Inotropic and Sympathetic Responses to the Intracoronary Infusion of a $\beta_2$-Receptor Agonist
A Human In Vivo Study

Gary E. Newton, MD; Eduardo R. Azevedo, MD; John D. Parker, MD

Background—On the basis of the presence of $\beta_2$-receptors within the sympathetic nervous system, $\beta_2$-stimulation may increase cardiac sympathetic outflow. We addressed the hypothesis that sympathoexcitatory $\beta_2$-receptors are present in the human left ventricle.

Methods and Results—The $\beta_2$-agonist salbutamol was infused into the left coronary artery in 3 groups of patients: group 1 (n=9, no $\beta$-blocker therapy), group 2 (n=7, $\beta_1$-selective blockade with atenolol), and group 3 (n=6, nonselective $\beta$-blockade with nadolol). Left ventricular $+dP/dt$ in response to increasing concentrations of salbutamol was measured in all groups, and cardiac norepinephrine spillover was measured in group 1. There were no systemic hemodynamic changes in any group. Salbutamol resulted in a 44±6% increase in $+dP/dt$ in group 1, a 25±6% increase in group 2 ($P<0.05$ versus group 1), and no increase in group 3. Salbutamol also resulted in a 124±37% increase in cardiac norepinephrine spillover in group 1 ($P<0.05$).

Conclusions—Evidence that salbutamol increased norepinephrine release from cardiac sympathetic nerves was provided by the observations that atenolol suppressed the salbutamol inotropic response, demonstrating that this response was mediated in part by $\beta_1$-receptors and that salbutamol also resulted in an increase in cardiac norepinephrine spillover. This result provides in vivo evidence, in humans, for the role of sympathoexcitatory cardiac $\beta_2$-receptors. (Circulation. 1999;99:2402-2407.)

Key Words: salbutamol ■ atenolol ■ nadolol ■ ventricles ■ norepinephrine

Stimulation of $\beta_2$-adrenergic receptors increases both ventricular contractility and sympathetic outflow to the heart. Activation of $\beta_2$-receptors on ventricular myocytes directly increases contractility. Activation of $\beta_2$-receptors within the peripheral vasculature causes vasodilation, which results in reflex sympathetic activation and parasympathetic withdrawal, both of which can augment contractility. $\beta_2$-Receptors have also been described at various sites within the efferent sympathetic nervous system. In animal studies, stimulation of $\beta_1$- and $\beta_2$-receptors within intrathoracic sympathetic ganglia and on intrinsic cardiac neurons increases postganglionic cardiac sympathetic nerve discharge rate. $\beta_2$-Receptors have been reported to be present on postganglionic cardiac sympathetic nerve terminals. Stimulation of these prejunctional receptors in animal experiments also facilitates norepinephrine release from cardiac sympathetic nerves. Thus, in addition to $\beta_2$-receptor–mediated positive inotropic and vasodilation, stimulation of $\beta_2$-receptors within the efferent sympathetic nervous system may result in a direct (nonreflexive) increase in cardiac sympathetic outflow.

Stimulation of sympathoexcitatory cardiac $\beta_2$-receptors has the potential to contribute to the increase in cardiac sympathetic activity, which occurs in the setting of congestive heart failure. These receptors may also be involved in the mechanism of action of widely used cardiac medications, including $\beta$-agonists and antagonists. Despite their potential importance, the physiological and pathophysiological role of sympathoexcitatory cardiac $\beta_2$-receptors in the human heart is not well understood. Human studies have demonstrated that the inotropic response to intravenous $\beta_2$-agonists is mediated in part by postsynaptic $\beta_2$-receptors, as evidenced by partial inhibition of the $\beta_2$-inotropic response by selective $\beta_1$-antagonists. Although consistent with augmented norepinephrine release due to stimulation of sympathoexcitatory $\beta_2$-receptors, this observation may also be explained by reflex sympathetic activation resulting from $\beta_2$-receptor–mediated vasodilation. Studies of patients with congestive heart failure also provide indirect evidence for sympathoexcitatory cardiac $\beta_2$-receptors. In congestive heart failure, $\beta_1$-selective antagonists increase cardiac sympathetic activity, an effect that does not occur with nonselective $\beta$-blockade. To date, human studies examining direct cardiac stimulation with $\beta_2$-receptor...
agonists have been limited. Hall et al.\(^{19}\) examined the heart rate response to right coronary artery injections of the β\(_{-}\)-agonist salbutamol. They observed that practolol, a β\(_{-}\)-selective agent, did not increase the mean dose of salbutamol required to augment heart rate by 30 bpm. This result suggests that β\(_{-}\)-receptor stimulation does not facilitate nor-epinephrine release from sympathetic nerves at the level of the sinoatrial node.

