

Avoidance therapy in reactive dye-induced occupational asthma: long-term follow-up

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Background: Previous studies reported that early diagnosis and avoidance therapy are the most important factors for prevention of permanent lung impairment; however, few studies have evaluated the long-term prognosis of reactive dye-induced occupational asthma (RD-OA).

Objective: To evaluate the long-term outcomes of RD-OA.

Methods: Methacholine airway hyperresponsiveness (AHR) and lung functions were evaluated and compared in 26 patients with RD-OA at the time of diagnosis and after complete avoidance of the causative agents. Patients with continued ($n = 13$) or remitted ($n = 6$) AHR were further monitored for up to a mean $\pm$ SD of 8.7 ± 1.8 years.

Results: The AHR resolved in 10 (38%) of 26 patients a mean $\pm$ SD of 2.2 ± 1.3 years after complete avoidance of RDs; however, prebronchodilator forced expiratory volume in 1 second (FEV₁) values were not different. Levels of IgE specific to the RD-human serum albumin complex were markedly decreased at first follow-up in 5 RD-atopic patients from whom paired serum samples were compared ($P = .02$). The AHR disappeared in an additional 5 patients and improved in 4 by the second follow-up. The FEV₁ values also improved compared with diagnosis and first follow-up levels. Favorable prognosis was associated with early diagnosis of RD-OA and complete avoidance of the causative agent. No association was found with smoking history, latent periods, the presence of RD specific IgE, baseline provocation concentration that caused a decrease in FEV₁ of 20%, or FEV₁.

Conclusions: Early diagnosis and avoidance therapy are the most important prognostic factors in RD-OA. The AHR and lung function of patients with RD-OA can sometimes be recovered steadily and slowly through avoidance measures.

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INTRODUCTION

Reactive dyes (RDs) have molecular weights that range from 500 to 1,000 Da and contain chromogen and reactive functional groups designed to form irreversible covalent bonds to cellulosic fiber amino acid residues.^{1,2} Frequently, RDs elicit occupational asthma (OA) in exposed workers, and they are the second most common identified cause of OA in Korea.^{3–6} Through a hapten process, RDs induce specific IgE, which has been detected in most patients with RD-OA.^{5–9} Therefore, it is possible that an IgE-mediated mechanism is involved in the development of RD-OA. Mechanisms of OA are heterogeneous, and the natural history may differ depending on the sensitizing agent.^{10,11} The natural course of OA has been reported for high-molecular-weight IgE-sensitizing agents¹² and low-molecular-weight non-IgE-mediated agents, including diisocyanate,^{11,13–17} colophony fume,¹⁸ and western red cedar.^{19,20} These studies reported early diagnosis and avoidance therapy as the most important factors for the prevention of permanent lung impairment. However, few studies are available on the long-term prognosis of RD-OA.²¹

The pattern of recovery measured by the provocation concentration that caused a decrease in forced expiratory volume in 1 second (FEV₁) of 20% (PC₂₀) and spirometric lung function after complete avoidance is controversial. Malo et al^{22,23} reported that airway hyperresponsiveness (AHR) and spirometric lung function in patients with OA rapidly recover in the initial 1 to 2 years after avoidance and then plateau. Other researchers^{14,16,24} have reported contrary results; therefore, further studies are required for consensus. In this study, we followed up patients with RD-OA who had complete avoidance of causative agents after diagnosis to evaluate the long-term outcomes of RD-OA.

METHODS

Participants

Between August 1, 1988, and September 30, 2000, 42 workers were diagnosed as having RD-OA at the Severance Hospital Allergy & Asthma Clinic, Seoul, Korea. Of those, 26 resigned from their jobs after diagnosis and were enrolled in this study. All 26 workers were employed in RD-producing factories and had asthmatic symptoms on RD exposure. The presence of IgE specific to RDs was determined by means of skin prick testing with 10 mg/mL of RD or by means of enzyme-linked immunosorbent assay (ELISA) performed using RD-human serum albumin complex.^{6,8} Diagnosis was established by methacholine challenge testing and bronchial provocation testing with causative RDs. All the patients had a mean $\pm$ SD follow-up of 2.2 ± 1.3 years (first follow-up);

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19 patients (13 with continued AHR and 6 with remitted AHR) were further monitored for up to a mean $\pm$ SD of 8.7 ± 1.8 years (second follow-up).

Spirometry, Methacholine Challenge Testing, and Bronchial Provocation Testing With RDs

The FEV₁ levels were measured using spirometry (Sensor-medics, Yorba Linda, CA); spirometric flow-volume curves were determined using international criteria.²⁵ Patients used nose clips and were coached through the standard forced expiratory maneuver. The best of 3 reproducible attempts from a possible maximum of 8 trials was chosen for final data analysis.

