Study objectives: Although inhaled $\beta_2$-agonists are in widespread use, several reports question their potential arrhythmogenic effects. The purpose of this study was to evaluate the cardiac electrophysiologic effects of a single, regular dose of an inhaled $\beta_2$-agonist in humans.

Design: Prospective study.

Setting: Tertiary referral center.

Patients: Six patients with bronchial asthma and 12 patients with mild COPD.

Interventions: All patients underwent an electrophysiologic study before and after the administration of salbutamol solution (5 mg in a single dose).

Measurements and results: Sinus cycle length, sinus node recovery time (SNRT), interval from the earliest reproducible rapid deflection of the atrial electrogram in the His bundle recording to the onset of the His deflection (AH), interval from the His deflection to the onset of ventricular depolarization (HV), Wenckebach cycle length (WCL), atrial effective refractory period (AERP), and ventricular effective refractory period (VERP) were evaluated just before and 30 min after the scheduled intervention. Salbutamol, a selective $\beta_2$-agonist, administered by nebulizer had significant electrophysiologic effects on the atrium, nodes, and ventricle. The AH length decreased from $86.1 \pm 19.5$ ms at baseline to $78.8 \pm 18.4$ ms ($p < 0.001$), and the WCL decreased from $354.4 \pm 44.2$ to $336.6 \pm 41.7$ ms ($p = 0.001$). Salbutamol significantly decreased the AERP and VERP too while leaving the HV unchanged. Additionally, inhaled salbutamol increased heart rate (from $75.5 \pm 12.8$ beats/min at baseline to $93.1 \pm 16$ beats/min, $p < 0.001$) and shortened the SNRT (from $1,073.5 \pm 178.7$ to $925.2 \pm 204.9$ ms, $p = 0.001$).

Conclusion: Inhaled salbutamol results in significant changes of cardiac electrophysiologic properties. Salbutamol enhances atrioventricular (AV) nodal conduction and decreases AV nodal, atrial, and ventricular refractoriness in addition to its positive chronotropic effects. These alterations could contribute to the generation of spontaneous arrhythmias.

(CHEST 2005; 127:2057–2063)

Key words: $\beta_2$-agonist; electrophysiologic effects; refractory period; salbutamol

Abbreviations: AERP = atrial effective refractory period; AH = interval from the earliest reproducible rapid deflection of the atrial electrogram in the His bundle recording to the onset of the His deflection; AV = atrioventricular; ERP = effective refractory period; HV = interval from the His deflection to the onset of ventricular depolarization; SCL = sinus cycle length; SNRT = sinus node recovery time; VERP = ventricular effective refractory period; WCL = Wenckebach cycle length

The autonomic nervous system and especially its sympathetic component play an important role in the development of cardiac arrhythmias.\(^1\quad 3\) The increased sympathetic activity and the consequent enhanced catecholamine release result in the activation of myocardial adrenergic receptors, which mediate its arrhythmogenic effects.\(^1\quad 4\)

Until recently it was believed that all myocardial $\beta$-receptors belonged to the $\beta_1$ subtype. Now it has become clear that the atrial and ventricular myocardium consist of both $\beta_1$- and $\beta_2$-adrenergic receptors.\(^5\quad 8\) It has been demonstrated that $\beta_2$-adrenergic receptors constitute 20 to 40% of the total number of $\beta$-receptors in the human heart and play a significant role in physiologic and pathologic conditions.\(^7\quad 8\)
Inhaled β₂-adrenoceptor agonists are the most effective known bronchodilators. Apart from their therapeutic benefits, inhaled β₂-agonists have been associated with adverse cardiac events such as cardiac arrest and acute cardiac death. Although the cause and underlying mechanism are unclear, arrhythmias could be a contributory factor.

As sufficient data do not exist concerning the cardiac electrophysiologic effects of β₂-agonists, particularly the inhaled β₂-agonists, we planned to investigate the electrophysiologic characteristics of salbutamol, one of the most effective selective β₂-agonists, administered by nebulization and thus provide a further insight into the possible arrhythmogenic effects of inhaled β₂-agonists.

**Materials and Methods**

**Patient Selection**

The ethics committee of our institution approved the study. This investigation conforms to the principles outlined in the Declaration of Helsinki. Signed informed written consent was obtained from all subjects before their participation in the study.