In the present study, we addressed the hypothesis that sympathoexcitatory β\(_{-}\)-receptors are present in the left ventricle. To answer this hypothesis, we used a left main coronary artery infusion technique for the direct application of a β\(_{-}\)-agonist to the left ventricle. This approach was chosen to avoid activation of reflex systems associated with systemic β\(_{-}\)-agonist infusions. Using this method, we measured the inotropic response, both β\(_{-}\)- and β\(_{2}\)-mediated, and the cardiac norepinephrine spillover response to an intracoronary β\(_{-}\)-agonist.

**Methods**

**Study Population**

The study population consisted of 22 subjects with a stable chest pain syndrome who had been referred for a diagnostic heart catheterization. All subjects had normal ventricular function by either 2-dimensional echocardiography or left ventriculography, and none had symptoms of congestive heart failure.

Three groups were studied. Subjects in group 1 (n = 9; 8 men, 1 woman; mean age, 52 ± 4 years; range, 32 to 61 years) were not receiving β-blocker therapy. Medical therapy in this group included calcium channel blockers (n = 5), nitrates (n = 1), and ACE inhibitors (n = 1). By coronary angiography, 4 subjects in group 1 did not have coronary disease, 1 had single-vessel disease involving the left anterior descending coronary artery (LAD), 3 had 2-vessel disease (LAD and circumflex coronary artery in 2, LAD and right coronary artery in the third), and 1 had 3-vessel disease. Group 2 (n = 7; 6 men, 1 woman; mean age, 57 ± 4 years; range, 44 to 71 years) included subjects receiving the β\(_{-}\)-selective β-blocker atenolol at a dose of 50 mg po daily for at least 1 week before the study. Medical therapy in this group, in addition to atenolol, included calcium channel blockers (n = 2) and nitrates (n = 2). Two subjects in group 2 did not have coronary disease, 1 had single-vessel disease (LAD), 2 had 2-vessel disease (LAD and circumflex in both), and 2 had 3-vessel disease. Subjects in group 3 (n = 6; 5 men, 1 woman; mean age, 62 ± 4 years; range, 53 to 74 years) received the nonselective β-blocker nadolol at a dose of 40 mg po daily for at least 1 week before the study. Medical therapy in this group, in addition to nadolol, included calcium channel blockers (n = 1), nitrates (n = 1), and ACE inhibitors (n = 1). One subject in group 3 did not have coronary disease, 2 had 1-vessel disease (LAD and right coronary artery), and 3 had 3-vessel disease. Subjects in groups 2 and 3 received their usual dose of atenolol or nadolol, respectively, 1 hour before beginning the catheterization study.

This protocol was approved by the University of Toronto ethical review committee for experimentation involving human subjects. Written informed consent was obtained in all cases.

