Cardiac Arrhythmias After Inhaled Bronchodilators in Patients With COPD and Ischemic Heart Disease*

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Selective β₂-agonist aerosols may produce significant cardiovascular effects. In the present study we used Holter monitoring to compare the arrhythmogenic effects of inhaled terbutaline (TE), a β₂-agonist, with that of ipratropium bromide (IB), a nonabsorbable cholinergic drug. Fourteen patients with concomitant obstructive lung disease, ischemic heart disease, and complaints of postinhalation palpitations were studied in a random, double-blind, cross-over fashion. Both drugs significantly improved vital capacity and FEV₁. Heart rate and the frequency of premature beats were not significantly affected by the bronchodilators. We conclude that no clear connection between inhaled bronchodilators and arrhythmias could be demonstrated. (Chest 1993; 104:1070-74)

Inhaled bronchodilators have been used for many years in the treatment of asthma and chronic obstructive lung diseases (COPD). The introduction of β₂-selective sympathetic agonists has markedly reduced systemic side effects, and has been proven to be most effective for acute bronchoconstriction. However, many patients complain of palpitations after inhalation of β₂-agonists, and Holter monitoring has revealed some increase in heart rate and frequency of ventricular arrhythmias after inhalation of these drugs.1,2 These findings are of particular importance, since several recent studies have demonstrated an association between excessive use of inhaled β₂-agonists and mortality in patients with asthma.3-6 Although no causal relationship has been demonstrated, the arrhythmogenic effect of these drugs and their potential to induce hypokalemia3 place them under special suspicion. The possibility that at least some instances of death in patients with bronchial obstruction may be primarily cardiac and iatrogenic in origin cannot be excluded.8 In particular, those patients with obstructive lung disease and concomitant ischemic heart disease being treated with adrenergic drugs could be at special risk of developing new arrhythmias or of aggravating pre-existing ones.

In the present study we evaluated the chronotropic and arrhythmogenic effect of inhaled terbutaline in patients with COPD and ischemic heart disease, who complained of palpitations after inhalation. Terbutaline (TE) inhalation was compared to inhaled ipratropium bromide (IB) in a double-blind, randomized, cross-over protocol.

METHODS

Patients

Fourteen patients were selected to participate in this study. All patients were previously hospitalized for exacerbation of their pulmonary disease. At the time of recruitment, they were in stable condition and were followed regularly in the pulmonary outpatient clinic. All patients met the following predetermined criteria: (1) diagnosis of asthma or COPD according to standard criteria; (2) diagnosis of ischemic heart disease (IHD) based on previous myocardial infarction, chronic stable angina, and ECG changes compatible with IHD in the absence of other heart diseases; and (3) complaints of palpitations after inhaled bronchodilators. Additional admission criteria were reliability and good compliance and having an electrically driven nebulizer at home. None of the patients had recent myocardial infarction, decompenated heart failure, unstable angina, or known severe arrhythmias.

Treatment Regimens

Patients inhaled TE, 2 ml (5 mg) on one day, and IB, 2 ml (0.5 mg) on another study day. Inhaled drugs were given on both study days in four identical bottles, and their content was not known to the patients or the researchers. The first inhalation was given in the pulmonary function laboratory, and the patients were instructed to take the remaining three inhalations (containing the same drug) every 4 h at home. Patients were randomly assigned to receive TE or IB on the first study day, and the other drug on the second day. Inhalations were delivered in the hospital with a hand-held, pressure driven nebulizer (Europe Medical Nebulizer chamber). At home, patients used their own nebulizer (Pari Inhaler Boy, Germany, and Aerosol 70, Italy). All nebulizers were specified to deliver aerosols of 0.5 to 6 μm particle volume, and inhalation of drugs lasted for 10 to 15 min.

Patients were instructed to continue all regular medications on the study days but to avoid regular inhaled bronchodilators if this treatment was prescribed. They could use a metered dose TE inhaler whenever needed and were instructed to record the number of puffs and hour of inhalation, the exact timing of study-inhalation, and also any other unusual event.

