Role of $\beta_1$-Receptors and Vagal Tone in Cardiac Inotropic and Chronotropic Responses to a $\beta_2$-Agonist in Humans

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To assess the contribution of cardiac $\beta_2$-receptors in the cardiac inotropic and chronotropic responses to a $\beta_1$ agonist, terbutaline was infused (0.2 and 0.4 $\mu$g/kg/min), alone or after pretreatment with either oral atenolol 50 mg or atropine 0.04 mg/kg i.v. or both in six healthy subjects with a multiple crossover design. Terbutaline 0.2 $\mu$g/kg/min increased heart rate by 15±2 beats/min, and this response doubled (to 29±3 beats/min) when the terbutaline infusion followed atropine pretreatment, whereas atenolol pretreatment had no significant effect. Heart rate increased by 44±2 beats/min in response to terbutaline 0.4 $\mu$g/kg/min. This response was not affected by atropine. Pretreatment with atenolol diminished the chronotropic response to the higher dose of terbutaline to 27±4 beats/min. The inotropic response (i.e., changes in pressure:volume ratio) to terbutaline 0.2 $\mu$g/kg/min was potentiated by atropine (from 1.6±0.3 to 3.4±0.8 mm Hg/ml), whereas atenolol pretreatment had no effect. At the higher dose of terbutaline, atropine pretreatment had no additional effect, whereas atenolol decreased the rise in pressure:volume ratio from 6.0±1.4 to 2.6±1.0 mm Hg/ml. The results with atenolol pretreatment indicate that cardiac $\beta_1$ responses are associated with the higher dose of terbutaline, either through direct $\beta_1$ stimulation or indirectly from presynaptic $\beta_2$ activity. The atropine data show that vagal tone actually increased during the terbutaline infusions, blunting the cardiac effects. The results of the present study support the existence of functional chronotropic, as well as inotropic, $\beta_2$ receptors in the healthy human heart. (Circulation 1989;79:107–115)

The original classification of $\beta_2$-receptors in the heart and $\beta_2$-receptors in the vascular and bronchial smooth muscles by Lands and coworkers1 defined a high degree of organ specificity for the two receptor subtypes. However, in recent years, it has become clear that $\beta_1$- and $\beta_2$-receptor subtypes may coexist in virtually every organ.2 Studies with radioligand-binding techniques have demonstrated that in the human heart the percentage of $\beta_2$-receptors in ventricular myocardium may range from 14% to 40% and in atrial tissue from 20% to 50%.3–8 Biochemical studies have demonstrated that stimulation of cardiac $\beta_2$-receptors causes an increase in cAMP,9 and in vitro studies have shown that $\beta_2$-receptors are coupled to positive inotropic and chronotropic responses.4,10

Evidence for functional cardiac $\beta_1$ chronotropic receptors in vivo has come from studies showing that nonselective $\beta$-blockade had a greater ability to antagonize isoproterenol-induced tachycardia than $\beta_1$-selective blockade,11 that selective $\beta_2$-blockade significantly decreased the heart rate response to a nonselective $\beta$-adrenoceptor agonist,12 and that selective $\beta_1$-blockade only slightly decreased the heart rate response to a $\beta_2$-agonist or epinephrine.13,14 In vivo data suggestive for functional cardiac $\beta_2$-inotropic receptors in humans was obtained in our studies on the effects of terbutaline and epinephrine on left ventricular function in the presence or absence of atenolol.13,14 However, besides stimulation of cardiac $\beta_2$-receptors, several alternative explanations for these effects exist, as outlined in Figure 1. Systemic $\beta_2$-receptor stimulation may stimulate cardiac $\beta_2$-receptors via baroreceptor-mediated increases in sympathetic tone or via presynaptic $\beta_2$ stimulation.15,16 In addition, a $\beta_2$ agonist such as

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Supported by an operating grant from the Heart and Stroke Foundation of Ontario, by the Pfizer Fellowship in Clinical Pharmacology from the Canadian Society for Clinical Pharmacology (M.A.H.L.), and by a research scholarship from the Canadian Heart Foundation (F.H.H.L.).

