Studies concerning the ability of an inhaled β₂-agonist to produce dose-related bronchodilation are conflicting. In five asthmatic, five bronchitic, and five normal subjects, specific airway conductance (Gaw/Vl.), flow-volume curves, and single-breath nitrogen washout were recorded after noncumulative inhalation of 0.65 mg, 1.30 mg, 1.95 mg, and, in some subjects, 2.60 mg of metaproterenol sulfate. Bronchodilatation appeared to be dose-related and was best assessed by using Gaw/Vl.; in all but one subject with chronic bronchitis, there was a significant linear relationship between log dose and percent change in Gaw/Vl. Measurements of flow rate could demonstrate significant log dose-responses in eight subjects, maximum midexpiratory flow being the most sensitive measurement of flow rate, followed in order by forced expiratory volume in one second, flow at 50 percent of forced vital capacity, peak expiratory flow rate, and flow at 75 percent of forced vital capacity. No log dose-response curve could be observed by using the single-breath nitrogen-washout technique. This demonstration of significant log dose-responses to inhaled metaproterenol is consistent with the response to drugs acting upon receptors and suggests that patients may benefit from increasing doses of bronchodilators.

The purpose of our investigation was to determine if, in man, noncumulative administration of an inhaled bronchodilator with known particle size would produce dose-related responses of the airways and, if so, which of the physiologic tests currently used for the detection of bronchodilatation would best document this relationship. Metaproterenol sulfate was chosen as the bronchodilator studied for the following reasons: (1) it is nebulized as a dry powder, a form which is more stable than the liquid aerosol; (2) bronchial changes are maximal within 30 to 60 minutes and persist at the same level for an additional 60 to 90 minutes, a property which allows the recording of more than a single measurement; and (3) metaproterenol has fewer cardiovascular side effects than isoproterenol.

**Material and Methods**

Fifteen subjects were studied; five patients had asthma, five had chronic bronchitis, and five were healthy subjects. One of the subjects with chronic bronchitis produced 40 to 50 ml of purulent sputum per day and might have had bronchiectasis. Two of the subjects with bronchial asthma were in “free intervals,” defined as a period of at least three months in which no attacks were recorded. The other three asthmatic subjects were having two to three attacks of asthma per week at the time of the study. Therapy with bronchodilators was discontinued for at least 12 hours before the administration of metaproterenol. No subject was treated with steroids. Table 1 summarizes the clinical data and the baseline respiratory function of the subjects with asthma and

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†Assistant Professor of Medicine.

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CHEST, 70: 2, AUGUST, 1976 DILATATION OF AIRWAYS AFTER INHALATION OF METAPROTERENOL SULFATE 205
Table 1—Clinical Data and Respiratory Function in Subjects with Chronic Bronchitis and Asthma*  

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<td>M/51</td>
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<td>(157)</td>
<td>(WNL)</td>
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<td>(WNL)</td>
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*Numbers within parentheses indicate percent of predicted value. Predicted values for Gaw/Vt were obtained from Pellegr et al. and Thompson; for FVC, FEV₁, FEF50%, and FEF75% from Bass; for FEF25-75% from Bates et al; and for CV/VC% and N₂ slope from Buist and Ross. WNL, Within normal limits.

**CB, Chronic bronchitis; A, asthma.†Bronchiectasis.‡Frequent attacks. §"Free interval."

Chronic bronchitis.

Metaproterenol sulfate (Alupent®) was administered at the beginning of a maximal inspiration. Each subject received on successive days four whiffs of a placebo and one whiff (0.65 mg), two whiffs (1.30 mg), and three whiffs (1.95 mg) of metaproterenol sulfate. To test the reproducibility of the responses, each of the 15 subjects had a repeat trial with the best values did not necessarily belong to the same flow-volume curve.

The single-breath nitrogen-washout test was performed as described by Buist and Ross;17,18 the closing volume (CV) was expressed as a percentage of the vital capacity (CV/Vc), and the slope of the alveolar plateau was expressed as ΔN₂/L. The electrocardiogram was continuously monitored; blood pressure and an ECG were recorded every 15 minutes throughout the study.

