Rhinology, 26, 51-58, 1988

Nasal airway response to infused phenylephrine in normals and in patients with allergic and non-allergic rhinitis

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SUMMARY

To find whether patients with chronic rhinitis might be congested because of hyporesponsiveness to adrenergic vasoconstrictive influences, we measured nasal airway resistance (NAR) in normals and allergic and non-allergic rhinitics during intravenous infusion of graded doses of phenylephrine. All responded with decreases in NAR and first evidences of NAR fall appeared no later in those with rhinitis than in normals. Nasal congestion and response were asymmetrical; absolute NAR in the low resistance side was similar in all groups and there was little response to phenylephrine. In the high resistance side, NAR reached its minimum by the time the total infused dose was 1400 mcg, indicating maximum response to drug was achieved within the dose range studied. Minimum NAR achieved on the high resistance side was higher in rhinitics suggesting residual vascular engorgement resistant to phenylephrine or non-vascular mucosal swelling. Resistance to adrenergic vasoconstriction does not appear to be the primary contributor to mucosal swelling in chronic rhinitis.

INTRODUCTION

Patients with chronic nasal symptoms can be categorized on the basis of clinical presentation, presence or absence of eosinophils, and identifiable causes such as drugs or allergens (Mullarkey, 1981; Slavin, 1982). This allows more precise prognostication but has not clarified the mechanisms responsible, especially in rhinitis of non-allergic origin. Patients with this problem are suspected of having a reflex-mediated process (Anggärd, 1979; Connell, 1983; Whicker et al., 1973), but have not been systematically evaluated as have asthmatics and other atopes (Kaliner et al., 1982).

We hypothesized that patients with non-allergic, chronic nasal congestion might be hyporesponsive to endogenous vasoconstrictive influences which, in normals, maintain nasal patency. To study this we looked for evidence of hyporeactivity to alpha-adrenergic stimulation in a group of such patients. This was assessed by measuring nasal airway resistance (NAR) during intravenous infusion of increasing amounts of the alpha-adrenergic agonist phenylephrine. For comparison we studied patients with allergic rhinitis and a group with no apparent nasal disease.

STUDY DESIGN

The study population consisted of 15 volunteers with allergic rhinitis, 15 with non-allergic rhinitis, and 14 normals. Admission criteria stipulated that the normals had neither history suggesting recurrent nasal disease nor evidence of non-manifest atopy (elevated lgE, eosinophilia). Those with allergic rhinitis had positive skin tests which correlated with history, while the non-allergics had to have perennial nasal symptoms, present evidence of obstruction, and no positive skin tests to common inhalant allergens. Among those with allergic rhinitis, the principal offending allergen was ragweed in 13, grass in one, and housedust or cat dander in one. All had flares of symptoms in seasons and situations of exposure, but 10 of the 15 also had at least some symptoms perennially. None were experiencing symptom exacerbations at the time of participation. Those whose diagnosis was non-allergic rhinitis seemed to have a valid history of perennial nasal symptoms and were skin test negative. Twelve had nasal eosinophilia.

The study consisted of a single clinic visit. The volunteer came to the laboratory and waited for about 30 minutes to acclimate to the indoor environment. An infusion was started in a peripheral vein and blood pressure and cardiac telemetry equipment placed. To establish a stable baseline, NAR (nasal airway resistance) was measured five to ten times, at three minute intervals, with the non-medicated solution infusing.

For measurement of nasal resistance we used a posterior rhinomanometry system designed and constructed locally (Young et al., 1984). In brief, the system uses a Fleisch pneumotachygraph, a Statham pressure transducer and a Gould bridge amplifier to generate a voltage proportional to the nasal air flow. A second transducer and amplifier do the same for pharyngeal pressure. These two analog signals feed into a 12 bit analog-to-digital converter on an NEC Macsym microcomputer. The computer calculates NAR in expiration at a preselected reference flow (in this study, 0.125 l/sec). It selects and records the median value from a series of breaths (we typically record at least three) and, all measurements having been made unilaterally, calculates the combined resistance. Airflow is directed through a nozzle which conforms to the naris while we block the contralateral side with a slack, water-filled finger cot. Our aim is to distort the nose minimally.

The sequence of phenylephrine dosing was 25, 50, 75, 100, 150, and 200 mcg/min. The nurse managing the infusion added drug-containing solution to the already-infusing carrier without notifying other study personnel but at some time after all had agreed that the volunteer was stable and it was appropriate to begin. We dosed the volunteer for three minutes at each level, during which we measured NAR twice and pulse and blood pressure once.

