauwolscine, suggests that both responses are mediated through \(\alpha_1\)-adrenergic receptors.

The heart rate data in Figure 3, following PE injection, were compared by ANOVA and orthogonal comparisons. The heart rate changes induced by PE with prazosin during vagal stimulation were not different from those induced by vagal stimulation alone \((p = 0.05)\). Further, PE with rauwolscine during vagal stimulation had the same effect on heart rate as did PE during vagal stimulation \((p = 0.05)\).

The dose-response relations for prazosin, rauwolscine, and another \(\alpha_2\)-selective antagonist, yohimbine, are compared in Figure 4 (curves were fitted to the data points by eye). At low doses (50–100 \(\mu g/kg\)), yohimbine and rauwolscine had no pronounced effect on heart rate or blood pressure and did not block the effects of PE during vagal stimulation. At much higher doses (1–2 mg/kg), these antagonists produced decreases in both heart rate and blood pressure and decreased the effects of PE on blood pressure and vagal bradycardia, as shown in Figure 4. Prazosin \((ID_{50} = 0.8 \mu g/kg)\), however, was about 1,000 times more potent than yohimbine \((ID_{50} = 600 \mu g/kg)\) or
FIGURE 4. Log dose-response curve for antagonist inhibition of the effects of PE on heart rate and blood pressure during vagal stimulation (4–6 animals/point). Upper panel: Change in blood pressure from vagal stimulation level. Lower panel: Change in heart rate from rate during vagal stimulation. (Means ± SEM, see Figure 1 legend.) ○—○ Prazosin (0.5, 5.0, and 50 μg/kg) (1.2 × 10^{-9}, 1.2 × 10^{-8}, and 1.2 × 10^{-7} mol/kg); □—□ yohimbine (0.1, 0.5, and 2.0 mg/kg) (2.6 × 10^{-7}, 1.3 × 10^{-6} and 5.1 × 10^{-6} mol/kg); ■—■ rauwolscine (0.05, 0.5, and 2.5 mg/kg) (1.3 × 10^{-7}, 1.3 × 10^{-6}, and 6.5 × 10^{-6} mol/kg).

rauwolscine (ID_{50} = 1,300 μg/kg) in inhibiting the heart rate response to PE during vagal stimulation at a dose of 5 μg/kg. Prazosin (ID_{50} = 1.2 μg/kg) was also considerably more potent than yohimbine (ID_{50} = 220 μg/kg) or rauwolscine (ID_{50} = 1,500 μg/kg) in blocking the effect of PE on blood pressure.

The role of an α_{1}-adrenergic receptor in mediating the effect of PE on vagal bradycardia was further supported by studies with the α_{2}-selective agonist BHT-920. In contrast to the effect of PE, BHT-920 did not attenuate the bradycardia resulting from vagal stimulation. Figure 5 shows that when BHT-920 was injected alone, it increased blood pressure (upper panel) and decreased heart rate only slightly (lower panel). When administered during stimulation of the vagus nerves, BHT-920 caused a slight increase in blood pressure but did not increase heart rate.

Statistical analysis of the blood pressure data in Figure 5 revealed that blood pressure was significantly higher with BHT-920 alone (p << 0.001) or with BHT-920 treatment during vagal stimulation (p < 0.05) when compared to vagal stimulation alone. This finding supports the argument that α_{2}-adrenoceptors are present in vascular smooth muscle where they mediate vasoconstriction.

Analysis of the heart rate data in Figure 5 indicated no significant difference between treatment with BHT-920 during vagal stimulation and vagal stimulation alone (p > 0.05).

In some animals, the same degree of bradycardia that resulted from electric stimulation of the vagus nerves was produced and sustained by administration of the muscarinic agonist bethanechol (2.5 mg/kg i.p.). When PE was injected during bethanechol induced bradycardia, no significant change in heart rate was seen (Table 1). In another experiment, the abdominal aorta was temporarily clamped to produce a sharp rise in blood pressure comparable to that resulting from PE administration. When this maneuver was performed during vagally induced bradycardia no further change in heart rate was seen (Table 1).

