

©原 著

Action mechanisms of complex spa therapy on steroid-dependent asthma

Yoshiro Tanizaki, Hikaru Kitani, Morihiko Okazaki, Takashi Mifune, Fumihiro Mitsunobu, Akimasa Takatori¹⁾, Hiroyuki Okuda¹⁾, Koji Ochi²⁾, Hideo Harada²⁾ and Ikuro Kimura³⁾

Division of Medicine, ¹⁾Gunecology, Misasa Medical Branch,
²⁾Department of Clinical Laboratory, ³⁾Second Department of
Medicine, Okayama University Medical School

Abstract : Effects of complex spa therapy, which comprises swimming training in a hot spring pool, inhalation of iodine salt solution and fango therapy, were analyzed in patients with steroid-dependent intractable asthma (SDIA) by comparison between the subjects with and without efficacy of the therapy. 1. The complex spa therapy was effective in the patients with lower levels of FEV_{1.0%} and %PEFR. 2. The complex spa therapy was not always effective in the patients with a low value of % \dot{V}_{25} , which represents depressed airflow in the small airways. 3. The efficacy of the complex spa therapy was found in the patients showing a low value of % \dot{V}_{25} accompanied by BAL neutrophilia, but not found in those without increased proportion (more than 10%) of neutrophils in BAL fluid. The results reveal that the complex spa therapy is effective in patients with SDIA showing low values of FEV_{1.0%} and %PEFR, and in those with a low value of % \dot{V}_{25} and BAL neutrophilia.

Key words : complex spa therapy, ventilatory function, BAL neutrophilia, bronchial asthma

Introduction

Bronchial asthma is usually controllable with antiasthmatic drugs except corticosteroid hormone. There are, however, some adult patients whose attacks cannot be controlled without corticosteroid therapy. In these patients, long-term corticosteroid therapy is required for the treatment of their attacks.

Our previous studies have shown that spa

therapy, particularly swimming training in a hot spring pool, is effective in patients with steroid-dependent intractable asthma (SDIA)¹⁻³⁾, and that the swimming training in a hot spring pool improves ventilatory function of patients with bronchial asthma⁴⁾.

Later inhalation therapy with iodine salt solution has been demonstrated to be effective on patients with bronchial asthma⁵⁾, particularly on those with type Ib. bron-

choconstriction + hypersecretion type and with type II. bronchiolar obstruction type⁶⁻⁹). More recently, we developed another spa therapy, fango therapy for the treatment of bronchial asthma¹⁰.

In the present study, the effects of complex spa therapy, which consists of swimming training in a hot spring pool, inhalation therapy with iodine salt solution and fango therapy, were evaluated in patients with bronchial asthma to analyze the action mechanism of the complex spa therapy.

Subjects and Methods

To analyze the direct action of the complex spa therapy on the airways of patients with bronchial asthma, 12 adult asthmatics were selected in this study. All of them had the complex spa therapy for one to three months during their admission at Misasa Branch Hospital. Of these, 6 were effective (group A) and 6 were non-effective cases (group B) with the complex spa therapy. The mean age of the effective cases (3 females and 3 males) was 56.3 years (range, 46-71 years), and that of the non-effective cases (4 females and 2 males) was 43.3 years (range, 23-71 years). All of the study subjects were non-smokers, and had been on corticosteroid therapy for over two years (steroid-dependent intractable asthma; SDIA).

The complex spa therapy, which comprises swimming training in a hot spring pool¹⁻³, inhalation with iodine salt solution⁵ and fango therapy¹⁰, was carried out for all subjects.

Bronchoalveolar lavage (BAL) was performed in all subjects by the method previously described when they were attack free⁷⁻⁹. Informed consent for the examination of BAL was obtained from all subjects. The

aspirates by a bronchoscope were filtered through sterile steel mesh, and the filtrates were centrifuged at 1200 rpm for 10 min at 4°C. Smear preparations were made using the cell suspension. The slides were air dried and stained with May Giemsa. The BAL cells were differentiated by observing 500 cells excluding epithelial cells. The results were expressed as a percentage of the total cells.

Ventilatory function test was performed in all subjects by a Box Spiro 81 (Chest Co) when they were asymptomatic.

Immediate skin reaction to allergens, house dust (HD), *Candida* (Ca), ragweed, silk, *Aspergillus* (As), *Alternaria* (Al), was examined with 0.02 ml of commercial allergen extract (Torii Pharmaceutical Co). The diameters of flare and wheal at 20 min were measured in millimeters after the test. The diameter of flare larger than 20 mm or wheal larger than 9 mm was regarded as positive.