In order to keep the variability of the functional determinations low, the following precautions were taken: (1) the tests were always performed at 3:00 P.M.; (2) the day-to-day variation of the baseline (mean) FEV₁ was within 10 percent; (3) on each recording, the values of FEV₁ retained for analysis had a range of variation of less than 7 percent; (4)
the changes in mean FEV\textsubscript{1} produced by placebo had to be less than 10% of the baseline value; and (5) the changes in FEV\textsubscript{1} produced by the same dose given at different times had to be statistically similar (Student's t-test, P > 0.05).

To confirm that a plateau in the response of the airways to metaproterenol existed, five subjects (one asthmatic, three bronchitic, and one normal subject) were given a dose of 1.30 mg of metaproterenol sulfate. For each measurement, in all subjects, the maximum changes were observed at 60 minutes and persisted up to 105 minutes.

The dose-response relationships were analyzed by the least-squares method.\textsuperscript{19} If not otherwise noted, the log dose-response curves mentioned throughout this report are statistically significant (P < 0.05). The study was approved by the Committee on Human Investigation, and informed consent was obtained from each subject.

**RESULTS**

In all subjects but one who had bronchitis (patient 5, Table 1), there was a linear relationship between the log dose and the percent change (or change in log units) of Gaw/\textsubscript{VL}.

Detailed information on each subject can be obtained upon request from the authors.

![Graph showing dose-related responses in asthmatic subject (patient 10, Table 1), (baseline values, normal Gaw/\textsubscript{VL} and FEV\textsubscript{1}/FVC ratio larger than 75 percent). Statistically significant log dose-responses are marked by plus sign. Lines representing nonsignificant log dose-responses were drawn by connecting mean responses. In spite of straight line which connects mean FEV\textsubscript{1} responses at different log doses, this is not statistically significant log dose-response curve. It exemplifies pitfalls of constructing log dose-response curves by drawing lines through mean responses without analyzing their statistical significance.](image-url)

Measurements of flow rate were less sensitive in demonstrating a log dose-response relationship. In eight subjects, log dose-response curves were obtained by using the mean value of various flow measurements. Seven were obtained by use of the FEF\textsubscript{25-75\%}, four by the FEV\textsubscript{1}, four by the FEF\textsubscript{50\%}, two by the FEF\textsubscript{max}, and one by the FEF\textsubscript{75\%} and the FVC. In the same subjects and recording the same flow measurement, log dose-response curves were also obtained by using the best values instead of the mean values. In two subjects (patients 3 and 7, Table 1), additional log dose-response curves were recorded by using the best values for FEF\textsubscript{25-75\%} and in patient 3 also by using the best values for FEF\textsubscript{max}.

No log dose-response curves could be obtained by using either CV/VC\% or \DeltaN\textsubscript{2}/L (Fig 1 to 3).

In all normal subjects, log dose-response curves were obtained by using Gaw/\textsubscript{VL} and, in one subject, by using the FEF\textsubscript{50\%} and the FEF\textsubscript{25-75\%} as well. Similarly, the asthmatic subjects with FEV\textsubscript{1}/FVC ratio greater than 75 percent and minimal, if any,
Figure 2. Dose-related responses in asthmatic subject (patient 9, Table 1) (baseline values, decreased Gaw/VL and FEV₁/FVC ratio below 75 percent). Statistically significant log dose-responses are marked by plus sign. Lines representing nonsignificant log dose-responses were drawn by connecting mean responses.

An unusual pattern of dose-related airway responses was noted in two subjects; in one normal subject (Fig 3) and in a subject with chronic bronchitis (patient 3, Table 1), 0.65 mg of metaproterenol sulfate increased Gaw/VL but decreased the measurements of flow rate. This pattern was reproducible in both subjects. At higher doses, Gaw/VL continued to increase in a log-dose fashion; however, instead of further decreasing, the flows increased either to the baseline level (in the normal subject) or above it (in patient 3 with bronchitis).