Study Design

The study was approved by the hospital ethics committee, and informed consent was obtained from each patient. On the study morning, a 16-h Holter monitoring (Oxford Medical System) was initiated. After 1 h of monitoring, baseline spirometry (vitalograph)
was performed, and the first inhalation was administered. Spirometry was repeated after 30 and 60 min. The patient then received treatment with the remaining three inhalation solution bottles and was instructed to take the next inhalation 4 h after the first one, and every 4 h thereafter. The same procedure was repeated on the second study day, which was 2 to 5 days after the first one.

On the first study day, lung volume was measured by helium dilution (Jaeger Instruments). In addition, blood samples were drawn for arterial blood gases, BUN, potassium, sodium, and whenever applicable, theophylline blood level determinations.

Data Analysis

Respiratory and cardiac responses to the inhaled bronchodilators were evaluated in a blinded fashion. Mean heart rate and the occurrence of arrhythmias were assessed separately for each hour. Each inhalation initiated a new 4-h evaluation period. For arterial and ventricular premature beats (AFBs and VPBs), only the occurrence of more than ten premature beats per hour was considered. Holter recordings were analyzed on a Pathfinder high-speed electrocardiographic analyzer with observer interaction for the evaluation of heart rate and atrial and ventricular premature beat counts. Statistical comparison of cardiac and respiratory responses to the two bronchodilators was evaluated using paired ANOVA. Relationships between blood test values and arrhythmias were assessed using $\chi^2$ analysis. All data are given as mean ± 1SE.

RESULTS

Patients

The patients were nine men and five women, aged 48 to 82 years (69.5 ± 2.6). Four patients had bronchial asthma, the other ten were considered to have chronic bronchitis and emphysema. These ten patients all had a history of prolonged smoking (mean 24 ± 3 pack-years). The duration of respiratory symptoms was 2 to 40 years (mean 9 ± 6). All patients were hospitalized at least once for shortness of breath, and all received long-term treatment for their respiratory disease. Five patients were treated regularly with nebulized $\beta_2$-agonists and/or IB. The remaining patients used nebulized bronchodilators on exacerbations. Nine patients were treated regularly with slow release theophylline preparations, and seven patients received inhalated or oral corticosteroids. Six patients had a history and ECG documentation of previous transmural myocardial infarction. The other eight patients had chronic stable angina and ECG changes consistent with IHD and were regularly treated with nitrates and/or calcium channel blocker. Four patients had hypertension. Six patients received diuretics for congestive heart failure.

Baseline Tests

Mean arterial blood gases and other laboratory test results are given in Table 1. The PaO$_2$ (on room air) ranged from 48 to 98 mm Hg, and PaCO$_2$ from 37 to 72 mm Hg. Three patients were chronic CO$_2$ retainers (PaCO$_2$ > 45 mm Hg). Blood pH values, K$^+$ and Na$^+$ levels were within normal range in all patients. Blood urea nitrogen values above normal range (highest level 32 mg/dl) were observed in nine patients. Theophylline levels in treated patients ranged from 6.6 to 19.7 µg/ml.

Pulmonary Function Tests

A pattern consistent with airway obstruction was present in all patients, with mean FEV$_1$/vital capacity of 57 ± 5 percent. FEV$_1$ values ranged from most severe (19 percent of predicted) to the normal range, with 12 out of 14 subjects having subnormal values (<80 percent of predicted). Mean residual volume was

![Graph](image-url)

**Figure 1.** Forced vital capacity (FVC) and FEV$_1$ responses to inhaled bronchodilators. Mean ± SE p<0.01 for all comparisons between control (C) and postinhalation results.

| Table 1 — Blood Test Results (Mean ± 1SE) |
|-------------------------------|-----------------|
| PaO$_2$, mm Hg                | 71.8 ± 5.3      |
| PaCO$_2$, mm Hg               | 46.3 ± 2.7      |
| HCO$_3^-$, mEq/L              | 26.8 ± 1.1      |
| pH                            | 7.38 ± 0.01     |
| BUN, mg/dl                    | 24.1 ± 1.3      |
| K$^+$, mEq/L                  | 4.2 ± 0.1       |
| Na$^+$, mEq/L                 | 139.7 ± 0.7     |
| Theophylline, µg/ml*          | 14.0 ± 1.3      |