In the present study, 18 patients were enrolled. All patients had mild COPD with postbronchodilator FEV₁/FVC ratio ≤ 70% and FEV₁ ≥ 50% of predicted normal value, or mild persistent bronchial asthma with FEV₁ ≥ 80% of the predicted normal value and ≥ 15% reversibility 15 min after inhalation of a single dose of salbutamol. All patients were > 18 years of age, with no history of myocardial infarction, unstable angina, heart failure, or known severe arrhythmias. The patients were clinically stable during the 4 weeks preceding the intervention, with no upper or lower respiratory tract infections. Oral and inhaled corticosteroids and oral bronchodilators were discontinued for at least 1 month prior to the study. Inhaled short- and long-acting bronchodilator agents were not permitted for at least 12 h and 24 h prior to the study, respectively. Patients were asked to avoid smoking and drinks containing any form of caffeine before the study.

**Measured Variables**

**Effective Refractory Period Assessment:** A 6F quadripolar catheter (USCI; Norcross, GA) was inserted via the right femoral vein and advanced to the right atrial appendage under fluoroscopic guidance for the atrial effective refractory period (AERP) assessment. After stable placement, the AERP was assessed by the incremental method at two basic cycle lengths (500 ms and 400 ms). Eight-beat stimulation trains at twice the diastolic threshold were used, with a 2-s pause between them. A starting coupling interval of 150 ms was selected for the extra stimulus and was increased initially in 10-ms steps. When atrial capture was noted, stimulation was repeated, starting from a coupling interval 20 ms lower than that where atrial capture occurred and increased in steps of 2 ms.

In order to evaluate the ventricular effective refractory period (VERP), the same catheter (USCI) was advanced in the right ventricular apex. The VERP was assessed by the incremental method in steps of 2 ms at two basic cycle lengths (500 ms and 400 ms) as has been described above.

A 2-min interval was allowed between effective refractory period (ERP) determinations at each cycle length. The AERP and VERP were defined as the longest S₁-S₂ coupling interval that failed to result in atrial and ventricular capture, respectively. All intracardiac recordings were stored on an optical disk (EP Lab; Quinton; Washington, DC).

**Measurements of Conduction Intervals:** An electrode catheter (USCI) was advanced into the right atrium and across the tricuspid valve until it was clearly in the right ventricle. The catheter was then withdrawn across the tricuspid orifice with fluoroscopic monitoring until the His bundle potential was recorded. The interval from the earliest reproducible rapid deflection of the atrial electrogram in the His bundle recording to the onset of the His deflection (AH) and the interval from the His deflection to the onset of ventricular depolarization (HV) were measured during the electrophysiologic study (Fig 1), according to the standard method. The sinus node recovery time (SNRT) and corrected SNRT were determined after 60 s of atrial pacing at a cycle length of 500 ms, according to the standard method. A 500-ms cycle length was used to avoid interference with high sinus node activity, as caused by salbutamol administration. The Wenckebach cycle length (WCL) was determined by atrial pacing and was used as an indirect reflection of atrioventricular (AV) nodal refractoriness.
All patients underwent the aforementioned stimulation protocol at the beginning of our study. Subsequently, salbutamol solution (5 mg in a single dose) with an ECONOheb nebulizer (Medix Limited; Lutterworth, UK) was administered. The nebulizer is driven by compressed air and is reported to produce a mass median particle diameter of 3.5 μm with an average of 84% particles < 5 μm. According to our protocol, all baseline electrophysiologic measurements were repeated 30 min after salbutamol inhalation when all potential changes were expected to be maximal.11,10

ECG leads I, II, and V1, systolic and diastolic BPs, as well as the RR interval were recorded in all patients. Venous blood was obtained for measurement of baseline plasma potassium and glucose concentrations.

**Statistical Analysis**

Data are presented as mean ± SD. The statistical differences of paired data were evaluated by paired t test or one-way, repeated-measures analysis of variance followed by contrasts for mean values comparison. A p value < 0.05 was considered significant.

**Results**

**Patients**

The patient population included 11 men and 7 women between 44 years and 71 years of age (mean, 57 ± 4 years). Six patients had bronchial asthma, and the remaining 12 patients had mild COPD. Nine patients also had arterial hypertension and were receiving an angiotensin-converting enzyme inhibitor drug regimen. No patients were receiving administered β-blockers. All patients were receiving administered β-blockers. All patients were evaluated with lung function tests at the beginning of the study. All subjects had normal left ventricular function as assessed by two-dimensional echocardiography.