Discussion

In the studies presented here, blood pressure and heart rate were monitored from rats that received electric stimulation of vagus nerves, drug injections, or both. Pulse train electric stimulation of the cardiac ends of the transected right and left vagus nerves resulted in a maintained bradycardia (Figure 1). The injection of PE alone caused an increase in blood pressure with no change in heart rate (Figure 1). However, when PE was injected during vagal stimulation, not only was the expected increase in blood pressure observed but also an increase in heart rate (Figure 1).

The increases in heart rate and blood pressure resulting from PE administration during vagal stimulation
both occurred over the same dosage range, as shown in Figure 2. To rule out the possibility that the increase in heart rate was secondary to the effect of PE to increase blood pressure, an additional experiment was performed in which the abdominal aorta was temporarily clamped to produce a sharp rise in blood pressure comparable to that resulting from PE administration. When this maneuver was performed during vagally mediated bradycardia, there was no significant change in heart rate (Table 1). We also considered the possibility that the effect of PE was a rate related event, attributed to the decrease in heart rate resulting from vagal stimulation. To test this, the same degree of bradycardia that resulted from vagal stimulation (A) was performed during vagally mediated bradycardia during vagal stimulation (B). In heart rate resulting from vagal stimulation. The positive chronotropic and positive inotropic effects of catecholamines in the heart are largely mediated by \( \beta \)-adrenergic receptors. There is some evidence that \( \alpha \)-adrenergic receptors may contribute to the positive inotropic response to sympathetic activity, but a direct role for \( \alpha \)-adrenergic receptors in mediating chronotropic responses is unlikely. Our data are consistent with this latter point; no changes in heart rate were seen in our preparation with the administration of either the \( \alpha \)-agonist PE (Figure 1) or with the administration of \( \alpha \)-antagonists (Figure 3). A number of studies suggest that prejunctional \( \alpha \)-adrenergic receptors do serve an important role in controlling the release of norepinephrine from sympathetic nerve endings in the heart. Several \( \alpha \)-agonists decreased, while \( \alpha \)-antagonists increased, the outflow of norepinephrine from isolated rabbit hearts subjected to electric sympathetic nerve stimulation. That this prejunctional \( \alpha \)-adrenergic inhibitory feedback mechanism is subserved by \( \alpha \)-adrenergic receptors is supported by much evidence and has been reviewed. However, several studies suggest that prejunctional receptors subtyped as \( \alpha \)-adrenergic may also play a role in this function. Prejunctional \( \alpha \)-adrenoceptor activity was determined by monitoring changes in aortic blood flow during vagal stimulation (Figures 1 and 5). An \( \alpha \)-assignment is further supported by studies with specific \( \alpha \)-adrenoceptor antagonists. The effects of PE on heart rate and blood pressure during vagal stimulation were uniquely blocked by the \( \alpha \)-antagonist prazosin over a dosage range consistent with other characterizations of \( \alpha \)-adrenoceptor binding or physiology. In contrast, blockade by the \( \alpha \)-antagonists yohimbine and rauwolscine was evident only in much higher doses (Figures 3 and 4), well above those generally needed for \( \alpha \)-blockade. The similarity between the antagonist dose-response curves shown here for in vivo heart rate (Figure 4) and that of Wetzel et al. for in vitro ACh release is strong evidence that both parameters are regulated through the same (\( \alpha \)-adrenergic) receptor.

### Table 1. Changes in Rat Blood Pressure and Heart Rate With Various Treatments

<table>
<thead>
<tr>
<th>Treatments (A followed by B)</th>
<th>Change in blood pressure (mm Hg)</th>
<th>Change in heart rate (bpm)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vagal stimulation (A) with PE injection (B)</td>
<td>-15.0 ± 1.0</td>
<td>-169 ± 12</td>
<td>6</td>
</tr>
<tr>
<td>Vagal stimulation (A) with aortic clamp (B)</td>
<td>-5.2 ± 4.4</td>
<td>-107 ± 2</td>
<td>4</td>
</tr>
<tr>
<td>Bethanechol injection (A) with PE injection (B)</td>
<td>-22.6 ± 4.4</td>
<td>-162 ± 19</td>
<td>5</td>
</tr>
</tbody>
</table>