*$_n$ = 9.
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4.72 ± 0.32 L (204 ± 15 percent of predicted) and mean total lung capacity 6.61 ± 0.24 L (116 ± 4 percent of predicted). Responses to inhaled bronchodilators are given in Figure 1. On average, vital capacity increased after TE from 1.70 ± 0.13 to 2.04 ± 0.17 and 2.06 ± 0.19 L after 30 and 60 min, respectively, and after IB from 1.78 ± 0.19 to 1.99 ± 0.20 and 2.02 ± 0.20 L after 30 and 60 min, respectively (p < 0.01 for both). The FEV₁ after TE increased from 1.09 ± 0.11 to 1.26 ± 0.16 and 1.25 ± 0.16 L after 30 and 60 min, respectively, and following IB from 1.03 ± 0.16 to 1.19 ± 0.17 and 1.21 ± 0.16 L after 30 and 60 min, respectively (p < 0.01 for both). Significant improvement in FEV₁ (>20 percent) was observed in six and seven patients after TE and IB, respectively. Comparison of changes observed with TE to those observed with IB revealed no significant difference.

**Cardiac Rhythm**

All patients reported having taken the inhalations appropriately as scheduled, and no additional inhalations were taken on the study days. The mean heart rate for all patients on both study days is shown in Figure 2. No consistent response to either drug could be observed. The largest increase in heart rate was observed after the first inhalation of TE, with the heart rate increasing from 85 ± 7 to 96 ± 9 beats/min after 3 h, but this change did not reach statistical significance, and no similar change was observed after further inhalations. In none of the patients, including one patient with chronic atrial fibrillation, was a recurrent increase in pulse rate observed after inha-
lations. Pulse rate tended to be lower on the IB day, but this difference was not significant.

The APBs were \( >10/\text{h} \) at any time and were observed in five patients (four and three patients on the TE and IB days, respectively [two patients on both days]). On both study days, APB frequency during the control hour was equal to the hour after inhalation. Combined analysis of all postinhalation 4-h periods in the patients with APBs (Fig 3) revealed that APBs were more frequent in the first hour after TE inhalation, with gradual decline in the subsequent 3 h, but this pattern was observed in only two of the patients.

Multiple VPBs (\( >10/\text{h} \) at any time) were observed in five patients on the TE day and in four of these patients on the IB day. In one patient, VPBs frequency in the first hour after TE inhalation was consistently higher than during the fourth hour after each inhalation. In another patient, after one of the TE inhalations, 8 VPBs/min were observed for 2 h, but none at any other time. On average, however, VPBs frequency was not related to inhalation timing (Fig 3). Also, no runs of VT (\( >3 \) consecutive VPBs) were observed in any of the patients.

**Relationship Between Arrhythmias and Other Data**

Eleven patients reported palpitations, usually mild, postinhalation (nine after TE, three after IB) on the study days (one on both days). There was no relationship between APBs and VPBs and the occurrence of palpitations. Also, there was no relationship between BUN, electrolyte levels, hypoxemia (\( \text{PaO}_2 < 60 \) mm Hg) or hypercapnia, and extrasystoles. However, all four patients with serum theophylline levels at the higher range (\( >15 \) \( \mu \text{g/ml} \)) had multiple APBs (one patient) or VPBs (three patients). In comparison, none of the other patients treated with theophylline (serum levels \( <15 \) \( \mu \text{g/ml} \)) had extrasystoles (\( p < 0.05 \)).

**Follow-up**

All patients were followed for 16 to 20 months. During this period, four patients died, all of them while in the hospital. Three older patients died of exacerbation of severe COPD. All were monitored, and no important arrhythmias had been reported. One patient was resuscitated at home during a severe asthmatic attack by a rescue team, and sinus rhythm was recorded. She died few days later of hypoxic brain damage.