**Physiologic Parameters**

Serum electrolytes, glucose concentration, and arterial blood gases were measured throughout the study. In all patients, blood pH values, PaO₂, PaCO₂, K⁺, Na⁺, and glucose levels were within normal range (Table 1). There were no significant changes in these parameters after the administration of salbutamol. Furthermore, no significant changes in systolic and diastolic arterial BPs (Table 1) were detected. Heart rate increased in response to salbutamol from 75.5 ± 12.8 beats/min at baseline to 93.1 ± 16 beats/min (p < 0.001).

**Electrophysiologic Data**

Salbutamol inhalation produced significant changes in the cardiac electrophysiologic properties (Table 2; Fig 1, 2). On the part of sinus node function, salbutamol resulted in shortening of the sinus cycle length (SCL) and the SNRT. The SCL shortened from 817.7 ± 147.4 ms at baseline to 665.5 ± 131.2 ms (p < 0.001), and the SNRT decreased (Fig 2) from 1,073.5 ± 178.7 to 925.2 ± 204.9 ms (p = 0.001).

In addition, salbutamol enhanced AV nodal conduction and decreased AV nodal refractoriness. The WCL was used as an indirect reflection of AV nodal refractoriness because our ability to determine the actual AV nodal ERP was limited by atrial tissue refractoriness. In response to inhaled salbutamol, the AH interval decreased from 86.1 ± 19.5 ms at baseline to 75.8 ± 18.4 ms (p < 0.001), and the WCL decreased from 354.4 ± 44.2 to 336.6 ± 41.7 ms (p = 0.001). According to our results, salbutamol

<table>
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<th>Variables</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>57 ± 4</td>
</tr>
<tr>
<td>Male/female gender</td>
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<tr>
<td>Pulmonary disease</td>
<td>COPD 12</td>
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<td>6</td>
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<td>PaO₂, mm Hg</td>
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<td>K⁺, mEq/L</td>
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<td>Na⁺, mEq/L</td>
<td>140.2 ± 1.9</td>
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<td>Systolic BP, mm Hg</td>
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<tr>
<td>Diastolic BP, mm Hg</td>
<td>86.3 ± 5.08</td>
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*Values are expressed as mean ± SD or No.

<table>
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<th>Variables Baseline Salbutamol p Value</th>
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<tbody>
<tr>
<td>SCL, ms</td>
</tr>
<tr>
<td>SNRT500, ms</td>
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<td>CSNRT500, ms</td>
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<tr>
<td>AH, ms</td>
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<td>HV, ms</td>
</tr>
<tr>
<td>AERP500, ms</td>
</tr>
<tr>
<td>AERP400, ms</td>
</tr>
<tr>
<td>VERP500, ms</td>
</tr>
<tr>
<td>VERP400, ms</td>
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*Values are expressed as mean ± SD. SNRT500 = SNRT at a drive cycle length of 500 ms; CSNRT500 = corrected SNRT at a drive cycle length of 500 ms; AERP500 = AERP determined at 500 ms; AERP400 = AERP determined at 400 ms; VERP500 = VERP determined at 500 ms; VERP400 = VERP determined at 400 ms; NS = not significant.
had greater effects on sinus node parameters than AV node parameters. We observed a decrease of 18.6% in SCL and of 13.8% in SNRT vs a decrease in AH of 8.3% and in WCL of 5.01%.

Finally, salbutamol significantly decreased myocardial tissue refractoriness. The AERP (at a drive cycle length of 500 ms) decreased from $220.6 \pm 26.4$ to $204.2 \pm 22.6$ ms. A similar reduction was observed when the AERP was determined at a drive cycle length of 400 ms (Table 2). Although the VERP (both at 500 ms and at 400 ms) decreased too (Table 2), the effects of salbutamol on VERP were less pronounced than those on AERP. In particular, AERP decreased by approximately 7% while VERP decreased by approximately 4%. No effect on His-Purkinje conduction was found.