A slight modification of the method reported by Chai et al²⁶ was used for methacholine bronchial provocation testing. Aerosol was generated using a nebulizer (DeVilbiss 646; DeVilbiss Health Care Inc, Somerset, England) connected to a compressed air tank. Patients received 5 inhalations up to vital capacity at 5-minute intervals with isotonic sodium chloride solution and incrementally doubled methacholine doses (0.075–25 mg/mL) until PC₂₀ was observed. The reference range of methacholine PC₂₀ values at the Severance Hospital Allergy & Asthma Clinic was greater than 8 mg/mL.

Causative RDs used for bronchial provocation testing were black GR (18 patients), brilliant orange 3R (4 patients), red BBN (3 patients), and yellow 3R (1 patient); RDs were dissolved in 0.4% phenol saline and were delivered by means of a nebulizer (DeVilbiss 646) connected to a compressed air source. Patients inhaled aerosol to vital capacity for 5 attempts. Serial increases in RD concentration (0.01, 0.1, 1.0, and 2.5 mg/mL) were administered at 10-minute intervals until PC₂₀ was observed. The FEV₁ levels were then measured for 8 hours after inhalation. Early and dual responses were found in 16 and 10 patients, respectively. All airway medications, such as cromolyn, theophylline, inhalant corticosteroids, and sympathomimetics, were withheld for 72 hours before provocation studies.

Statistical Analysis

Statistical analysis was performed using a software program (SPSS 9.0; SPSS Inc, Chicago, IL). The Wilcoxon signed rank test was used to evaluate changes in methacholine PC₂₀, specific IgE to RD, and FEV₁ after avoidance. Association between final PC₂₀ values and previous values were evaluated by means of Pearson correlation analysis. The Mann-Whitney *U* test, the χ^2 test, and logistic regression analysis were used to evaluate prognostic factors. Results are given as mean $\pm$ SD.

RESULTS

Changes in Methacholine AHR With Avoidance Therapy

Twenty-six patients with RD-OA were studied 2.2 ± 1.3 years after diagnosis. Twenty-five patients underwent methacholine challenge; 1 patient was excluded because of severe asthmatic symptoms. Methacholine AHR disappeared (PC₂₀ >8 mg/mL) in 10 (38%) of 26 patients, and in 2 patients,

PC₂₀ values were increased 3-fold. The log₂(PC₂₀) values were significantly increased at the first follow-up compared with at diagnosis (0.063 ± 0.251 vs 1.362 ± 0.345 mg/mL; $P = .009$) (Fig 1). Nineteen patients were followed up for up to 8.7 ± 1.8 years after diagnosis; 3 of these patients were excluded from further methacholine challenge testing because of symptoms. Of the remaining 16 patients who underwent additional methacholine challenge testing, 6 had no AHR (PC₂₀ >8 mg/mL) and 10 had AHR at the first follow-up. Compared with the first follow-up, log₂(PC₂₀) was significantly increased at the second follow-up (1.283 ± 0.463 vs 2.369 ± 0.335 mg/mL; $P = .001$). In the 10 patients with previous AHR, the AHR disappeared in 5, improved in 4, and remained the same in 1. All 6 patients with RD-OA and previous resolution of AHR remained in remission. Compared with values at initial evaluation, log₂(PC₂₀) was markedly improved at the second follow-up (0.019 ± 0.367 vs 2.369 ± 0.335 mg/mL; $P < .001$). The log₂-transformed final PC₂₀ values were not related to initial PC₂₀ values; however, a strong relation was found with the first follow-up values (Fig 2).

Changes in Spirometric Lung Functions and Specific IgE Levels With Avoidance Therapy

Spirometric FEV₁ values at diagnosis and the first follow-up were analyzed in 12 patients with RD-OA. Prebronchodilator FEV₁ levels at the first follow-up were not statistically different from those at baseline ($n = 12$; $82.5\% \pm 3.6\%$ vs $86.7\% \pm 4.9\%$; $P = .13$) but were improved at the second follow-up compared with baseline ($n = 9$; $83.6\% \pm 2.1\%$ vs $94.9\% \pm 5.3\%$; $P = .04$) and the first follow-up ($n = 16$;