Serum Level of IgE was measured by radioimmunosorbent test (RIST), and specific IgE antibody was estimated by radioallergosorbent test (RAST).

The level of serum cortisol was determined between 7 and 8 o'clock in the morning by radioimmunoassay (RIA).

Results

Characteristics of the study subjects

Table 1 shows the characteristics of the study subjects. The serum IgE level of the subjects was considerably low with a mean of 188 IU/ml (range, 36-888 IU/ml). Immediate skin reaction was positive to HD in 3 (25%) and to Ca in 5 (41.7%) out of the twelve subjects. Specific IgE to inhalant allergens was found in only one case (8.3%).

The level of serum cortisol was low in all subjects with a mean of 2.2 mcg/dl (range, 0–5.6 mcg/dl) (Table 1).

Table 1. Characteristics of the patients with complex spa therapy during hospitalization

Case no	Age, years	Sex	Effect*	Serum IgE (IU/ml)	Skin test	RAST score	Serum cortisol**
1	71	M	+	108	Ca	-	1.3
2	46	M	+	238	Ca,As	-	0
3	56	F	+	105	-	-	2.0
4	53	F	+	36	Ca	-	5.6
5	65	M	+	106	As	-	2.2
6	47	F	+	888	Ca,HD	-	3.8
7	37	M	-	201	-	-	0
8	46	F	-	114	As,Al	-	2.5
9	23	F	-	87	HD	HD2+	1.7
10	58	M	-	113	-	-	3.5
11	71	F	-	149	HD	-	2.9
12	25	F	-	114	Ca,	-	1.4

*Effect of complex spa therapy; **mcg/dl. Ca, Candida albicans; As, Aspergillus; Al, Alternaria; HD,house dust

Ventilatory function and efficacy of the therapy

The value of FEV_{1.0%} under 60% was found in 3 of the six effective subjects (group A) and in 2 of the six non-effective subjects (group B). The value of %PEFR under 70% was observed in 5 cases of group A and in 2 of group B. The values of %MMF, % \dot{V}_{50} and % \dot{V}_{25} were generally lower in group A than in group B, and the value of % \dot{V}_{25} under 10% was found in 4 cases of group A and in 3 of group B (Table 2).

Table 2. Ventilatory function of the patients with bronchial asthma before complex spa therapy

Case no	Effect*	%FVC	FEV _{1.0%}	%PEFR	%MMF	% \dot{V}_{50}	% \dot{V}_{25}
1	+	35.5	35.5	41.2	19.7	9.1	7.8
2	+	60.4	41.8	30.1	10.5	7.8	7.6
3	+	120.5	51.1	63.4	25.2	19.7	12.0
4	+	74.0	61.2	47.2	21.4	15.0	8.9
5	+	44.7	45.4	51.4	7.6	13.1	6.7
6	+	129.2	80.4	134.0	77.1	59.8	51.5
7	-	70.5	80.4	80.2	42.8	35.9	28.9
8	-	114.2	84.4	117.2	76.3	55.0	44.0
9	-	71.5	69.0	71.0	22.1	14.4	7.1
10	-	79.9	56.1	59.0	17.5	14.2	8.4
11	-	65.6	57.3	52.5	15.7	11.1	7.5
12	-	88.5	70.6	61.8	37.4	32.2	20.3

* Effect of complex spa therapy.

The mean values of FEV_{1.0%} and %PEFR were significantly lower in group A with efficacy of the therapy compared with the values in group B without efficacy (FEV_{1.0%}, p<0.05; %PEFR, p<0.02). The difference was, however, not significant in the values of %MMF, % \dot{V}_{50} and % \dot{V}_{25} between the groups A and B (Fig. 1). The results reveal that the complex spa therapy is effective for the patients with SDIA showing low values of FEV_{1.0%} and %PEFR.

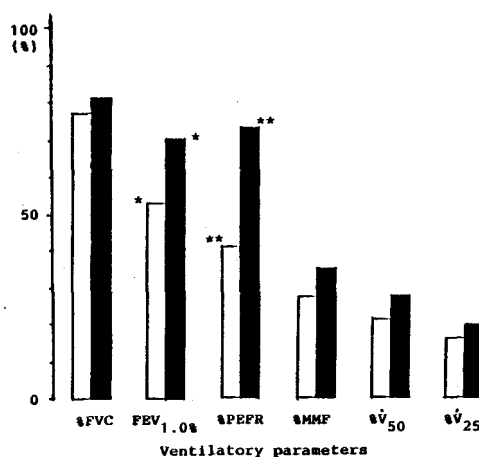


Fig. 1. Comparison of ventilatory function between the patients with (□) and without efficacy (■) of complex spa therapy. *p<0.02, **p<0.05.

