

EFFECTS OF SUGGESTION ON TOTAL RESPIRATORY RESISTANCE IN MILD ASTHMATICS*

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Abstract—Thirteen mild asthmatics were given inhalations of saline (described as either a neutral substance or a bronchoconstrictor) and Isuprel (described as either a bronchodilator or a bronchoconstrictor). Measurements of Total Respiratory Resistance (R_T) were taken before and after each inhalation. Following inhalations of saline described as a bronchoconstrictor, four subjects evidenced increases in R_T of 20 per cent or more (beyond their responses to saline described as a neutral substance). Some evidence was found of attenuation of the bronchodilative effect of Isuprel when it was described as a bronchoconstrictor. These data corroborate the findings obtained in other investigations, that one subgroup of the asthmatic population responds mainly to the pharmacological effect of the inhalant, while the other subgroup responds to its suggested effect. The observed bronchial changes could not be attributed to the stimulus value of the measurement technique.

PROGRESS in the experimental study of psychological mechanisms in asthma has been hampered by a lack of sensitive, specific, objective measurements of airway resistance to assess the effects of psychological stimuli. Now that equipment to measure respiratory resistance is more generally available, meaningful studies are possible. A promising approach to the experimental study of psychological mechanisms in bronchial asthma involves the use of suggestions designed to effect changes in the subject's respiratory resistance.

Luparello *et al.* [6] described a paradigm which essentially involves a communication to the subject that he will inhale a substance designated as a bronchoconstrictor or -dilator, whereas in reality a neutral substance (usually saline) is administered. Observed changes in respiratory resistance can then be attributed to the effects of suggestion, since the inhaled substance was functionally inert. Then various combinations of bronchoactive substances and saline, coupled with verbal suggestions, allow the investigator to examine the relative effects of psychological and pharmacological factors, independently or in interaction. To date five experiments employing this paradigm have been reported in the literature.

Luparello *et al.* [5, 6] and McFadden *et al.* [7] studied the effects of suggestion on asthmatic subjects whose respiratory resistance was followed in a body plethysmograph. They found saline inhalation caused bronchoconstriction when described as an allergen or chemical bronchoconstricting agent. Placebo described as a bronchodilator aborted asthmatic attacks precipitated by inhalation of the bogus allergen. In addition, they found that the pharmacologic effect of real bronchoconstricting drugs or bronchodilating drugs could be enhanced by combining it with a corresponding suggestion. Likewise, when a "counter-suggestion" was presented, i.e., a

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suggestion contrary to the expected inhalant effect, the effect of the drug was attenuated.

An unsuccessful attempt was made by Weiss *et al.* [11] to confirm these results. However, Weiss used a less sensitive respiratory measure (Peak Expiratory Flow Rate), as well as a more severely ill, hospitalized patient sample. Recently Philipp *et al.* [9] used the suggestion paradigm and found that Intrinsic (non-allergic) and Extrinsic (allergic) asthmatics differed in response to suggestion. When subjects inhaled nebulized saline described as a constrictor, the Intrinsic responded with marked decreases in Forced Expiratory Volume in the first second (FEV₁), by comparison with their response to saline correctly described as a neutral inhalant. Extrinsic, on the other hand, responded equivalently to saline under both constrictor and neutral suggestions.

The present investigation explores the influence of suggestion on airway resistance in mild asthmatics, but differs from most previous studies: (a) we used a double blind procedure; (b) we attempted to assess the effects of the measurement techniques and experimental procedures alone; and (c) we employed a different respiratory measure, Total Respiratory Resistance (R_T) obtained by means of the forced oscillation technique. This measure has two characteristics which make it particularly suitable for research of this nature. First, it is sensitive to small changes in airway constriction or relaxation. Secondly, it does not require the tightly confining environment of a body plethysmograph, which itself seems to produce a psychological stimulus in some respiratory patients.

METHOD

Subjects. Thirteen mild asthmatics were recruited from the college population at Vanderbilt University. As a preliminary procedure, each subject was required to undergo a physical examination, be interviewed, and complete a general questionnaire. The asthmatic subjects were mild asthmatics as defined by; (a) infrequent attacks which were of short duration, (b) not being on chronic medication, and; (c) seldom requiring physician or emergency room visits. *S*'s received a \$10 remuneration for their participation in the study.