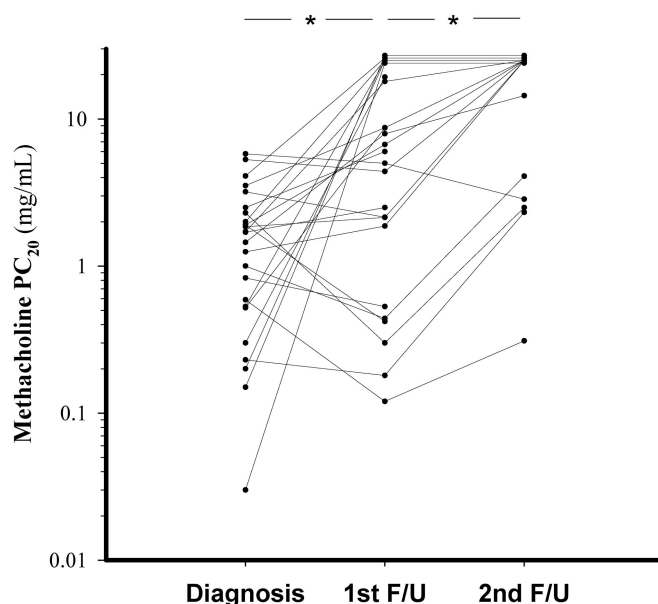


Figure 1. Changes in the methacholine provocation concentration that caused a decrease in forced expiratory volume in 1 second of 20% (PC₂₀) at the first ($n = 25$) and second ($n = 13$) follow-ups. * $P < .01$.

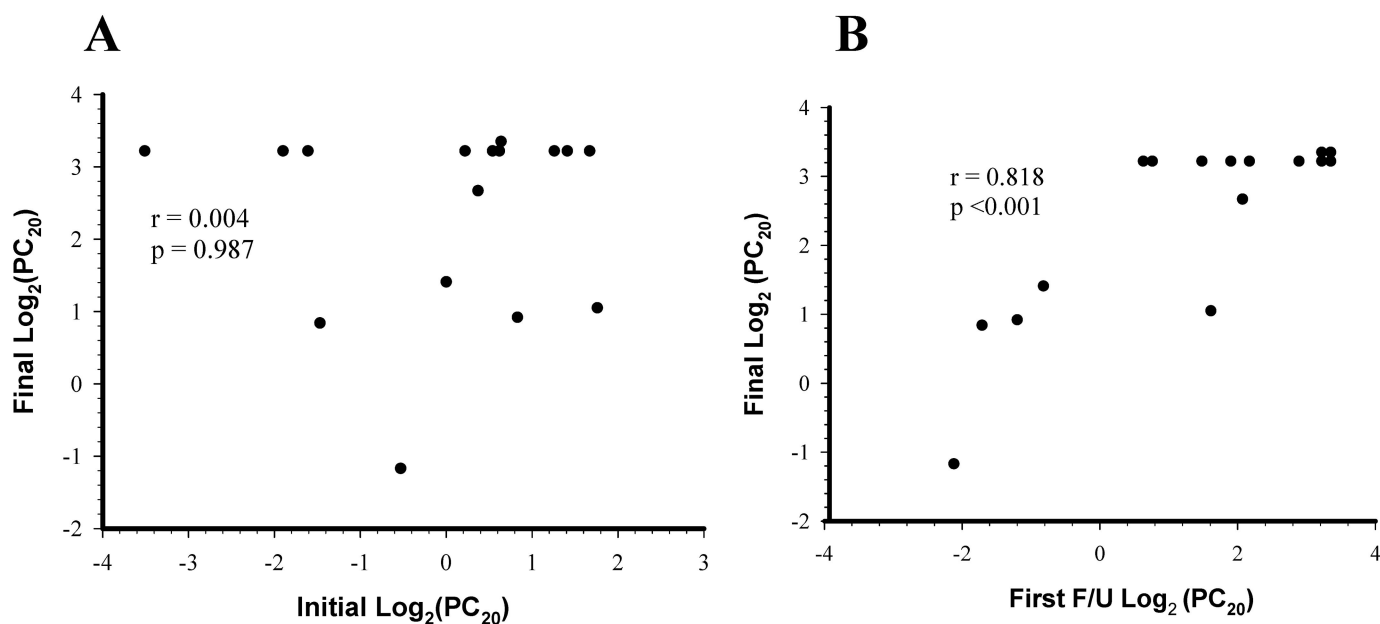


Figure 2. Relation of final provocation concentration that caused a decrease in forced expiratory volume in 1 second of 20% (PC₂₀) with initial PC₂₀ values (A) and first follow-up (F/U) (B).