**DISCUSSION**

Despite the widespread use of $\beta_2$-agonists, their safety has been questioned. Several studies\(^9-15\) have reported an increased incidence of cardiac arrhythmias in patients treated with these agents, and other studies\(^13-15\) found an increased cardiovascular death with the use of oral and nebulized $\beta_2$-agonists.\(^9-15\) Although no causal relationship has been demonstrated, the possible arrhythmogenic effects of these drugs place them under considerable suspicion. Clarifying the effects of $\beta_2$-agonists on myocardial conduction and refractoriness could provide a significant insight into the potential arrhythmogenic role of these agents. This study is the first to evaluate the cardiac electrophysiologic effects of a single, regular dose of an inhaled $\beta_2$-agonist in humans. Salbutamol was selected, as it is one of the most widely used inhaled $\beta_2$-agonists and would ensure improved correlation with standard clinical practice. The main finding of this study is that the inhalation of a standard dose of the $\beta_2$-agonist salbutamol results in significant changes of cardiac electrophysiologic properties.

We found that inhalation of a single regular dose of salbutamol significantly enhanced AV nodal conduction, as reflected by shortening of the AH interval and decreased atrial and ventricular refractoriness without any remarkable effect on His-Purkinje conduction. The refractoriness of the AV node was also decreased, as indicated by shortening of the atrial pacing cycle length that resulted in AV node Wenckebach block. In addition, inhaled salbutamol produced a significant increase in heart rate and shortened the SNRT.
However, our findings cannot be interpreted on the basis of changes in heart rate. Since all refractory periods were determined at the same drive cycle length (both 500 ms and 400 ms), the observed changes in refractory periods are independent of the underlying heart rate and indicate the effects of salbutamol on myocardial conduction and refractoriness. Moreover, we found a shortening of the AH interval after the inhalation of salbutamol, which seems to be due to the effect of the drug, as the AH interval normally decreases with a sympathetic driven heart rate increase.

The above electrophysiologic effects of salbutamol are in accordance with the known cellular effects of the β-adrenergic stimulation (shortening of the action potential duration in the nodes and in atrial and ventricular muscle, increase in upstroke velocity of the action potential in the AV node, and no effect on the upstroke velocity of the action potential in the His-Purkinje system or ventricular myocardium). Therefore, our findings could be explained by a direct activation of β2-adrenergic receptors. It has indeed been increasingly recognized that β1- and β2-adrenergic receptors coexist in the human heart. β2-adrenergic receptors constitute 20 to 30% and 30 to 40% of the total number of β-adrenergic receptors in human ventricles and atria, respectively. In addition, salbutamol, a selective β2-agonist, would not be expected to stimulate β1-adrenergic receptors under the conditions applied. Furthermore, salbutamol in our study produced a greater proportional decrease in atrial tissue refractoriness compared with the ventricular tissue refractoriness. These differential effects on atrial and ventricular refractoriness could be explained by the different density of β2-adrenergic receptors in atrial and ventricular myocardium, suggesting that the effects of salbutamol were mediated by direct activation of these receptors.

The activation of prejunctional β2-adrenoceptors leading to an enhanced noradrenaline release and indirect stimulation of β1-adrenergic receptors is also unlikely. The intracoronary infusion of salbutamol caused significant changes on temporal dispersion of cardiac repolarization, and no blunting of these effects in patients receiving the β1-selective adrenergic receptor antagonist, atenolol, was noted in one study. In another study, intracoronary injection of salbutamol caused increases in heart rate that were not affected by the β1-adrenoceptor antagonist practolol but were blocked by the nonselective β-adrenoceptor antagonist propranolol. Reflex release of catecholamines secondary to β2-adrenergic receptor-mediated peripheral vasodilatation is not likely to influence our findings, as no measurable changes to systolic or to diastolic BP were observed. Moreover, in heart transplant recipients after pretreatment with the β1-adrenoceptor antagonist bisoprolol, isoprenaline is found to increase heart rate under conditions where it acts solely via β2-adrenergic receptors, an effect that cannot be due to any reflex mechanisms since the transplanted human heart is a denervated organ.

The results of our study demonstrate that salbutamol, a selective β2-agonist, administered by nebulizer has significant electrophysiologic effects on the atrium, nodes, and ventricle. The dosages administered reflected the regular recommended clinical dose, emphasizing that our findings are of particular importance since there is significant correlation with the everyday clinical practice. Larger doses of salbutamol, such as those used in asthmatic exacerbations, could have led to even more pronounced changes in myocardial conduction and refractoriness.