*Protocol similar to that used in Figure 1.
†Treatment A was ongoing for 1 minute (vagal stimulation) or 5 minutes (bethanechol injection, 2.5 mg/kg i.p.) before initiation of treatment B (injection of PE, 25 \( \mu \)g/kg i.v.; or clamping of abdominal aorta). Change in blood pressure and heart rate from pretreatment (control) value was recorded for treatment A prior to initiation of treatment B, and again at 10 seconds after treatment B for blood pressure and 60 seconds after treatment B for heart rate (means ± SEM).
§These data are from Figure 1.

\( \alpha \)-adrenergic receptor activity was determined by monitoring changes in aortic blood flow during vagal stimulation (Figures 1 and 5). An \( \alpha \)-assignment is further supported by studies with specific \( \alpha \)-adrenoceptor antagonists. The effects of PE on heart rate and blood pressure during vagal stimulation were uniquely blocked by the \( \alpha \)-antagonist prazosin over a dosage range consistent with other characterizations of \( \alpha \)-adrenoceptor binding or physiology. In contrast, blockade by the \( \alpha \)-antagonists yohimbine and rauwolscine was evident only in much higher doses (Figures 3 and 4), well above those generally needed for \( \alpha \)-blockade. The similarity between the antagonist dose-response curves shown here for in vivo heart rate (Figure 4) and that of Wetzel et al. for in vitro ACh release is strong evidence that both parameters are regulated through the same (\( \alpha \)-adrenergic) receptor.

The positive chronotropic and positive inotropic effects of catecholamines in the heart are largely mediated by \( \beta \)-adrenergic receptors. There is some evidence that \( \alpha \)-adrenergic receptors may contribute to the positive inotropic response to sympathetic activity, but a direct role for \( \alpha \)-adrenergic receptors in mediating chronotropic responses is unlikely. Our data are consistent with this latter point; no changes in heart rate were seen in our preparation with the administration of either the \( \alpha \)-agonist PE (Figure 1) or with the administration of \( \alpha \)-antagonists (Figure 3). A number of studies suggest that prejunctional \( \alpha \)-adrenergic receptors do serve an important role in controlling the release of norepinephrine from sympathetic nerve endings in the heart. Several \( \alpha \)-agonists decreased, while \( \alpha \)-antagonists increased, the outflow of norepinephrine from isolated rabbit hearts subjected to electric sympathetic nerve stimulation. That this prejunctional \( \alpha \)-adrenergic inhibitory feedback mechanism is subserved by \( \alpha \)-adrenergic receptors is supported by much evidence and has been reviewed. However, several studies suggest that prejunctional receptors subtyped as \( \alpha \)-adrenergic may also play a role in this function. Prejunctional \( \alpha \)-adrenoceptor activity was determined by monitoring changes in tachycardia elicited by electric stimulation of spinal sympathetic roots in the pithed rat preparation. This tachycardia was inhibited by several agonists (including the \( \alpha \)-selective agonist methoxamine), an effect that was selectively blocked by prazosin. Quantitative comparison of their agonist and antagonist data suggests that most of the adrenoceptors at this site are of the \( \alpha \)-subtype but supports the existence of a popula-
tion of $\alpha_1$-prejunctional receptors on cardiac sympathetic neurons. Somewhat similar experiments in dog$^{22}$ and studies with isolated guinea pig atria$^{23}$ have also provided evidence that prejunctional $\alpha_2$-adrenoceptors, as well as $\alpha_2$-adrenoceptors, modulate norepinephrine release from cardiac sympathetic nerves.