**Hemodynamic and Inotropic Measurements**

After a diagnostic heart catheterization, 20 minutes elapsed before we began this investigation. A 7F micromanometer-tipped catheter (Millar Industries) was placed in the left ventricle. A 7F left Judkins catheter (Cordis Laboratories), placed from the opposite femoral artery, was advanced to the ostium of the left main coronary artery for intracoronary drug infusions. Femoral artery pressure was monitored via an 8F side-arm sheath (Cordis Laboratories). The ECG, left ventricular pressure, and its first derivative (dP/dt, continuous electronic differentiation) were recorded on a strip chart recorder at a paper speed of 100 mm/s. Measurements of heart rate, left ventricular pressure, and femoral artery pressure were made by averaging at least 15 beats under each experimental condition. Left ventricular pressure and the ECG were digitally recorded at 300 Hz with a Macintosh personal computer equipped with a multichannel analog-to-digital converter. Data files were stored to disk for later analysis. With customized software developed in Labview (Version 3.0, National Instruments Corp), left ventricular peak +dP/dt was calculated offline. In all cases, +dP/dt values represent the mean calculated from a minimum of 20 cardiac cycles during each experimental condition.

**Experimental Approach**

The effect of the β\(_{-}\)-agonist salbutamol on left ventricular function and cardiac norepinephrine spillover was assessed by the intracoronary drug infusion technique.\(^{2,4}\) The sequence of intracoronary infusions was as follows: (1) control 5% dextrose in water (D\(_{5}\)W), the vehicle for intracoronary drug infusion, at 1.25 mL/min; (2) intracoronary salbutamol sulfate (Glaxo Canada Inc) at infusion rates of 0.125, 0.625, 1.25, 2.5, and 5.0 μg/min; (3) recontrol D\(_{5}\)W. Intracoronary drugs were administered into the left main coronary artery via the Judkins catheter with a Harvard pump for 4 to 5 minutes, with measurements made in the final minute. All solutions were infused at 1.25 mL/min. After completion of the protocol, radiographic contrast was injected to confirm the continued position of the catheter in the left main coronary ostium. Indications for discontinuation of salbutamol included chest discomfort and ventricular extrasystoles. In group 1 (no β-blocker therapy), 6 subjects received the maximum salbutamol infusion (5.0 μg/min), 1 subject received a maximum infusion of 2.5 μg/min, and 2 subjects received a maximum infusion of 1.25 μg/min. In group 2 (atenolol-treated), 5 subjects received the maximum salbutamol infusion, and 1 subject received a maximum infusion of 2.5 μg/min. All subjects in group 3 (nadolol-treated) received the maximum salbutamol infusion.

**Cardiac Norepinephrine Spillover Measurements**

To evaluate the effect of salbutamol on norepinephrine release from cardiac adrenergic nerves, cardiac norepinephrine spillover was measured in 5 patients in group 1. Cardiac norepinephrine spillover is the rate at which norepinephrine from the heart appears in plasma and as such is an indirect index of norepinephrine release from cardiac sympathetic nerves. This index was measured at control, at peak dose of salbutamol, and at recontrol. In these patients, in addition to the instrumentation described above, a 7F coronary sinus thermodilution flow catheter (type CCS-7U-90B, Webster Laboratories) was inserted from an antecubital vein. Coronary sinus blood flow measurements were performed in triplicate at each measurement point according to the method of Ganz et al.\(^{21}\) A tracer dose of tritiated norepinephrine (1 to 1.2 μCi/min, with a 16 μCi priming bolus of [2,5,6-\(^{3}\)H]NE; New England Nuclear) was infused into a peripheral vein to steady-state concentration in plasma. Cardiac norepinephrine spillover and clearance rates were calculated as follows:\(^{1,3,22}\) Cardiac NE spillover (pmol/min) = (NE\(_{cs}\) - NE\(_{ext}\) + (NE\(_{ext}\) × NE\(_{cs}\)))/CSFP, and cardiac NE clearance (ml/min) = NE\(_{cs}\) × CSFP, where [\(^{3}\)H]NE is tritium-labeled norepinephrine, NE\(_{cs}\) is transcatheter fractional extraction of tritium-labeled norepinephrine, NE\(_{ext}\) and NE\(_{ext}\) are cardiac sinus and arterial plasma norepinephrine concentra- tions, respectively, and CSFP is coronary sinus plasma flow calculated from the hematocrit and coronary sinus blood flow. Catecholamine concentrations were measured by high-performance liquid chromatography (HPLC) with electrochemical detection. Fractions from the HPLC effluent containing tritium-labeled norepinephrine were assayed by liquid scintillation spectroscopy. These analyses were performed by established methods in our laboratory.\(^{17,23}\)