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Received May 2, 1988; revision accepted September 6, 1988.
terbutaline may cause direct $\beta_1$ stimulation because it is not 100% $\beta_2$ selective.\textsuperscript{17} By combining terbutaline with the $\beta_1$-receptor blocker atenolol, we have shown that $\beta_1$-receptor stimulation plays only a minor role in the chronotropic response and a moderate role in the inotropic response to this $\beta_2$ agonist.\textsuperscript{13} Other possible mechanisms involved in the cardiac effects of a $\beta_2$-receptor agonist include $\beta_2$-receptor–mediated increase in preload via vasodilation in the splanchic outflow resistance bed,\textsuperscript{18} more efficient left ventricular emptying because of a decrease in afterload secondary to $\beta_2$-mediated arterial vasodilatation, and baroreceptor-mediated reflex withdrawal of vagal tone.\textsuperscript{11,13,19}

To assess the contribution of changes in vagal activity in the cardiac responses to a $\beta_2$-receptor agonist, we administered terbutaline after pretreatment with either atropine or atenolol or both.

**Subjects and Methods**

**Subjects**

Six healthy male volunteers 23±0.4 years old and weighing 70±3 kg (mean±SEM) participated in the study. Subjects were instructed to refrain from alcohol and caffeine ingestion 24 hours before and during each study day and to not use any medication while enrolled in the study. All subjects were nonsmokers. The study was approved by the Human Ethics Committee of the University of Toronto and written, informed consent was obtained.

**Experimental Protocol**

The study was performed as a single-blind randomized multiple crossover trial. Each subject was studied on five separate days at least 1 week apart for the following drug regimens: terbutaline only; atropine and terbutaline; atenolol, atropine, and terbutaline; atenolol and terbutaline; and atropine only. On the atropine-only day, intravenous phenylephrine was administered before and after the atropine to assess the effectiveness of the vagal blockade.

On each study day, after a 12-hour overnight fast, a standardized liquid breakfast was given at 8:00 AM. An indwelling venous catheter was inserted in the forearm and kept patent with a dilute solution of heparin (5,000 IU/30 ml). Subjects remained in the supine position from the period after breakfast until completion of the study day. The time course for the study day protocol is outlined in Figure 2. At 9:00 AM, atenolol 50 mg or an identical-appearing placebo tablet was given. Atropine (or saline), in a sequence of three intravenous dosages (0.02, 0.01, and 0.01 mg/kg), was given 90, 120, and 150 minutes after the atenolol (or placebo) tablet. Terbutaline was infused at two dosages, 0.2 and 0.4 $\mu$g/kg/min, each for 30 minutes starting at 120 and 150 minutes, respectively, after atenolol (or placebo). On the atropine-only day, phenylephrine in incremental continuous infusions (each for 5 minutes) was administered in dosages of 0.42–1.60 $\mu$g/kg/min during the 20 minutes preceding the first dosage of atropine and 0.11–0.42 $\mu$g/kg/min beginning after the third dosage of atropine. The maximum allowable increase in systolic blood pressure was 30 mm Hg.

Supine heart rate and blood pressure were monitored every 2 minutes for 20-minute periods before the administration of either atenolol, atropine, or terbutaline and during the final 20 minutes for each dose of terbutaline. The mean value for the final five readings was used for analysis. Heart rate was
derived from the electrocardiogram recorded by a Hewlett-Packard 78351A monitor (Mississauga, Ontario, Canada), and blood pressure was measured automatically by a Roche Arteriosonde 1225 (Roche Medical Electronics, Cranbury, New Jersey) on the arm contralateral to the venous catheter.

Left ventricular (LV) echocardiograms were obtained at the end of each of the above mentioned 20-minute periods. Echocardiograms were obtained with the subjects in the supine position, as described previously.20 The following parameters were measured or calculated: LV end-diastolic and LV end-systolic dimension and volume; cardiac index; stroke volume; percent fractional shortening; ejection fraction; and systolic blood pressure:LV end-systolic volume ratio (P:V ratio).21 Echocardiographic measurements were performed in a blinded fashion, and individual parameters were calculated with a DBase III program.