Apparatus. Respiratory resistance was determined by the method of forced oscillation* using a Lexington Instruments Respiratory Resistance Unit (RRU-C) in conjunction with a Grass Model 7 polygraph and a Hewlett-Packard 2114A digital computer. The RRU-C is designed to provide a measure of total respiratory resistance during the course of normal breathing. The *S* breathes through a tube attached to the RRU-C, while a pneumotachograph records his air flow in liters per second (L.P.S.). By the forced oscillation technique, the RRU-C imposes a 3 Hz sinusoidal oscillation at a constant pressure. This oscillation, in turn, induces a flow which is superimposed on the pneumotach record. The amplitude of the induced 3 Hz flow signal is inversely proportional to the *S*'s respiratory resistance, which can be determined by the formula:

$$\text{Resistance } (R_T) = \frac{\text{Pressure (cm H}_2\text{O)}}{\text{Flow (L.P.S.)}}$$

The RRU-C is interfaced with the laboratory computer, which provides an on-line calculation of *S*'s resistance. A more detailed description of this system has been presented by Levenson [4].

Procedure. *S*'s were scheduled for three experimental sessions on two consecutive days. Session I was conducted on the first day. Sessions II and III, separated by at least 4 hr, were conducted in the morning and afternoon of the second day. *S*'s were instructed to refrain from taking medication on days of participation.

The procedure followed in each session was similar (Fig. 1). A registered nurse handled all interactions with the *S*, administered the nebulized substance and conveyed the suggestion relative to its

*This technique is based on the original work of Dubois *et al.* [1] and subsequent refinements [E8, 3, 2]. The resulting measure of total respiratory resistance has been favorably compared to that of airway resistance obtained from the whole body plethysmograph [3].

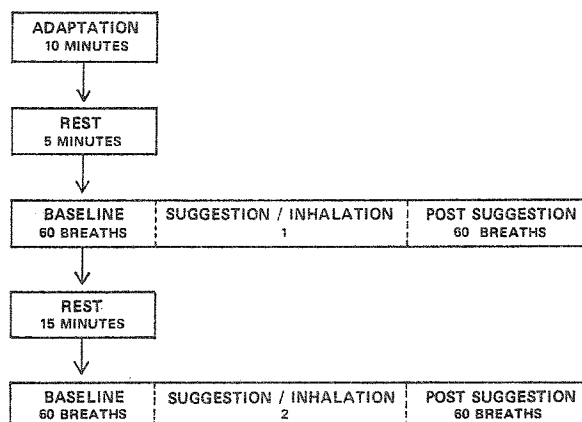


FIG. 1.—Procedure for experimental sessions.

function. All other personnel and all the recording and data processing equipment were situated in an adjacent room which had no visual contact with the patient room but was provided with an intercom system. The nurse, as well as the *S*, was blind as to the actual substance which had been mixed by another member of the team and given unlabeled to the nurse. Each session started with an adaptation period of approximately 10 min during which time the subject breathed on the apparatus. A 5-min rest period followed, after which *S* resumed breathing on the apparatus, with respiratory resistance being determined for the next 60 breaths. Each session consisted of two aerosol inhalations. The procedure for both inhalations was the same, and a 15 min rest period separated the two.

The two nebulized solutions consisted of 0.8 cc saline, and 0.15 cc of 1:200 Isuprel suspended in 0.65 cc saline. The taste of the two solutions was indistinguishable. The Isuprel dose was low enough so as to avoid an increase in pulse rate which might be detected by the patient. The order of inhalations is diagrammed below:

Session	Inhalation 1		Inhalation 2	
	Drug	Suggestion	Drug	Suggestion
I	Saline	“Neutral”	Isuprel	“Dilator”
II	Saline	“Constrictor”	Saline	“Constrictor”
III	Isuprel	“Constrictor”	Isuprel	“Constrictor”