Blood pressure and heart rate did not change significantly after administration of metaproterenol. With the exception of patient 4 (Table 1), who, after inhalation of 2.60 mg of metaproterenol sulfate, had inversion of his precordial T waves, no subject showed an electrocardiographic abnormality.

**Discussion**

This study shows that statistically significant non-cumulative log dose-response curves to inhaled metaproterenol can be recorded in normal, asthmatic, and bronchitic subjects; however, not all of the physiologic parameters were equally valuable in demonstrating log dose-response curves. With the exception of one bronchitic subject (patient 5, Table 1) with possible large-airway involvement (bronchiectasis), measurement of Gaw/VL revealed log dose-response curves in all subjects, whereas measurements of flow rate (mean values) demonstrated...
log dose-response curves in only eight subjects. The CV/VC% and ΔN:L could never define statistically significant log dose-response curves.

The sensitivity of Gaw/VL for the determination of airway responses to single inhaled doses of bronchodilators is well established. The reason for this special sensitivity of Gaw/VL as compared to flow responses is not readily apparent. The following three explanations can be offered: (1) the preferential deposition of the inhaled aerosol in large airways, or (2) the avoidance of dynamic compression of airways during the determination of Gaw/VL, or (3) both.

In this study, there was no ceiling of response on the log dose-response curves obtained by using Gaw/VL. This finding is in agreement with the reports of Warrel et al and Paterson and underscores the usefulness of the determination of Gaw/VL in the evaluation of airway responses to administration of bronchodilators.

In two asthmatic patients in free intervals (patients 8 and 10, Table 1) (Fig 1), Gaw/VL was normal, and the flow rate measurements were only minimally abnormal. The fact that the dose-related Gaw/VL responses of these two subjects to metaproterenol therapy were comparable to those of normal subjects (eg, the subject of Fig 3) suggests that β-adrenergic blockade was not present. If β-adrenergic blockade had been present, one would have expected the log dose-response curve to shift to the right. Our conclusion is also supported by the findings of Sobol et al who reported that in controls and asthmatic subjects with a normal Gaw/VL, single doses of isoproterenol produced a comparable increase in the Gaw/VL.

It is interesting to note that log dose-response curves could be obtained by plotting log dose either against percent changes of the Gaw/VL or, as reported by Warrel et al and Paterson against log changes in the Gaw/VL. The use of log Gaw/VL normalizes the skewed distribution of Gaw/VL. Because we could obtain log dose-response curves by using either plot, the preference for a log Gaw/VL-log dose diagram remains to be demonstrated by a study in a larger population with a wider range of Gaw/VL.

In eight subjects, there was a linear relationship between log dose and changes in various flow measurements. Nineteen log dose-response curves could be obtained in these subjects by using FEF25-75% (seven curves), using FEV1 and FEF50% (four curves each), using FEFmax (two curves), and using FEF25% and FVC (one curve each). The latter three measurements defined dose-response curves only in those subjects in whom these curves were also detected by FEF25-75%, FEV1, or FEF50%. Previous reports have signaled the reduced sensitivity of FEFmax and FVC in detect-
ing response to single doses of bronchodilators.

As most of the log dose-response curves were obtained by using Gaw/Vt, FEV1, FEF50%, and FEF25-75%, but not by using FEF75%, it is a likely assumption that in this study the large and medium-sized airways played a much more important role in the dose-related response than did the small airways.