Analytic Methodology

Blood samples were drawn through the indwelling forearm venous catheter into heparinized collection tubes at the times illustrated in Figure 2. Samples for atenolol and catecholamines were centrifuged at 3,000 rpm for 10 minutes at 4°C, and the plasma was removed and frozen at −60°C until assayed. Plasma norepinephrine and epinephrine were measured by a radioenzymatic assay,22 and atenolol levels were measured by high-performance liquid chromatography.23 All samples from one subject were measured in one assay in duplicate. Serum potassium concentration was measured by flame photometry.

Analysis of Data

Changes in dependent variables were compared between study days at similar times by ANOVA for multiple comparisons (Duncan’s multiple range test). The between-study day comparison of the cardiovascular responses to the different dosages of terbutaline (the covariate) was performed by an analysis of covariates. Within-study day changes from baseline were tested for significance by an analysis of variance for repeated measures. Pulse interval and systolic blood pressure response to phenylephrine were evaluated by linear regression analysis. Data are presented as mean ± SEM.

Results

Hemodynamic Effects of Atropine and Atenolol

Cardiovascular indexes at rest before administration of any pretreatment were similar for the 5 study days and showed no significant differences (data not shown). Values after pretreatments before the start of terbutaline are presented in Table 1 and the legends of Figures 3 and 4.

Atropine alone resulted in a substantial \( p < 0.001 \) increase in heart rate but also increased \( p < 0.05 \) diastolic and systolic blood pressure. Despite the marked increase in heart rate, LV end-diastolic volume did not decrease. With LV emptying, P:V ratio, and stroke volume not affected, the increase in heart rate was associated with a significant \( p < 0.01 \) increase in cardiac index. On the atropine-only day, the hemodynamic effects of the first dose of atropine as shown in Table 1 and Figures 3 and 4 persisted after administration of the subsequent two doses (e.g., heart rate at 90±3 beats/min after the last dose compared with 89±2 beats/min after the first dose, and P:V ratio of 2.8±0.4 mm Hg/ml compared with 3.0±0.4 mm Hg/ml).

Atenolol induced significant \( p < 0.05 \) decreases in heart rate and cardiac index and small, nonsig-
significant decreases in systolic blood pressure and P·V ratio. Atropine administered after pretreatment with atenolol induced rather similar cardiovascular effects as atropine alone, except for somewhat smaller increases in heart rate and systolic and diastolic blood pressure.

**Hemodynamic Effects of Terbutaline With and Without Atropine and Atenolol**

To assess the effects of vagal blockade with atropine and β₁-blockade with atenolol on the hemodynamic responses to terbutaline, the hemodynamic changes in the final 10 minutes of the terbutaline infusions were compared.

**Heart rate.** Terbutaline 0.2 and 0.4 μg/kg/min increased the heart rate by 15±2 and 44±2 beats/min, respectively (p<0.001) (Figure 3). Atropine pretreatment potentiated (p<0.001) the heart rate response to the lower dosage of terbutaline but not to the higher dosage. Atenolol pretreatment did not affect the heart rate response to the lower dosage of terbutaline but inhibited (p<0.001) the response to terbutaline 0.4 μg/kg/min.

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**TABLE 1. Changes in Cardiovascular Parameters in Response to Terbutaline With Different Pretreatments**