89.1% $\pm$ 2.7% vs 94.8% $\pm$ 3.3%; $P = .03$) (Fig 3). Paired serum samples from 5 RD-atopic patients at diagnosis and follow-up were compared. The interval between sampling was 23.2 $\pm$ 8.8 months. The ELISA optic densities of spe-

cific IgE to the black-GR-human serum albumin complex, one of the most common causative RDs, was markedly attenuated in all 5 patients (0.175 $\pm$ 0.071 vs 0.037 $\pm$ 0.016; $P = .02$).

Factors Determining RD-OA Prognosis

Overall, 15 (58%) of 26 patients with RD-OA experienced resolution of methacholine AHR (PC₂₀ >8 mg/mL) after long-term avoidance of the causative RDs. At first follow-up, resolution occurred in 39% of patients but without significant change in the FEV₁ values. Resolution had improved by the second follow-up; however, the other 42% of patients retained nonspecific AHR or permanent lung function impairments.

Compared with the nonremission group, the interval from the development of RD-OA symptoms to the time of diagnosis (12.7 $\pm$ 9.5 vs 30.8 $\pm$ 21.5 months; $P = .001$) and the age of patients (40.5 $\pm$ 2.2 vs 46.6 $\pm$ 1.3 years; $P = .02$) were significantly lower in the remission group. No differences were observed in previous smoking history, latent period, total IgE level, tendency of atopy to common inhaled allergens, or the presence of specific IgE to RDs (Table 1). Logistic regression analysis was used to determine whether the time from the development of RD-OA symptoms to the time of diagnosis and age were independent factors; only the interval from the development of RD-OA symptoms to diagnosis was found to be a prognostic factor ($P = .04$) (Table 2).

DISCUSSION

The results of this study indicate that the RD-OA recovery process is slow but steady, with AHR resolution improving

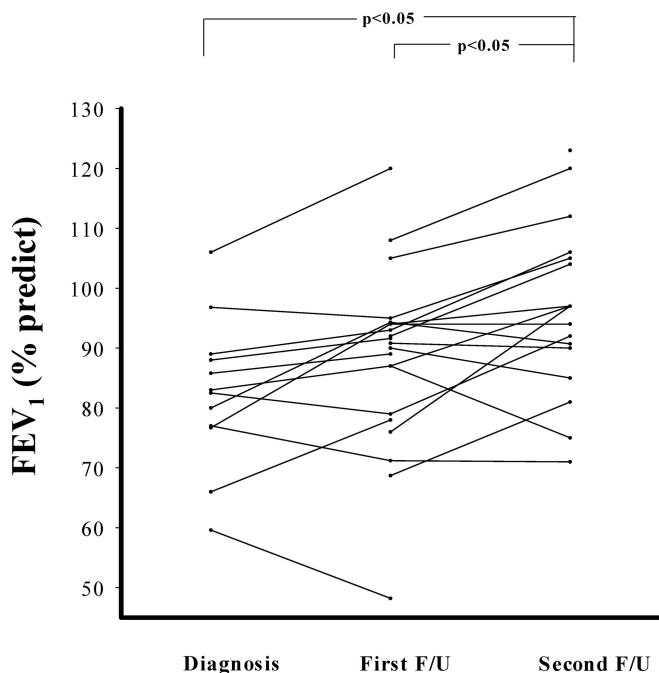


Figure 3. Changes in forced expiratory volume in 1 second (FEV₁) at the first (n = 12) and second (n = 16) follow-ups (F/Us).

Table 1. Factors Affecting AHR Status After Long-term Avoidance Therapy

	AHR remission	
	Yes (n = 15)	No (n = 11)
Age, mean $\pm$ SD, y	40.5 $\pm$ 2.2*	46.6 $\pm$ 1.3
Sex ratio, M:F	10:5	5:6
Atopy to common inhalant allergens, No. (%)	7 (47)	6 (55)
FEV ₁ , mean $\pm$ SD, % predicted	83.3 $\pm$ 2.0 (n = 10)	77.1 $\pm$ 7.5 (n = 6)
Total IgE, geometric mean, IU/L	279.9	309.8
IgE specific to RDs (SPT or ELISA), No. (%)	12 (80)	9 (82)
Smoking, No. (%)	10/13 (77)	3/6 (50)
Initial log ₂ (PC ₂₀), mean $\pm$ SD	-0.139 $\pm$ 0.369	0.262 $\pm$ 0.286
Pattern of RD challenge test, early/dual response, No.	11/4	5/6
Latent period, mean $\pm$ SD, mo	57.4 $\pm$ 19.1	38.9 $\pm$ 6.9
Interval from development of symptoms to diagnosis, mean $\pm$ SD, mo	12.7 $\pm$ 2.5†	30.8 $\pm$ 6.5

Abbreviations: AHR, airway hyperresponsiveness; ELISA, enzyme-linked immunosorbent assay; FEV₁, forced expiratory volume in 1 second; PC₂₀, provocation concentration that caused a decrease in FEV₁ of 20%; RD, reactive dye; SPT, skin prick test.