An analogous regulatory mechanism has been described in the parasympathetic system. Thus, prejunctional muscarinic receptor activation has been shown to inhibit ACh release from various preparations, for example chicken heart$^{24}$ and rat right atrium.$^7$

In addition to prejunctional autoreceptor regulation of neurotransmitter release, heteroreceptor inhibition of transmitter release has been proposed as a mechanism contributing to the complicated interactions between the sympathetic and parasympathetic innervations of several organs, including the heart.$^{1-3}$ Löeffelholz and Muscholl$^{24,25}$ demonstrated that the addition of ACh to isolated perfused rabbit atria reduced the quantity of norepinephrine released in response to sympathetic nerve stimulation. In an open-chest dog preparation, Levy and Blattberg$^7$ found that stimulation of the left cardiac sympathetic nerve produced an increase in ventricular contractile force and an increase in norepinephrine overflow into the coronary sinus. Concurrent vagal stimulation caused a reduction in contractile force and a decrease in norepinephrine overflow. Levy and Blattberg$^7,13$ concluded that ACh released from vagus nerves can, through a prejunctional mechanism, exert a potent inhibitory effect on the release of norepinephrine from sympathetic nerve endings.

Several studies on gut preparations suggest that the converse of this heteroreceptor inhibitory mechanism, adrenergic inhibition of ACh release from parasympathetic neurons, also occurs.$^{26}$ Starke$^6$ first reported that $\alpha$-agonists inhibit the vagally induced bradycardia in isolated rabbit heart by decreasing the release of ACh. This hypothesis was not supported by Lew and Angus,$^{27}$ who studied the electric responses of isolated guinea pig right atria to field stimulation. However, more recent reports from Wetzel and coworkers$^{6,8}$ and from Langer's group$^{28}$ provide strong support for the $\alpha$-prejunctional control of ACh release. In the superfused rat right atrium, prelabelled with $[^3]$H]-choline, both groups demonstrated that $\alpha$-agonists inhibit the overflow of $[^3]$H]-acetylcholine from the atrium in response to potassium stimulation or field stimulation. Unlike the prejunctional $\alpha$-adrenergic receptors described in most systems, which are of the $\alpha_2$-subtype, the receptor described by Wetzel et al$^6$ appears to be of the $\alpha_1$-subtype. They found that the overflow of $[^3]$H]-acetylcholine was inhibited by norepinephrine and by the $\alpha_1$-selective adrenergic agonist methoxamine,$^8$ as well as by phenylephrine.$^6$ The adrenergic inhibition of ACh release was blocked by the $\alpha_1$-selective adrenergic antagonists prazosin and YM-12617 but not by yohimbine or rauwolscine. The $\alpha_1$ characterization of this receptor was very recently confirmed by Benkiran et al$^{26}$ in similar studies on the effects of several other selective $\alpha$-agonists and antagonists on the release of $[^3]$H]-acetylcholine from superfused rat atrial slices.

Therefore, the study presented here provides physiologic evidence to support the hypothesis of Wetzel et al$^{6-8}$ that prejunctional $\alpha_1$-adrenergic receptors participate in the control of ACh release from parasympathetic nerve endings in the rat heart. The studies of Wetzel and coworkers showed that norepinephrine and epinephrine were very effective at inhibiting ACh release from isolated rat atria, suggesting that increased sympathetic tone might attenuate parasympathetic responses under certain physiologic conditions. In the in vivo preparation, we were unable to use norepinephrine or epinephrine because the dose of propranolol necessary to completely block the $\beta$ effects of these catecholamines was toxic to our animals. Nonetheless, our series of observations made with PE support the proposed inhibition of ACh release from parasympathetic varicosities by activation of prejunctional $\alpha_2$-adrenergic receptors.$^6,8$ The mechanism demonstrated here may contribute to the interactions between the sympathetic and parasympathetic branches in the autonomic control of cardiac function. This mechanism may also underlie the lack of significant tachycardiac side effects in the treatment of hypertension with prazosin. Because of its $\alpha_1$-selectivity, prazosin would not disrupt activation of prejunctional $\alpha_2$-receptors by nor-epinephrine, and thus normal sympathetic feedback inhibition would occur.$^{26}$ At the same time, this selective antagonism would interfere with the proposed $\alpha_1$-adrenoceptor inhibition of ACh release. The combination of decreased norepinephrine release and increased ACh release may explain the low incidence of tachycardia in prazosin therapy.

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