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Terbutaline dose (μg·kg⁻¹·min⁻¹)</th>
<th>Systolic blood pressure (mm Hg)</th>
<th>Diastolic blood pressure (mm Hg)</th>
<th>LV end-systolic volume (ml)</th>
<th>LV end-diastolic volume (ml)</th>
<th>Ejection fraction (%)</th>
<th>Fractional shortening (%)</th>
<th>Stroke volume (ml)</th>
<th>Cardiac index (l/min/m²)</th>
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<tr>
<td>None</td>
<td>0</td>
<td>113±4</td>
<td>67±2</td>
<td>44±5</td>
<td>139±9</td>
<td>69±2</td>
<td>32±2</td>
<td>95±5</td>
<td>2.7±0.3</td>
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<td>Atropine</td>
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<td>121±4</td>
<td>77±4</td>
<td>43±5</td>
<td>137±9</td>
<td>69±2</td>
<td>32±2</td>
<td>94±5</td>
<td>4.5±0.3</td>
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<td>Atropine</td>
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<td>-14±2</td>
<td>-11±4</td>
<td>+14±6</td>
<td>+10±3</td>
<td>+8±2</td>
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<td>-23±5</td>
<td>-23±4</td>
<td>+1±7</td>
<td>+17±3</td>
<td>+15±3</td>
<td>24±10</td>
<td>3.5±0.4</td>
</tr>
<tr>
<td>Atropine+atenolol</td>
<td>0.2</td>
<td>+5±5*</td>
<td>-21±4</td>
<td>-22±6</td>
<td>-25±9</td>
<td>+12±3</td>
<td>+11±3</td>
<td>-3±5*</td>
<td>+1.3±0.3</td>
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<tr>
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<td>+17±3</td>
<td>-29±5</td>
<td>-25±6</td>
<td>-31±9</td>
<td>+14±4</td>
<td>+13±3</td>
<td>-6±7*</td>
<td>1.8±0.3</td>
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<tr>
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<td>108±2</td>
<td>67±4</td>
<td>45±4</td>
<td>137±8</td>
<td>67±2</td>
<td>31±2</td>
<td>92±5</td>
<td>2.3±0.2</td>
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<td>-9±4</td>
<td>-5±3*</td>
<td>+15±6</td>
<td>+7±2</td>
<td>+6±2</td>
<td>21±6</td>
<td>+1.2±0.1</td>
</tr>
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<td>Atenolol</td>
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<td>+12±2</td>
<td>+10±2</td>
<td>28±4</td>
<td>+2.4±0.2</td>
</tr>
</tbody>
</table>

LV, left ventricular.

Values represent mean±SEM for absolute values before start of terbutaline and the changes induced by terbutaline at two rates. All changes are significantly (p<0.05) different from baseline except *NS). Significant differences between changes after different treatments versus no pretreatment (none) are indicated in “Results.”

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**FIGURE 3. Bar chart of change in heart rate from baseline (preterbutaline) in response to terbutaline 0.2 (□) and 0.4 μg/kg/min (●) with and without pretreatments.** Values are mean±SEM. Baseline values are 55±3 (control), 89±2 (atropine), 47±1 (atenolol), and 76±3 (atropine and atenolol) beats/min.
the higher dosage. After combined atropine and atenolol, terbutaline induced similar increases in heart rate as with atropine alone (i.e., atenolol did not inhibit the potentiating effect of atropine).

**Diastolic and systolic blood pressure.** Terbutaline 0.2 and 0.4 μg/kg/min decreased diastolic blood pressure by -14 ±2 and -23 ±5 mm Hg, respectively (p <0.01) (Table 1). There were no significant differences in the effects of terbutaline on diastolic blood pressure between the study days with pretreatment versus without pretreatment.

Terbutaline 0.2 and 0.4 μg/kg/min increased systolic blood pressure by 24 ±2 and 45 ±5 mm Hg, respectively (p <0.01). Vagal blockade diminished (p <0.01) the systolic blood pressure response to terbutaline, and the increase in systolic blood pressure was only significant with the higher dose of terbutaline. With β₁-blockade, the systolic blood pressure response to terbutaline decreased significantly (p <0.05) only when evaluating the overall response to both dosages of terbutaline. After combined β₁-blockade and vagal blockade, the systolic blood pressure response to terbutaline was similarly blunted as it was after vagal blockade alone.

**Left ventricular volumes.** Terbutaline 0.2 and 0.4 μg/kg/min increased LV end-diastolic volume slightly (NS) by 14 ±6 and 1 ±7 ml, respectively (Table 1). After pretreatment with atropine, terbutaline caused a marked fall in LV end-diastolic volume (p <0.01). Atenolol pretreatment resulted in a change in LV end-diastolic volume similar to terbutaline alone. Combined vagal blockade and β₁-blockade with terbutaline produced results similar to the pretreatment with only atropine.