Since the subjects usually had asymmetry of nasal resistance and response, we analyzed NAR results deriving from the higher and lower resistance sides separately. Designation of higher and lower resistance sides was made after the fact by

considering the pre-drug-infusion measurements from each individual. To control for inter-individual variation, we converted the data to ratios before analysis. The reference value for each subject was the mean of the two lowest NAR values. This was assigned a value of 1.0 and all other NAR values were expressed as multiples of the reference. We compared these data across the three treatment groups at each of the dosing intervals.

We also evaluated sensitivity to infused phenylephrine as reflected in the total cumulative dose which had been infused when the measured NAR first showed a sustained fall of 15% or greater from the levels measured pre-infusion. We compared this value, designated Falldose, across the three diagnostic groups.

NAR measurements are inherently highly variable. This resulted in a few extreme values in our data. Non-parametric statistics are most appropriate for such data. We used medians as measures of central tendency and a rank sum test (Wilcoxon's) to test for group differences.

RESULTS

Figure 1 shows the ratios of NAR to least NAR for the lower resistance side of the nose. These median values fell modestly as a result of phenylephrine infusion and were similar across the three diagnostic groups. The median least values, shown in Table 1, were likewise similar confirming the comparability of the low resistance side in the three groups and the unilaterality of the process. Phenylephrine-induced "least values" from the higher resistance side are in the same table. There was a significant difference across the three groups ($p = 0.034$, Wilcoxon); median values were lower for the normals than for rhinitics. The table contains absolute values in contrast to the ratios shown in Figures 1 and 2.

Figure 2 shows the NAR ratios for the higher resistance side of the nose. If the rhinitis patients were more resistant to the effects of the alpha adrenergic agonist than normals the beginning of their drug-induced NAR fall should be delayed

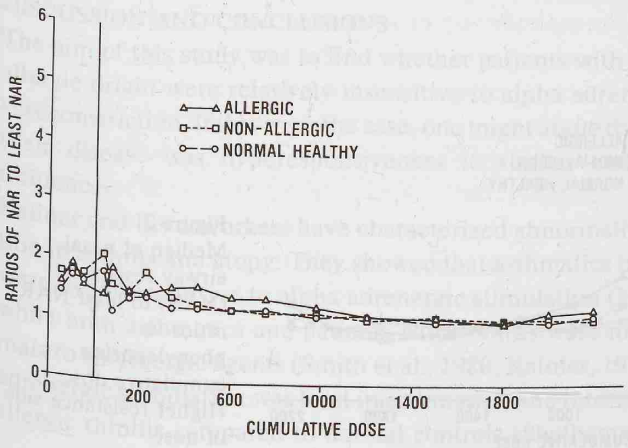

Figure 1. Median of nasal airway resistance (NAR) to least NAR ratios vs. phenylephrine cumulative dose. Lower resistance side of nose.

Table 1. Individual least nasal airway resistances resulting from phenylephrine infusion. High and low resistance sides of nose tabulated separately.

	HIGHER RESISTANCE SIDE			LOWER RESISTANCE SIDE		
	Allergic	Non-Allergic	Normal	Allergic	Non-Allergic	Normal
INDIVIDUAL LEAST NAR VALUES, $cmH_2O/L/SEC$	7.02	15.03	1.98	0.76	1.38	1.43
	15.96	1.92	0.93	1.94	1.32	0.57
	2.68	1.82	0.75	1.23	0.53	0.54
	2.41	1.70	1.59	0.44	0.77	1.30
	15.80	1.66	1.34	1.18	1.22	1.03
	2.28	1.88	1.10	2.30	2.31	1.43
	1.08	2.25	0.68	0.50	2.32	0.98
	4.65	1.04	1.44	1.60	1.32	0.98
	3.50	0.94	1.52	0.65	0.82	0.72
	0.78	8.79	1.48	0.72	0.96	1.37
	1.44	1.59	2.42	0.97	0.76	1.74
	0.83	2.38	1.89	0.91	1.12	1.71
	1.93	1.43	2.53	2.90	2.04	0.90
	2.57	6.21	0.99	1.26	0.96	0.85
	4.36	0.21		3.66	0.19	
MEDIAN (95% Confidence Limits)	3.04 (1.73, 8.37)	1.89 (1.41, 5.22)	1.46 (1.10, 1.82)	1.24 (0.84, 1.95)	1.14 (0.82, 1.58)	1.14 (0.85, 1.36)
	Groups differ significantly P = .034, Wilcoxon			Groups not significantly different		

and their curve shifted to the right. Such a pattern was not evident. Both allergic and non-allergic rhinitis subjects started with NAR ratios suggestively (though not significantly) higher than those of the normal group. The rhinitics showed evidence of decongestive drug effect as soon as the phenylephrine infusion began. The fall in NAR ratio in these patients rebounded transiently at the second measurement after beginning drug, then fell again. Generally the ratios followed parallel courses and values did not differ except in the 750 to 1000 mcg