In session I, *S*'s were first administered saline, correctly identified as a neutral substance (“this is a test substance which has no effect and is used only to calibrate our equipment”). This was followed by inhalation of the Isuprel solution, accurately presented as a bronchodilator (“this is a substance frequently used to help people open up their airways and breathe more easily”). For both sessions on the second day, *S*'s received the suggestion that each inhalant would produce constriction in the airways and breathing difficulties (“this substance is known to produce marked airway constriction in individuals with your predisposition”). In both sessions II and III, *S* was actually administered either saline or Isuprel; the order of saline and Isuprel sessions was balanced across *S*'s. While the foregoing suggestions were probably not very powerful and were given only once preceding each inhalation, their effect was undoubtedly heightened by the presence of a uniformed nurse and various items of medical equipment (nebulizer, syringes, RRU, etc.) as well as previous screening by a specialist in pulmonary medicine (JDS) and signing a consent form. On the other hand, *S*'s knew that the experiment was not being conducted in a hospital.

RESULTS

Respiratory resistance data for all 13 subjects were subjected to a $2 \times 3 \times 2$ repeated measures analysis of variance (ANOVA) in which the factors were drug (Isuprel or saline), session (I, II, III), and period (pre-suggestion or post-suggestion). The finding of primary interest from this overall

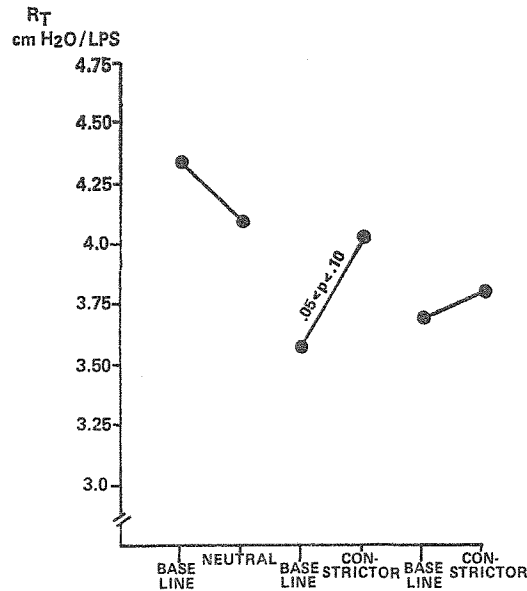
analysis was a significant interaction between these three factors ($F = 4.91$, $df = 2/24$, $p = 0.016$). Means, standard deviations, and t -tests for this interaction are presented in Table 1.

TABLE 1.—MEANS, STANDARD DEVIATIONS, AND t -TESTS FOR DRUG-SUGGESTION PAIRINGS

Session	Drug-suggestion	Pre-suggestion		Post-suggestion		t	df	p
		Mean	SD	Mean	SD			
I	Saline-"neutral"	4.30	2.30	4.13	2.08	0.70	24	N.S.
I	Isuprel-"dilator"	3.60	1.03	3.04	0.92	2.28	24	<0.025
II	Saline-"constrictor"	3.60	0.84	3.98	1.10	1.52	24	<0.10
II	Saline-"constrictor"	3.74	1.08	3.78	1.29	0.16	24	N.S.
III	Isuprel-"constrictor"	4.72	1.70	3.44	1.09	5.18	24	<0.01
III	Isuprel-"constrictor"	3.35	1.25	3.14	0.82	0.84	24	N.S.

N.S.: Not significant.

Figure 2 depicts the group reactions to saline under the "neutral" and first and second "constrictor" suggestions. It may be seen that the group as a whole tended to show a reduction in R_T under the

FIG. 2.—Group reaction to saline. $N = 13$.

neutral suggestion while evincing increased resistance under the "constrictor" suggestions. Individual comparisons by t -test revealed that the increase in resistance under the first "constrictor" suggestion was the only change which approached statistical significance ($p < 0.10$).

In a similar manner, Fig. 3 portrays the group reaction to Isuprel under the "dilator" and "constrictor" suggestions. Statistically significant reductions in R_T occurred under both the "dilator" suggestion ($p < 0.025$) and the first "constrictor" suggestion ($p < 0.01$). The unusually high baseline preceding the first "constrictor" suggestion is attributable to several subjects who reported for that session in a highly constricted state.*

*The baseline elevations of airway resistance on many study occasions (in absence of symptoms) confirm what has been known for many years, that asthmatics may have problems with airway resistance increases only detectable by sensitive equipment like the RRU or the plethysmograph.