**Discussion**

In this randomized, double-blind, cross-over study in a group of patients with airway obstruction and IHD who complained of palpitations postinhalations, we found no consistent relationship between inhalation of bronchodilators and tachycardia or the incidence of premature beats.

The similar effect of TE and IB on pulmonary function tests is consistent with previous studies.\(^{10,11}\) Usually, peak bronchodilation is reached faster with \( \beta \)-agonists than with IB, but the final improvement in airway conductance is similar, and the effect of IB may last longer than that of TE.

As IB is not absorbable, the IB study day could be evaluated as a control for TE inhalation in respect to systemic effects. Contrary to previous studies,\(^1,2\) we did not find, with the doses used in this study, a significant increase in heart rate following TE inhalation, and the heart rate response to TE inhalation in our patients did not differ from that reported in COPD patients without IHD;\(^{12,13}\) there was neither a significant difference in the mean heart rate between the first and the fourth hour after inhalation, nor was there a difference between the TE and IB day. The heart rate seemed rather to be dependent both days on other factors related to daily activity. The patients were not instructed to maintain a particular pattern of activity before and after inhalations, and possible inhalation-induced changes in cardiac rhythm were probably minor compared to other activities affecting heart rate. Although we had to rely on the patients' compliance regarding the timing of inhalations, we selected patients considered to be conscientious, and the personal clinical relevance of the study was explained to each patient. In addition, we failed to find any association between heart rate and TE inhalations after patients treated with digoxin or diltiazem had been excluded, nor when patients treated with theophylline only or patients presenting with palpitations only were evaluated. It is known that awareness of arrhythmias among patients does not correlate with the frequency and complexity of the arrhythmia.\(^{14}\) As in our study, others have shown that symptoms are present in the absence of arrhythmias.\(^{15}\) Possible additional factors may be related to the inotropic effect of adrenergic drugs and its influence on the stroke volume.

Evaluation of the effect of drugs on the frequency of extrasystoles is difficult, due to the irregularity in their occurrence. For example, only with a \( >80 \) percent reduction in the number of VPBs is an antiarrhythmic drug considered to be efficacious, and probably only a similar rise could clearly indicate an association between inhalation of \( \beta_2 \)-agonists and arrhythmias. In the present study no such relationship, or even such a trend, could be demonstrated. Therefore, although a much larger group of patients with arrhythmias would be needed to exclude such an association, our findings suggest that if TE inhalation induces frequent VPBs, it does so rather seldomly. However, the absence of a general relationship does not diminish the relevance of an arrhythmogenic effect of \( \beta_2 \)-agonists in the individual patient. Although the
recurrent increase in the frequency of VPBs after inhalation of TE in one of our patients, as well as the occurrence of VPBs in high frequency after one of the TE inhalations in another patient may be entirely coincidental, it may also indicate such individual sensitivity to the drug. Also, tendency to arrhythmias may be increased in the presence of hypoxemia, acute respiratory failure, and electrolyte imbalance. In particular, caution should be exercised when using combined theophylline and adrenergic inhalations, since the clinical toxicity and the cardiac stimulatory effects of theophylline are dose-dependent.

Many studies have linked inhaled β-adrenergic agonists use with an increased risk of death from asthma. Rapidly progressive respiratory failure was the most common cause of death, but the possibility that some of the excess mortality was primarily cardiac and caused directly by the cardiotoxic effects of adrenergic inhalers cannot be excluded. Conradson et al concluded that combined theophylline and oral β-agonist therapy is not contraindicated in obstructive lung disease patients with concomitant ischemic heart disease, but Holter monitoring is recommended to assess the individual patient’s response to such therapy. Our findings with inhaled bronchodilators support this conclusion and further emphasize that in these patients, high-dose theophylline should be avoided, and inhaled IB may be preferable to adrenergic bronchodilators.

REFERENCES
1. Eidelman DH, Sami MH, McGregor M, Cosio MG. Combination of theophylline and salbutamol for arrhythmias in severe COPD. Chest 1987; 91:508-12