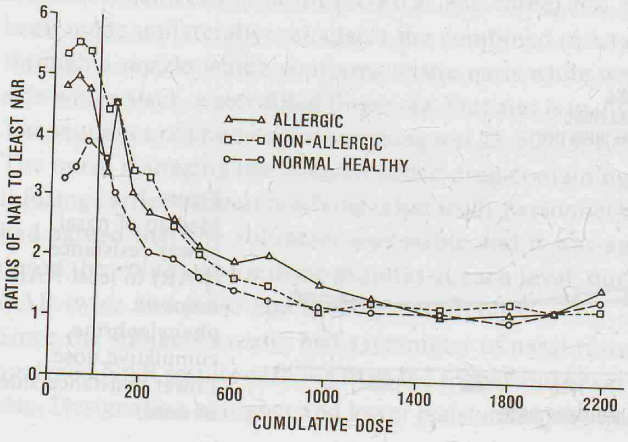

Figure 2. Median of nasal airway resistance (NAR) to least NAR ratios vs. phenylephrine cumulative dose. Higher resistance side of nose.

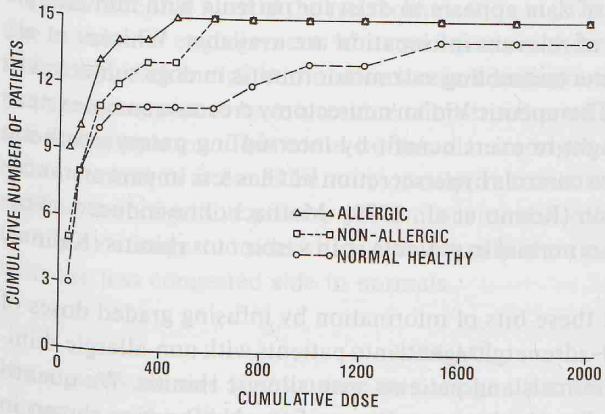

Figure 3. Falldose. Cumulative number of patients showing first 15% fall from pre-infusion NAR vs. cumulative dose infused.

cumulative dose range. At that point the normals and those with non-allergic rhinitis showed similar ratios while the allergic rhinitics were significantly higher. The median ratios for all diagnostic groups had achieved their greatest fall in NAR by the time 1400 mcg of drug had been infused. This indicated that maximum drug response was achieved within the range of doses studied.

To try to quantitate a threshold of responsiveness to phenylephrine, we identified the dose at which measured NAR first showed a sustained fall of 15% or greater from the pre-drug baseline. This we called "Falldose". Results for the high resistance side are in Figure 3. Some normals had atypically high Falldoses, but overall the groups did not differ. Median values were 37.5 for allergics and 75 for normals and non-allergics. Since resistance to alpha adrenergic effect should have resulted in a higher Falldose, results do not confirm that non-allergic rhinitis is a state of vascular hyporesponsiveness to alpha adrenergic influences.

DISCUSSION AND CONCLUSIONS

The aim of this study was to find whether patients with chronic rhinitis of non-allergic origin were relatively insensitive to alpha adrenergic-induced mucosal vasoconstriction. If this were the case, one might argue that a basic mechanism of their disease was hyporesponsiveness to similar endogenous decongestant influences.

Kaliner and his coworkers have characterized abnormalities of autonomic function in asthma and atopy. They showed that asthmatics but not allergic rhinitics were hyperresponsive to alpha adrenergic stimulation (Henderson et al., 1979), while both asthmatics and patients with rhinitis were more sensitive than normals to cholinergic agents (Smith et al., 1980; Kaliner, 1976). Sensitivity to beta-adrenergic stimulation was least in asthmatics, and intermediate in patients with allergic rhinitis compared to normal controls (Shelhamer et al., 1983).

No such systematic body of data appears to exist for patients with non-allergic rhinitis. A few fragments of relevant information are available. Whicker et al., (1973) produced a syndrome resembling vasomotor rhinitis in dogs subjected to cervical sympathectomy. Therapeutic Vidian neurectomy creates a complex neurologic deficit but is thought to exert benefit by interrupting parasympathetic innervation. The procedure controls hypersecretion but has less impact on mucosal swelling and congestion (Konno et al., 1979). Methacholine-induced sweating, increased in atopics, is normal in patients with vasomotor rhinitis (Kaliner, 1976).