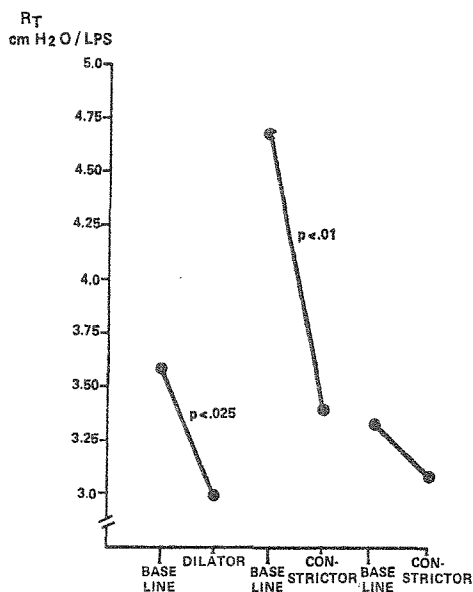


FIG. 3.—Group reaction to Isuprel. $N = 13$.

While providing useful information, the group data presented so far do not speak to a striking aspect of this kind of research; namely, the tendency for some subjects to consistently react to the pharmacological effect of the inhalant and for others to react more prominently to the suggested effect. To determine whether this tendency was exhibited by subjects in the present study, two procedures were utilized. First, the data for each subject were plotted and examined individually; second, an index of each subject's responsiveness to the suggestions was computed.

In Fig. 4, the reactions of two subjects are plotted individually. The "reactor" appeared to be responding in keeping with the suggestion that he was inhaling a constrictive agent. The "non-reactor" showed little change. While this presentation of individual data provides a graphic picture,

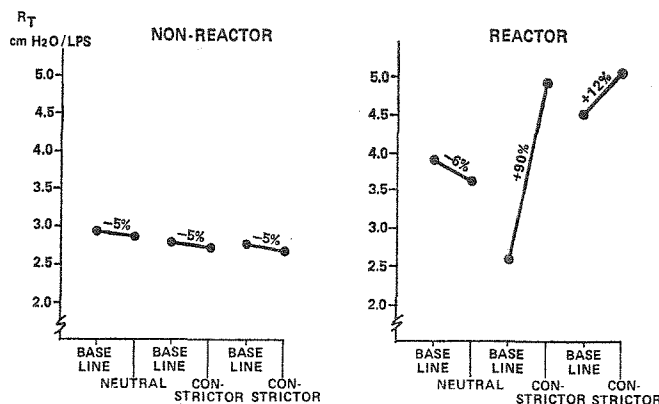


FIG. 4.—Reaction of two subjects to saline under the "neutral" and "constrictor" suggestions.

it does not adequately summarize the degree of reactivity shown by each subject. Therefore, in order to obtain an index of each person's reactivity to the suggestions accompanying saline inhalations, a simple computational procedure was applied to the data of each S . This index was derived by averag-

ing the per cent change in R_T which followed the two inhalations of the drug described as a "constrictor", subtracting from it the per cent change in R_T occurring when the drug was described accurately. The index determined in this manner represents the subject's response to the drug described as a constrictor *beyond* his response to the drug described accurately. The results of this analysis are presented in Fig. 5.

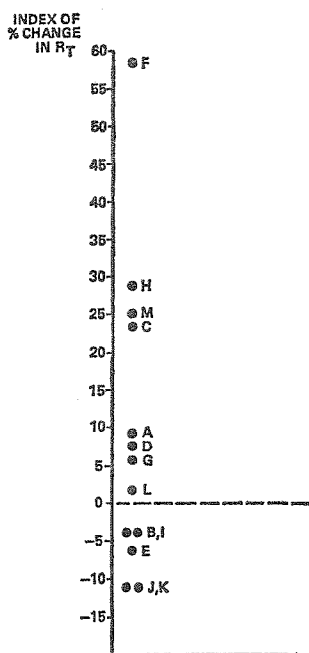


FIG. 5.—Reaction to saline under "constrictor" suggestions. ("Index of the per cent change in R_T " is explained in text.)