**Statistical Analysis**

Baseline characteristics and peak salbutamol responses were compared by 1-way ANOVA. Within-group and between-group comparisons of the effects of salbutamol on hemodynamics and left ventricular contractility were performed with a 2-way repeated-measures ANOVA with Student-Newman-Keuls test performed post.
TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>68±3</td>
<td>65±2</td>
<td>57±4</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
<td>16±1</td>
<td>21±2</td>
<td>22±2</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>14±1</td>
<td>16±1</td>
<td>20±2</td>
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<tr>
<td>Mean FA, mm Hg</td>
<td>97±3</td>
<td>98±2</td>
<td>86±4</td>
</tr>
<tr>
<td>CI, L·min⁻¹·m⁻²</td>
<td>3.0±0.2</td>
<td>2.8±0.2</td>
<td>2.5±0.1</td>
</tr>
<tr>
<td>+dP/dt, mm Hg/s</td>
<td>1328±77</td>
<td>1265±76</td>
<td>1131±72</td>
</tr>
</tbody>
</table>

HR indicates heart rate; PAP, pulmonary artery pressure; LVEDP, left ventricular end-diastolic pressure; FA, femoral artery pressure; CI, cardiac index; and +dP/dt, peak positive left ventricular dP/dt.

Results

Baseline Characteristics

Baseline hemodynamic characteristics in the 3 study groups are provided in Table 1. There were no significant differences between the study groups in age, any hemodynamic parameter, or left ventricular +dP/dt.

Hemodynamic Responses to Intracoronary Salbutamol

In the 3 study groups, there were no significant changes in systemic arterial blood pressure, left ventricular end-diastolic pressure, or heart rate in response to any dose of salbutamol infused into the left coronary artery (Table 2).

Inotropic Responses to Intracoronary Salbutamol

In group 1 (no β-blocker therapy), intracoronary salbutamol resulted in a large dose-dependent increase in left ventricular contractility as assessed by +dP/dt. The increase in left ventricular +dP/dt was significant at all doses of salbutamol >0.125 μg/min (Table 2, Figure 1). The maximal increase in left ventricular +dP/dt in group 1 was 578±78 mm Hg/s, or 44±6% (Figure 2).

Background β-blocker therapy resulted in smaller increases in contractility in response to intracoronary salbutamol. In group 2 (atenolol-treated), salbutamol resulted in a

| TABLE 2. Hemodynamic and Inotropic Responses to Intracoronary Salbutamol |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Parameter and Group          | Control 0.125 | 0.625 | 1.25 | 2.5 | 5.0 | Recontrol |
| HR                           | 68±3        | 69±4  | 69±4 | 71±4 | 73±4 | 78±7  | 73±4 |
| LVEDP                        | 14±1        | 14±2  | 15±1 | 13±1 | 13±2 | 14±2  | 15±1 |
| Mean FA                      | 97±3        | 97±3  | 97±3 | 96±4 | 93±4 | 93±4  | 99±3 |
| +dP/dt                       | 1328±77     | 1330±99 | 1507±77* | 1631±70* | 1893±54* | 2111±55* | 1464±85 |

Abbreviations as in Table 1.

*P<0.05 for within-group comparison vs control; †P<0.05 vs group 1; ‡P<0.05 vs group 2.
The inotropic response to intracoronary salbutamol was completely inhibited in group 3 (nadolol-treated). There were no significant increases in left ventricular +dP/dt in response to any dose of salbutamol. The lack of an increase in contractility in group 3 was significantly different from the responses in both group 1 and group 2 (Table 2, Figures 1 and 2).

The inotropic response to intracoronary salbutamol was completely inhibited in group 3 (nadolol-treated). There were no significant increases in left ventricular +dP/dt in response to any dose of salbutamol. The lack of an increase in contractility in group 3 was significantly different from the responses in both group 1 and group 2 (Table 2, Figures 1 and 2).