A reduction in LV end-systolic volume of -11 ±4 (p <0.05) and -23 ±4 ml (p <0.01) was observed with terbutaline 0.2 and 0.4 μg/kg/min, respectively. The addition of atenolol reduced this effect to -5 ±3 and -13 ±3 ml, and the decline associated with the lower dosage of terbutaline became nonsignificant. Adding atropine showed slight potentiation (p <0.09) of the decrease in LV end-systolic volume with the lower dosage of terbutaline.

Stroke volume increased by 25 ±7 and 24 ±10 ml with terbutaline 0.2 and 0.4 μg/kg/min, respectively (p <0.05). With atropine pretreatment, the increase in stroke volume associated with terbutaline was eliminated (p <0.01). There was no effect of pretreatment with atenolol on the stroke volume response to terbutaline.

Cardiac index increased by 1.7 ±0.3 (p <0.01) and 3.5 ±0.4 (p <0.001) l/min/m² with terbutaline 0.2 and 0.4 μg/kg/min, respectively. At the lower dosage of terbutaline, there was no difference between the responses to terbutaline alone or after pretreatment with atropine, atenolol, or both. With the higher dosage, the increase in cardiac index was less with atropine (p <0.001), with atenolol (p <0.05), or both.

**Parameters of left ventricular performance.** Effects of terbutaline on P:V ratio, as a measure of inotropy, are illustrated in Figure 4. P:V ratio increased by 1.6 ±0.3 and 6.0 ±1.4 mm Hg/ml with terbutaline 0.2 and 0.4 μg/kg/min, respectively (p <0.01). After vagal blockade, there was a potentiation (p <0.05) of the P:V ratio response with the

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**Figure 4.** Bar chart of change in pressure-volume ratio from baseline (preterbutaline) in response to terbutaline 0.2 μg/kg/min (□) and 0.4 μg/kg/min (■) with and without pretreatments. Values are mean ±SEM. Baseline values are 2.8 ±0.4 (control), 3.0 ±0.4 (atropine), 2.6 ±0.3 (atenolol), and 2.3 ±0.2 (atropine and atenolol) mm Hg/ml.
lower dosage of terbutaline. With β₁-blockade, the P:V ratio response with the lower dosage of terbutaline was not significantly affected, but the response to the higher dosage of terbutaline was significantly diminished (p<0.05). After pretreatment with combined vagal blockade and β₁-blockade, the P:V ratio response to terbutaline was similarly reduced as after atenolol alone [i.e., atenolol blocked (p<0.05) the potentiating effect of atropine].

Parameters of LV performance (i.e., ejection fraction and fractional shortening) were increased (p<0.001) in a dosage-related fashion to terbutaline 0.2 and 0.4 µg/kg/min (Table 1). Pretreatment with either atropine or atenolol did not significantly alter these responses to terbutaline.

Response to Phenylephrine

Phenylephrine induced the expected dose-related increases in systolic blood pressure and RR interval. Atropine significantly increased the pressor response to phenylephrine and inhibited the associated decrease in heart rate. For example, the increase in systolic blood pressure with phenylephrine 0.4 µg/kg/min was greater by 18±3 mm Hg (p<0.01) for postatropline values compared with pretropine values. The regression lines of RR interval to systolic blood pressure for the phenylephrine infusion praprotein and post- 
atropine are illustrated in Figure 5. The pretropine slope is 9.8±2.1 msec/mm Hg. and the postatroline slope is 2.4±0.03 msec/mm Hg. The slopes of the two lines are significantly different (p<0.001).

Biochemical Results

Plasma catecholamines. Plasma norepinephrine increased in response to terbutaline from 302±73 to 465±98 pg/ml (NS) after the lower dosage and to 543±94 pg/ml (p<0.05) after the higher dosage of terbutaline. There were no significant differences in the plasma norepinephrine levels after terbutaline when comparing study days with or without atropine or atenolol or both. Plasma epinephrine was not significantly affected by the various combinations of terbutaline, atenolol, and atropine (data not presented).

Potassium. The fall in serum potassium associated with terbutaline 0.2 and 0.4 µg/kg/min was −0.4±0.1 and −1.0±0.1 mmol/l, respectively. On the study day with previous administration of atenolol, the fall in serum potassium associated with the low and high dosage of terbutaline was 0.4±0.1 and −1.0±0.1 mM, respectively. The difference between the two study days (with and without atenolol) was nonsignificant.