It will be seen that in response to saline four subjects showed increases in respiratory resistance of 20 per cent or more; four showed increases of less than 10 per cent and the remaining five subjects evidenced decreases in resistance. These data support the earlier observations concerning the existence of the reactor and nonreactor group.

Identical calculations were made for each S's reactions to the Isuprel conditions (Fig. 6). It will be noted that only one subject (L) showed a marked increase in constriction; seven subjects showed increases in the 1–15 per cent range; and five subjects showed decreases in resistance. While the pharmacological (dilator) effect of Isuprel greatly complicates interpretation of these findings, it is probably safe to say that for some subjects the bronchodilative effect of Isuprel was *attenuated* by the suggestion that the inhaled substance was a constrictor.*

DISCUSSION

On the whole, the results of this study support the findings of Luparello [5–7] and Philipp [9], that a segment of the asthmatic population will exhibit changes in bronchial constriction in keeping with the suggested function of an inhaled substance. In contrast to the earlier investigations which dealt with severely ill patients, the present

*Further support for this finding is found in the data of four subjects whose R_T levels actually increased following inhalation of Isuprel. Two of these subjects showed increases in R_T beyond 25 per cent from their pre-suggestion level.

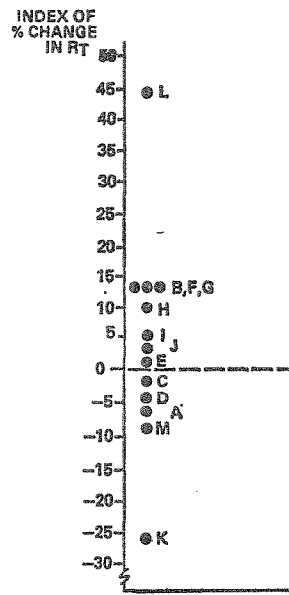


FIG. 6.—Reaction to Isuprel under “constrictor” suggestions. (“Index of the per cent change in R_T ” is explained in text.)

study demonstrates that this finding is applicable to a group of mild asthmatics as well. By presenting the inhalations and suggestions in a double blind situation, a possible confound of earlier findings has been ruled out.

In addition, the present study introduced the response measure of total respiratory resistance (R_T). The use of this technique addresses a second problem inherent in research of this nature, the confounding of the stimulus manipulation (suggestion) with other aspects of the experimental milieu. Specifically, an important factor in this research is the stimulus value of the respiratory measure itself. This point is exemplified by use of the Whole Body Plethysmograph which, owing to its sensitivity to small subclinical variations in bronchial tone, has been widely advocated. However, a potential drawback to this measure was pointed out by Stein [10], who warned that some asthmatics might develop symptoms solely by being encased in the plethysmographic apparatus. Along these lines, Weiss *et al.* [11] have speculated that Luparello's results might have been due to the stimulus value of the Body Box itself and not to the suggestions.

A dilemma facing the researcher has been the trade-off between the sensitivity of various respiratory measures and the degree of their obtrusiveness. Thus, the relatively benign measures such as vital capacity, forced expiratory volume in the first second (FEV_1), and the timed ratio between inspiration and expiration have all been criticized for being effort-dependent and less sensitive to small airway changes than the plethysmographic technique. In light of these criticisms, the forced oscillation technique appears to be a reasonable compromise between the sensitivity of the Body Box and the unobtrusiveness of the other measures mentioned. This assertion was supported by the finding that subjects evidenced only nonsignificant changes in R_T when inhaling

saline solution which was accurately described to them as a neutral substance. Consequently, greater credence can be placed in the results which showed that some subjects manifested marked changes in R_T when they were (falsely) informed that the inhaled substance was a bronchoconstrictor. Thus, there is much greater likelihood that they were responding to the suggestion rather than to aspects of the measurement and inhalation techniques.