Cardiac Norepinephrine Spillover Responses to Intracoronary Salbutamol

Cardiac sympathetic responses to peak doses of salbutamol were assessed in 5 patients in group 1 (1.25 μg/min in 1 subject, 5 μg/min in 4 subjects). Salbutamol resulted in a 124±37% increase in cardiac norepinephrine spillover (P<0.05), an index that provides an indirect assessment of norepinephrine release from cardiac adrenergic nerve terminals (Table 3, Figure 3). Salbutamol, a potent vasodilator, also resulted in a 72±23% increase in coronary sinus plasma flow (P<0.05) and a 22±2% reduction in the cardiac extraction of tritium-labeled norepinephrine (P<0.05). Probably as a result of these 2 opposite effects, the change in cardiac norepinephrine clearance in response to salbutamol was not significant.

Discussion

This investigation provides the first human in vivo description of the inotropic and cardiac sympathetic effects of an intracoronary infusion of a β2-agonist. Salbutamol was infused directly into the left coronary artery to prevent the stimulation of peripheral vascular β2-receptors and the confounding effects of systemic vasodilation. Furthermore, direct inotropic responses were assessed by use of left ventricular +dP/dt, a method that provides a sensitive and relatively load-independent measure of contractility in human in vivo studies.

The intracoronary infusion of salbutamol resulted in a 44±6% increase in left ventricular +dP/dt in the group without β-blocker therapy, a 25±6% increase in +dP/dt in the group receiving atenolol, and no increase in +dP/dt in the group receiving nadolol. The much smaller +dP/dt response in patients receiving atenolol, a β1-selective antagonist, provides evidence that both β1- and β2-receptors mediated the inotropic response to salbutamol. β2-Receptors, presumably on ventricular myocytes, have previously been demonstrated to mediate a positive inotropic response.

The β1-component of the inotropic response suggests that there was an increase in norepinephrine release from cardiac sympathetic nerves, a mechanism that is supported by the observed increase in

### Table 3. Cardiac Norepinephrine Spillover Responses to Salbutamol

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control</th>
<th>Salbutamol</th>
<th>Reccontrol</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSPF, mL/min</td>
<td>68±10</td>
<td>113±17*</td>
<td>75±12</td>
</tr>
<tr>
<td>NEart, pmol/mL</td>
<td>1.3±0.6</td>
<td>1.5±0.6</td>
<td>1.3±0.5</td>
</tr>
<tr>
<td>NECs, pmol/mL</td>
<td>1.5±0.6</td>
<td>1.8±0.6</td>
<td>1.3±0.4</td>
</tr>
<tr>
<td>[%H]NEart, %</td>
<td>77±3</td>
<td>60±4*</td>
<td>73±2</td>
</tr>
<tr>
<td>CANECL, mL/min</td>
<td>51±5</td>
<td>67±11</td>
<td>52±8</td>
</tr>
<tr>
<td>CANESP, pmol/min</td>
<td>85±42</td>
<td>138±40*</td>
<td>79±38</td>
</tr>
</tbody>
</table>

CSPF indicates coronary sinus plasma flow; NEart and NECs, norepinephrine concentration in arterial and coronary sinus plasma, respectively; [%H]NEart, cardiac extraction of tritium-labeled norepinephrine; CANECL, cardiac norepinephrine clearance; and CANESP, cardiac norepinephrine spillover.