Atenolol. Plasma atenolol levels at 3 hours after oral administration of atenolol 50 mg were 196±26 and 183±25 ng/ml on the 2 study days atenolol was administered.

Discussion

Several recent studies indicate that in humans cardiac β₁-receptors may mediate chronotropic11-14 and possibly also inotropic13,14 responses. In the present study, we assessed in vivo inotropic and chronotropic responses to the β₁-agonist terbutaline and evaluated the roles of both β₁-receptor activity as well as changes in vagal tone in these responses. The role of changes in vagal tone in the chronotropic response to the nonselective β-receptor agonist isoproterenol has been assessed previously: infusions of isoproterenol appear to cause an increase in vagal tone, but bolus injections cause a decrease.24 The relevance of changes in vagal tone for the cardiac responses to infusion of a selective β₁-agonist has not yet been assessed.
Methodologic Considerations

β1-Receptor blockade was induced by atenolol 50 mg. This dosage and the associated plasma levels induces a high degree of β1-receptor blockade as assessed by inhibition of exercise tachycardia or hydralazine-induced tachycardia. The β1 selectivity of atenolol 50 mg has been demonstrated previously and was confirmed in the present study by the failure of atenolol to alter the hypokalemic (β2-mediated) response to terbutaline.

Vagal blockade was induced by serial injections of atropine, and this was associated with substantial increases in heart rate and cardiac index, illustrating that vagal tone contributes significantly in the setting of the baseline heart rate and cardiac index. The increase in RR interval that accompanies the rise in blood pressure during phenylephrine infusion was markedly blunted after atropine and confirmed that adequate vagal blockade had occurred.

Terbutaline may improve LV performance due to effects on myocardial contractility, by increasing preload, or by decreasing afterload. The P:V ratio is a noninvasive measure of inotropy unaffacted by changes in preload or afterload and was used to evaluate myocardial contractility. Preload, as assessed by LV end-diastolic volume, did not change during infusion of terbutaline, suggesting that venous return increased sufficiently to maintain LV end-diastolic volume despite increases in heart rate and LV emptying. After atropine, terbutaline actually decreased LV end-diastolic volume, presumably as a result of a more pronounced increase in heart rate without a further increase in venous return. Administration of terbutaline does cause a marked decrease in afterload, as reflected in end-systolic wall stress, and this likely contributes to the increase in LV emptying after terbutaline.

β1-Receptors and Cardiac Responses to a β2-Agonist

β1-Blockade by atenolol did not affect the heart rate and inotropic response to the lower dosage of terbutaline but blunted the further increase by the higher terbutaline dosage. This suggests that at the higher dosage, direct β1-receptor stimulation was in part responsible for the chronotropic response, or alternatively, the higher dosage of terbutaline caused presynaptic β2 stimulation resulting in norepinephrine release and subsequent stimulation of postsynaptic β1-receptors. The increase in plasma norepinephrine levels supports the latter mechanism.

β-Receptor Stimulation and Vagal Tone

The increase in heart rate caused by β-agonists has in part been attributed to baroreceptor-mediated reflex withdrawal of vagal tone. This may indeed occur after bolus injections of isoproterenol, for example, when diastolic and mean blood pressure decrease. However, infusion of isoproterenol increases systolic blood pressure, and pulse pressure with no change in mean blood pressure and vagal activity actually then appears to increase.

The present study extends these observations to the chronotropic as well as inotropic effects of a β2-agonist and evaluated the role of both β1-receptors and vagal tone. As shown in Figures 3 and 4, β1-receptors did play a role but only at higher rates of the β2-agonist. In contrast, atropine increased both the chronotropic and inotropic response to terbutaline at the lower rate. These findings may indicate that vagal tone increased (rather than decreased) blunting the cardiac responses to terbutaline at the lower rate. Increases in systolic blood pressure and pulse pressure without a decrease in mean blood pressure can result in a baroreceptor mediated increase in vagal tone.