Of some interest is the finding that few *S*'s in the present study responded to the constriction suggestion under both saline and Isuprel inhalations and the fact that none experienced asthmatic symptoms of the magnitude reported by others [6, 7]. While these results might be interpreted as indicating that the suggestion phenomenon is less pervasive than previously noted, the discrepancy may be due to marked sampling and procedural differences. For example, our *S*'s were mild asthmatics who were not under chronic medication and who experienced only occasional attacks. In addition, the wording of the actual suggestion used in the present study was "weaker" than that employed by Luparello [6, 7], who informed *S*'s that they were to inhale "progressively increasing concentrations" of a substance related to their individual asthma attacks. *S*'s in the present study were merely told that they were to inhale a substance known to produce constriction in asthmatic patients like themselves. Thus, the degree of airway reactivity in studies of this kind may be partially a function of the strength of the suggestion as well as the severity of the asthma, such that more potent suggestions with more severe asthmatics elicit greater constriction.

A great deal of additional work obviously remains to be done within this paradigm. Two extremely important questions which need to be more clearly elucidated are, (1) aspects of the experimental environment which serve to augment or counteract the suggestion and, (2) individual differences between subjects who form the reactor and nonreactor groups.

To exemplify the first problem, it may make a difference whether the research is conducted in a hospital setting and whether the suggestion is administered by persons of high or low professional status. In addition, the precise manner of phrasing the actual suggestion could prove to be critical.

With respect to the problem of individual differences, much remains to be learned about the characteristics of individuals who react or fail to react to suggestions of the kind employed in this research. For example, we presented some evidence (see Figs. 5 and 6) that "saline reactors" were not necessarily "Isuprel reactors"; in other words, a person responding positively to a suggestion at one time and under one set of conditions does not necessarily respond under different circumstances and at another time. This is in contrast to the categorical association which Philipp *et al.* made between intrinsic asthma and response to suggestion.

Is the clinical status of asthmatic patients related to their responsiveness to suggestions? Is suggestibility an enduring trait? Is it relevant in a therapeutic program? Further exploration of these issues may bear on the basic problems relating to the role of psychological factors in bronchial asthma, and perhaps to a better understanding of psychological mechanisms in other psychosomatic disturbances.

SUMMARY

The effect of suggestion in combination with pharmacological agents on respiratory resistance was investigated in a homogeneous sample of 13 mild asthmatics. The

dependent measure was total respiratory resistance (R_T), calculated on-line by means of a three stage system involving a Lexington Instruments Respiratory Resistance Unit (RRU-C), a Grass Model 7 polygraph, and a Hewlett-Packard 2114A digital computer.

The experiment consisted of three experimental sessions for each *S*: An afternoon session on Day 1; a morning session on Day 2; and an afternoon session on Day 2. The procedure for each session consisted of two inhalations of a nebulized substance (either saline or Isuprel) with measurements of R_T taken for 60 breaths before and immediately following each of the inhalations. Prior to each inhalation, *S* was either provided accurate information concerning the effect of the drug, or informed that the inhaled substance would produce marked constriction. On Day 1, *S*'s were administered the saline inhalant followed by the Isuprel inhalant. These substances were correctly identified as inert and bronchodilative agents, respectively. On Day 2, *S*'s were given both Isuprel and saline inhalations, this time incorrectly identified as bronchoconstrictors. The order of Isuprel and saline sessions on Day 2 was balanced across sessions and all drugs and suggestions were administered double blind by a registered nurse.

The following results were obtained:

(1) Saline described as a neutral substance had no demonstrable effect on respiratory resistance, while the first suggestion that saline was a constrictor resulted in increased respiratory resistance. The second suggestion produced nonsignificant changes.

(2) Isuprel produced significant decreases in R_T when described as a bronchodilator and (for the first inhalation) when described as a bronchoconstrictor. There appeared to be a slight, although confounded, attenuation of the dilating effect on the second Isuprel-"constrictor" suggestion.

(3) Analysis of the individual data by an index of percentage change revealed two groups with respect to the suggestion effects, a "reactor" and a "non-reactor" group. However, these groups were not the same for both the Isuprel-"constrictor" and the saline-"constrictor" conditions.

The results of this study support the general finding that suggestion of imminent bronchial constriction produces increases in respiratory resistance in some asthmatics. In addition, the results demonstrate that the RRU-C provides a sensitive, efficient, and non-disruptive technique for determining mechanical changes in the airways.

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