*P<0.05 vs control.
cardiac norepinephrine spillover in response to salbutamol. Salbutamol may have enhanced norepinephrine release by directly stimulating sympathoexcitatory β2-receptors within the cardiac efferent sympathetic nervous system. Such receptors have been described on intrinsic cardiac neurons and on cardiac adrenergic nerve terminals.5,7,11,12 Both of these receptor systems may have been stimulated by intracoronary salbutamol. Of note, sympathoexcitatory β-receptors have also been described in locations that are not accessible to the intracoronary infusion technique, specifically within intrathoracic sympathetic ganglia.5,30

An alternative explanation for a salbutamol-mediated inotropic response to salbutamol was infused locally to avoid peripheral β2-stimulation. Other explanations for the β1-receptor–mediated inotropic response to salbutamol should be considered. Salbutamol may have increased contractility by directly stimulating cardiac β1-receptors. The β2-selectivity of this agent has been demonstrated in vitro in human atrial myocardium.31 In human in vivo studies, ICI 118,551, a selective β2-antagonist, was shown to abolish the cardiovascular responses to oral salbutamol.32 Furthermore, the heart rate effects of intracoronary salbutamol were shown not to be blocked by the selective β1-antagonist practolol.19 In the present study, the inotropic response in the atenolol group was reduced by nearly 50%. Therefore, the magnitude of the inotropic response that was β1-receptor–mediated is unlikely to have resulted entirely from the nonspecificity of salbutamol. In addition, a β1-receptor–mediated contractile response was apparent even at low salbutamol concentrations, when its action would be expected to be highly β2-specific. A reduced inotropic response to salbutamol might have occurred if atenolol nonselectively blocked β2-receptors. This does not appear to be the case, because atenolol 50 mg/d has been shown to be highly β1-selective in human studies.14,15 Furthermore, in humans, chronic β1-receptor blockade has been shown to sensitize cardiac β2-receptors,33 although this observation has been questioned.16 If β1-receptor antagonism increases cardiac responsiveness to β2-receptor stimulation, the inotropic response to salbutamol probably would have been augmented, not reduced, in patients treated with atenolol.

The increase in cardiac norepinephrine spillover provides evidence that intracoronary salbutamol resulted in increased norepinephrine release from cardiac sympathetic nerves. Although cardiac norepinephrine spillover does not provide a direct measure of norepinephrine release, animal studies have demonstrated that cardiac norepinephrine spillover is representative of the cardiac sympathetic nerve firing rate.34 Furthermore, human studies from our laboratory have shown that stimuli that result in baroreflex-mediated increases in sympathetic activity also cause increases in cardiac norepinephrine spillover.24 However, variables other than cardiac sympathetic activity may affect cardiac norepinephrine spillover. Relevant to the present study is the relationship found in animal studies between changes in coronary blood flow and changes in cardiac norepinephrine spillover rate.35 In the present study, salbutamol resulted in a significant increase in coronary sinus blood flow, which may have accounted for the increase in spillover. However, we have shown the flow independence of cardiac norepinephrine spillover in humans in response to various interventions.17,23,24 Similarly, we recently demonstrated that after coronary angioplasty, a large increase in coronary sinus blood flow was not associated with an increase in cardiac norepinephrine spillover.36 Limitations to the experimental approach used in this study should be considered. Patients were not randomly assigned to either β-blocker or no β-blocker therapy. However, patients had similar clinical and hemodynamic characteristics. Plasma concentrations of atenolol and nadolol were not measured in this study. However, the doses of atenolol and nadolol used in this study have previously been demonstrated to provide β1-selective and nonselective β-blockade, respectively.14,15,37 The limitations of the cardiac norepinephrine spillover technique have been discussed above. The cardiac norepinephrine spillover measurement was performed only in patients not receiving β-blocker therapy. Therefore, whether the sympathoexcitatory response to salbutamol resulted from the stimulation or the nonselective β2-receptors or from the stimulation of both β1- and β2-receptors cannot be determined from this study. This is relevant, given the description of β1- and β2-receptors within the efferent sympathetic nervous system.5,7

In summary, we have provided evidence that an intracoronary β2-agonist increases contractility through stimulation of both β1- and β2-receptors in the left ventricle and also increases sympathetic outflow from the heart. This result provides human in vivo evidence for the role of sympathoexcitatory cardiac β2-receptors. Activation of these receptors may provide a partial explanation for the observation of sympathetic activation directed at the heart in conditions such as heart failure and the striking
clinical effects of β-blockers, which antagonize these receptors.38

Acknowledgments
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