We aimed to supplement these bits of information by infusing graded doses of phenylephrine, an alpha-1-adrenergic agent, into patients with non-allergic rhinitis and, for comparison, normals and patients with allergic rhinitis. We quantitated resistance to the test agent by comparison of the NAR ratios shown in Figures 1 and 2 and by calculation of the Falldose, that amount of drug which had been infused when the subject's NAR values decreased from prestudy levels by 15% or more. Neither of these analyses suggested resistance to alpha adrenergic influence among the subjects with non-allergic rhinitis. Indeed the Falldose was suggestively, though not significantly, greater for the normals than for either of the groups of diseased subjects.

The vasculature of the human nasal mucosa is complex and includes arteriolar resistance vessels, a capillary exchange network, a-v shunts, and venous sinuses (Mygind, 1979; Cauna et al., 1979; Cauna, 1970). Innervation of this arrangement is likewise complex but certainly includes adrenergic, cholinergic and peptidergic elements (Cauna, 1970; Ishibe et al., 1983; Anggärd et al., 1983; Kurian et al., 1983). Mucosal vascular engorgement may be multifactorial both as regards site and control. Phenylephrine infusion may have had variable effects on different sites or functions. The least values for the three groups were dissimilar, but in all cases seemed to reflect maximum attainable drug effect. This suggests that the higher least NAR values in the rhinitis patients were due to non-phenylephrine-responsive vascular engorgement or to non-vascular tissue swelling.

Difference in response between the higher and lower resistance sides of the nose (Figures 1 and 2) was striking. Phenylephrine exerted modest decongestive effect on the low resistance side in all of the groups and the mean least NAR measurements for all three were similar (Table 1). This is doubtless an expression of the nasal cycle wherein alternate sides of the nose congest and decongest over periods of several hours (Principato et al., 1970; Hasegawa et al., 1977). In our patients, rhinitis-associated congestion was unilateral. In the decongested phase, airway resistance and behaviour were similar in diseased and healthy control subjects. The normals, many of whom did not notice a symptomatic nasal cycle, showed considerable asymmetry in obstruction and had a substantial amount of phenylephrine-sensitive mucosal swelling.

We conclude that most of the nasal obstruction in patients with chronic rhinitis is due to vascular engorgement. Mucosal vessels in these patients are no less sensitive to alpha adrenergic stimulation than are analogous vessels in normals. Rhinitis patients appear to have a residue of obstruction which is not sensitive to infused phenylephrine. This could be vascular in origin and under other forms of reflex control or it could be non-vascular mucosal swelling. In the volunteers studied the congestive process was almost entirely unilateral. Subjects with rhinitis had a decongested side which was virtually identical in reactivity and caliber with the less congested side in normals.

RÉSUMÉ

Nous avons mesuré la résistance au passage d'air nasal (NAR) chez des sujets normaux et chez des patients souffrant de rhinite allergique et non allergique, pendant la perfusion intraveineuse de phényléphrine. Le but de cette étude était de déterminer si la congestion nasale observée chez les patients avec rhinite chronique pouvait être due à une diminution de la réponse vasoconstrictrice adrénergique. Chez tous les sujets, la phényléphrine diminua la NAR, et cette diminution ne fut pas retardée chez les sujets souffrant de rhinite par comparaison aux témoins sains. La congestion nasale et la réponse adrénergique étaient asymmétriques; dans les cas de faible résistance, les valeurs absolues de NAR étaient semblables dans tous les groupes, alors qu'il y avait peu de réponse à la phényléphrine. Par contre, dans les cas de forte résistance, les valeurs minimales de NAR furent atteintes après perfusion de la dose totale de 1400 mcg, ce qui indique que les doses choisies provoquèrent une réponse maximale. Les valeurs minimales de NAR observeés dans les cas de forte résistance étaient plus élevées chez les rhinitiques, ce qui suggère que l'engorgement vasculaire résiduel est resistant à la phényléphrine ou au gonflement muqueux non vasculaire. La résistance à la vasoconstriction adrénergique ne semble pas jouer un rôle primordial dans la congestion muqueuse de la rhinite chronique.

ACKNOWLEDGEMENTS

Marta Kraus, R.N., Cheryl Titus, R.N., and Cristy Hanover, R.N. also assisted in the study. Marie Warren prepared the manuscript.

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