Atropine did not change the inotropic and chronotropic responses to the higher rate of terbutaline, suggesting that vagal tone had returned to control activity. It is possible that in this period the arterial baroreceptors reset (acute resetting), returning vagal activity to control. Alternatively, hemodynamic changes induced by the higher rate compared with the lower rate of terbutaline may explain the change in vagal activity. However, changes in systolic, diastolic, or mean blood pressure (Table 1) show no obvious differences in this regard.

The role of vagal tone in regulation of heart rate is well established. Its role in the control of LV performance is not as clear. The cholinergic innervation of the human ventricular myocardium is rather sparse, but negative inotropic effects of increased vagal tone have been reported, particularly when sympathetic tone was increased.

In the present study, atropine alone increased heart rate markedly but did not affect the P:V ratio, suggesting absent control of vagal tone in control of global LV myocardial contractility under resting conditions, in contrast to its major role in control of resting heart rate. If, indeed, vagal tone increased with infusion of terbutaline, blunting the chronotropic and inotropic responses to increased sympathetic activity, this would suggest that only high vagal activity exerts a negative inotropic effect (in addition to a chronotropic effect). Alternatively, differential activation of vagal fibers to atria compared with ventricles may occur, or the negative inotropic effect only may become discernible with increased cardiac sympathetic stimulation.

However, alternatives for increased vagal tone should be considered. For example, the increased inotropic response to terbutaline after atropine could be the direct result of the increase in the heart rate response to terbutaline.

Another explanation, however, deserves close evaluation. Terbutaline alone increased systolic
blood pressure, and mean blood pressure did not change. In contrast, after atropine, the decrease in diastolic blood pressure caused by terbutaline was somewhat larger but the increase in systolic blood pressure was markedly less, presumably related to the absence of an increase in stroke volume with combined atropine and terbutaline. This caused a decrease in mean blood pressure by 10–15 mm Hg. It is, therefore, possible that after atropine the different hemodynamic changes induced by terbutaline cause a baroreceptor-mediated increase in β1-receptor-mediated cardiac sympathetic activity, explaining the potentiated response rather than removal of vagal tone. To assess this possibility, terbutaline was also evaluated after both atenolol and atropine. After this combination, terbutaline still caused only a minor increase in systolic blood pressure and decreased mean blood pressure (by 5–7 mm Hg). However, the potentiating effect of atropine on the heart rate response to terbutaline was not blocked by the addition of atenolol, indicating that atropine did not increase the β1-receptor-mediated component of the heart rate response to terbutaline. In contrast, the potentiating effect of atropine on the P:V ratio response to terbutaline was no longer apparent with concomitant pretreatment with atenolol. If removal of a blunting effect by increased vagal tone would have been responsible, then the potentiating effect of atropine should have persisted after addition of atenolol. These results, therefore, indicate that after atropine the larger inotropic response at the lower rate of terbutaline relates to a larger β1-receptor-mediated component rather than removal of vagal tone. Regulation of heart rate and LV performance appear to differ under these circumstances, and this may, at least in part, relate to differences in vagal innervation of atria versus ventricles.

Conclusions

By blocking both vagal activity and β1-receptors, we have illustrated that the inotropic and chronotropic responses to a low dosage of the β2-agonist terbutaline (0.2 μg/kg/min) do not involve a reduction in vagal tone or stimulation of β1-receptors and may indeed be due to cardiac β2-receptor stimulation. The involvement of β1-receptors at the higher dosage of terbutaline (0.4 μg/kg/min) may be caused either by direct β1-receptor stimulation or indirectly by stimulation of presynaptic β2-receptors.

The results of the present study are consistent with previously published in vivo data suggestive for a functional role of β2-adrenoceptors in the inotropic13,14 and chronotropic activity11–14 of the healthy human heart.

Acknowledgments

We thank Mrs. F. Browning and Mrs. R. Farkas for their technical assistance and Astra Pharmaceuticals for providing the terbutaline.
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KEY WORDS • heart • β-receptors • vagal blockade • terbutaline • β<sub>1</sub>-blockade
Role of beta 1-receptors and vagal tone in cardiac inotropic and chronotropic responses to a beta 2-agonist in humans.
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Circulation. 1989;79:107-115
doi: 10.1161/01.CIR.79.1.107

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/79/1/107

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