The incidence of log dose-flow responses was different in normal, asthmatic, and bronchitic subjects; and to some extent, these differences appeared to be related to the presence of bronchial obstruction, as defined by a low FEV1/FVC. Indeed, three of the eight subjects with a value for FEV1/FVC greater than 75 percent had only four log dose-response curves by using measurements of flow rate. In contrast, in the subjects with bronchial obstruction, the dose-related flow response was more consistent; five of the seven subjects with a value for FEV1/FVC less than 75 percent had 15 log dose-response curves by using various flow parameters. These log dose-responses did not reach a plateau, a finding in agreement with two previous reports,7,8 but in sharp contrast to others.5,6 The recording of more than one forced expiratory flow parameter can detect the progressive increase in bronchodilation which may not be visible with one particular flow parameter. Consider patient 10 in Table 1 (Fig 1); FVC and FEFmax remained unchanged, FEV1, and FEF75% leveled off after one whiff of metaproterenol sulfate, but the FEF25-75% showed a continuously increasing bronchodilation within the dose range used. For this reason, it is difficult to compare our results with those obtained by others, because, among other differences, in all previous investigations only one flow measurement was recorded. Because log dose-response curves could rarely be documented by using measurements of flow rate and also selected the one with the lowest yield in log dose-responses (FEFmax).

In the assessment of dose-related flow responses, the best values appear to give a somewhat higher yield than mean values, since 22 log dose-response curves were generated by using best flow values and 19 by mean flow values; however, since variability of measurement is not taken into consideration when best values are used, we believe that mean values should be preferred for the assessment of the dose-related responses of the forced expiratory flows to inhaled bronchodilator therapy.

Inhalation of increasingly larger doses of metaproterenol produced changes in the CV/VC% and ΔN2/L unrelated to log dose and also lacking any consistent direction of variation, i.e., progressive increase or decrease, with the dose of metaproterenol (Fig 1 to 3). This observation indicates that the CV/VC% and the ΔN2/L should not be used for the determination of dose-related airway responses to administration of bronchodilators.

Bronchodilator-induced collapse of the large airways has been previously documented by Bouhuys and van de Woestijne.28 In our study, this phenomenon was suggested by the discordant flow-conductance response (decreased flows, increased conductance) to 0.65 mg of metaproterenol sulfate occurring in two subjects (patient 3, Table 1; and the subject of Fig 3). In this context, two aspects previously unreported are of interest. First, a patient with obstructive bronchitis (patient 3, Table 1) was able to display this pattern of response, suggesting that the large airways, even in the (probable) presence of infiltrates of the bronchial walls, can collapse. Second, in both subjects the discrepant flow-conductance response disappeared when the dose of bronchodilator was increased; the exact mechanism of this phenomenon remains unknown.

In spite of our efforts to control as many variables as possible, the airway responses to an inhaled bronchodilator are still dependent on many factors which are most difficult, if not impossible, to determine, e.g., deposition of the aerosol particles along the tracheobronchial tree, inflammatory infiltrates of the bronchial walls, receptor binding of the bronchoactive substance, etc. Moreover, the reproducibility of the airway responses to bronchodilators should be determined in large populations of normal, asthmatic, and bronchitic subjects before the log dose-response curves to an inhaled bronchodilator can be accepted as a standardized pharmacologic method. Nevertheless, we believe that the present study has demonstrated the feasibility of determining log dose-responses to an inhaled bronchodilator, has defined the tests most likely to reveal dose-related responses, and has confirmed and extended the prevalent clinical impression, as well as the results of most multiple-dose reports,4,6 that increasingly larger doses of bronchodilator produce larger responses.

The clinical implication of our findings is obvious. In patients with obstructive airway disease, an increase in the dose of a bronchodilator is followed by increased bronchodilation and, thus, further relief of airway obstruction; however, this should not lead to the indiscriminate use of high doses of β-adrenergic agonists, especially when their potentially dangerous side effects cannot be promptly identified.

ACKNOWLEDGMENT: We are very grateful to William Taylor, Ph.D., for his help in statistical analysis and to Dr. Marjorie Pyle for reviewing the manuscript.
REFERENCES

3 Williams MH, Kane C: Dose response of patients with asthma to inhaled isoproterenol. Am Rev Respir Dis 111:321-324, 1975
12 Morton JW, Ostenseo LG: A comparative study of aerosol, oral, and intravenous administration of bronchodilators in asthma with the use of isoproterenol (Isuprel), Th 152 and aminophylline. J Allergy 34:16-25, 1963
13 Ciba guest symposium: Terminology, definitions and classifications of chronic pulmonary emphysema and related conditions. Thorax 14:286-299, 1959

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