**Comparison With Other Studies**

Existing data on the effects of β2-agonists, especially those administered in an inhaled form, on myocardial electrophysiologic properties are rare. In a previous experimental study, inhaled metaproterenol, a β2-agonist, resulted in significant enhancement of AV node conduction and a decrease of cardiac tissue refractoriness in dogs. In a more recent human study, salbutamol produced similar effects but was administered IV. In general, our findings are in agreement with the results of the above-mentioned studies. There are, however, some significant differences. First, our study is the first to evaluate the effects of an inhaled, selective β2-agonist on AV node conduction and myocardial tissue refractoriness in humans. Secondly, the administration mode of salbutamol correlates well with everyday clinical conditions. In addition, unlike the study by Insulander et al, we found no measurable changes in systolic or diastolic BP after the administration of salbutamol, suggesting that no reflex mechanism influenced our findings. This could be explained by the fact that inhaled salbutamol has significantly fewer systemic effects than salbutamol one. Especially, in our study the proportional decrease of atrial refractory period after salbutamol inhalation was greater than the ventricular refractory period decrease, which is consistent with the different density of β2-adrenergic receptors in atrial and ventricular myocardium. Finally, salbutamol in our study produced more evident changes on the sinus node electrophysiologic properties compared with AV node. This finding is in contrast with the results of Insulander et al, but conforms with the recently published study by Rodefeld et al, which
shows that $\beta_2$-adrenoceptor density is about 2.5-fold higher in the human sinoatrial node than in the right atrial myocardium.

**Clinical Implications**

The cardiac effects of $\beta_2$-agonists include tachycardia, atrial and ventricular ectopic complexes, as well as atrial and ventricular arrhythmias.\textsuperscript{9–13} Our study allows us to speculate that the shortening of the cardiac tissue refractoriness may facilitate the induction of such arrhythmias and could explain the increased incidence of arrhythmias in certain patients receiving $\beta_2$-agonists. It is well known that the decrease in tissue refractoriness predisposes reentrant and triggered arrhythmias. This could be particularly important in certain clinical conditions, such as heart failure. The down-regulation of the $\beta_1$-receptors in chronic heart failure results in relative up-regulation of the cardiac $\beta_2$-receptors.\textsuperscript{30,31} As a consequence, $\beta_2$-agonists may produce significantly greater cardiac electrophysiologic changes in patients with compromised cardiac function, predisposing to atrial and ventricular arrhythmias. There is evidence that salbutamol increases the episodes of ventricular tachycardia in patients with heart failure\textsuperscript{32} and that $\beta_2$-receptor antagonists protect against ventricular fibrillation in animals shown to be susceptible to malignant arrhythmias.\textsuperscript{4} Furthermore, the decreases of AV node conduction time and refractoriness produced by salbutamol could result in an increase of the ventricular response during certain supraventricular arrhythmias such as atrial flutter and fibrillation.

**Study Limitations**

The design of our study does not allow us to evaluate the role of the $\beta_2$-adrenergic system in mediating the electrophysiologic effects of salbutamol. Moreover, there are no selective $\beta_2$-receptor antagonists available for use in vivo that would permit us to estimate the selectivity of the action of salbutamol. In any case, salbutamol is a selective $\beta_2$-agonist; as noted previously, our findings seem to be independent of any reflex mechanism.

The results of our study refer to the acute effects of inhaled salbutamol. Although our study assessed the short-term effects, as opposed to the long-term effects, the existing evidence of down-regulation of extrapulmonary $\beta_2$-receptors (including cardiac receptors) after prolonged administration of $\beta_2$-agonists\textsuperscript{33} suggests that the effects are likely to be more marked in patients who are not receiving these agents continuously.

**Conclusion**

We have demonstrated that inhaled salbutamol results in significant changes in cardiac electrophysiologic properties. These effects seem to be due to $\beta_2$-adrenergic stimulation and could explain the increased incidence of arrhythmias in some patients treated with these agents, especially in certain clinical conditions, such as heart failure. Care must be taken before extrapolating our findings to all human subjects, and further studies are required to clarify to what extent the electrophysiologic effects of salbutamol contribute to the generation of spontaneous arrhythmias.

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