* $P < .05$.

† $P < .01$.

Table 2. Logistic Regression Analysis of Prognostic Factors for AHR Remission

	β (SE)	OR (95% CI)	P value
Age	0.139 (0.107)	1.149 (0.931–1.417)	.20
Interval from development of symptoms to diagnosis	0.130 (0.063)	1.139 (1.007–1.289)	.04

Abbreviations: AHR, airway hyperresponsiveness; CI, confidence interval; OR, odds ratio.

between the first and second follow-ups. The patterns of AHR and lung function recovery in this study differed from previous studies of snow crab processing-induced OA.²² The FEV₁ levels of these patients improved only during the first year after avoidance, with no further improvement observed; AHR was no better after 31.4 $\pm$ 6.3 months. However, other investigators^{14,16,24} found continued recovery of AHR at 2 years and beyond. Furthermore, Malo et al,²² who studied snow crab processing-induced asthma, later reported that methacholine AHR rapidly improved in the first 2½ years and continued at a slower rate thereafter.²³ The present results are consistent with the later findings. We also found that initial PC₂₀ values were not associated with final PC₂₀ values; however, PC₂₀ values at 2 years were related to final PC₂₀ values. This finding may reflect rapid AHR recovery within 2 years and then slow, steady recovery thereafter. Yet other investigators have reported different results. Padoan et al¹⁶ monitored 87 patients with toluene diisocyanate (TDI)-induced asthma for up to 10 years after avoidance; they reported that initial PC₂₀ and spirometric values can predict later values. Findings have been conflicting regarding whether initial AHR is a prognostic factor.^{12,16,17,19,20,24,27,28} In the present study, no significant difference between baseline PC₂₀ values in the remission and nonremission groups was found. The discrepancies among different studies might suggest that the pattern of OA recovery differs according to the caus-

ative agent. Because even baseline AHR and lung function impairments varied compared with other studies, the pattern of recovery is also likely to be different.

In this study, prebronchodilator FEV₁ levels steadily improved after long-term avoidance of the causative agents. Malo et al²² reported a plateau of spirometric improvement after 1 year of avoidance; however, mean FEV₁ reached 100% of predicted. Therefore, their study population may not be adequate for evaluation of the FEV₁ recovery pattern. Limitations of this study include limited initial FEV₁ data (n = 12). Also, prebronchodilator FEV₁ levels were used, which are more variable than postbronchodilator levels and may have reflected disease activity rather than permanent lung function impairment.

In this study, early diagnosis and avoidance were found to be the most important factors for the prevention of permanent impairment. These factors have previously been reported in other OA studies.^{12,17–19,29,30} The present results are indirectly supported by the work of Lee et al.²¹ In their study, none of 12 patients with RD-OA showed remission after 42 months; the authors suggested that RD-OA had a poorer prognosis than TDI-OA. However, the mean duration of symptomatic exposure to RDs was 62 months, which is significantly longer than that in the present study (remission group: 12.7 $\pm$ 9.5 months; nonremission group: 30.8 $\pm$ 21.5 months).

The patterns of the RD bronchial challenge test were not found to be a significant predictor of prognosis in RD-OA; this finding is similar to results found for diisocyanate-induced OA.¹⁶ Other researchers^{11,17} suggested that the presence of specific IgE to low-molecular-weight agents, such as TDI, may be indicative of a good prognosis. In this study, no difference was seen in the presence of specific IgE to RDs between the AHR remission and nonremission groups. The significance of IgE-mediated immune response in RD-OA is more pronounced than in diisocyanate-induced OA, where specific IgE was detected infrequently.^{11,17,31} In RD-OA, 60% to 83% of patients have specific IgE.^{5,6} Because IgE epitopes of the RD carrier protein are markedly heterogeneous,⁸ the possibility of obtaining a false-negative result on either a skin prick test or ELISA needs to be considered; therefore, the presence of specific IgE may not be a differentiating factor in the prognosis of RD-OA. However, because the levels of specific IgE were attenuated by avoidance therapy, it may be a useful variable for monitoring the disease activity of RD-OA.

In conclusion, patients with RD-OA can recover steadily and slowly with complete avoidance. However, some patients have permanent lung impairment even after long-term avoidance. Early diagnosis associated with early avoidance therapy is the most important factor that determines the prognosis of RD-OA.

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