Cellular composition in BAL fluid and efficacy of the therapy

The proportion of neutrophils in the BAL fluid was higher in group A compared with group B. The mean frequency of neutrophils was 30.0% in group A and 10.9% in group B, but no significant difference was present between the groups A and B. While the proportion of eosinophils in the BAL fluid was higher in group B (mean, 5.4%) than in group A (mean, 2.4%). The difference in the

frequency of the BAL eosinophils was not significant between the groups A and B. The results demonstrate that cellular composition in BAL fluid is not always related to efficacy of the complex spa therapy (Table 3, Fig. 2)

Table 3. Cellular composition in BAL fluid of the patients with bronchial asthma before complex spa therapy

Case no	Effect *	BAL cells (%)				
		Mac	Lym	Neut	Eos	Bas
1	+	58.0	2.0	39.0	1.0	0
2	+	6.6	4.0	88.0	0.6	0
3	+	40.7	11.3	35.4	7.8	4.8
4	+	74.7	8.0	15.0	3.0	0
5	+	64.1	32.7	3.0	0.2	0
6	+	85.6	11.8	0.8	1.6	0.2
7	-	46.9	7.2	39.1	5.5	1.3
8	-	60.0	11.6	16.4	12.0	0
9	-	79.2	5.4	2.6	12.8	0
10	-	84.1	11.3	3.3	1.3	0
11	-	86.2	10.2	3.4	0	0
12	-	85.6	12.8	0.6	1.0	0

* Effect of complex spa therapy. Mac, macrophages; Lym, lymphocytes; Neut, neutrophils; Eos, eosinophils; Bas, basophils

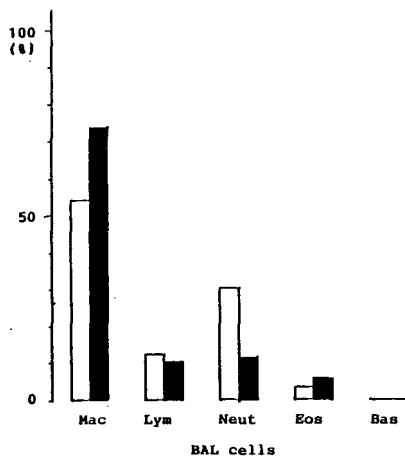


Fig. 2. Comparison of cellular composition in BAL fluid between the patients with (□) and without efficacy (■) of complex spa therapy. Mac, macrophages; Lym, lymphocytes; Neut, neutrophils; Eos, eosinophils; Bas, basophils.

Correlation between %neutrophils in BAL fluid and the value of $\% \dot{V}_{25}$ in relation to efficacy of the therapy

The complex spa therapy was effective in 4 subjects showing low value (less than 10%) of $\% \dot{V}_{25}$ accompanied by higher proportion of neutrophils (more than 10%) in the BAL fluid. While the therapy was not effective in 3 subjects showing the low value of $\% \dot{V}_{25}$ without the increased frequency of neutrophils in the BAL fluid. The results show that complex spa therapy is effective in patients with low value of $\% \dot{V}_{25}$ accompanied by BAL neutrophilia (Fig. 3).

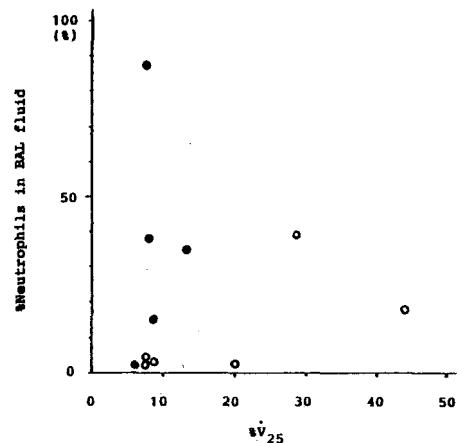


Fig. 3. Correlation between %neutrophils in BAL fluid and the value of $\% \dot{V}_{25}$ in the patients with (●) and without efficacy (○) of complex spa therapy

Discussion

Bronchial asthma is a disease characterized by bronchial hyperresponsiveness to various stimuli. The pathophysiological changes of the airways such as bronchoconstriction, bronchial membrane edema, mucus hypersecretion and bronchiolar obstruction are related to the therapy for the disease. By

addition of mucus hypersecretion and bronchiolar obstruction to simple bronchoconstriction, asthma is more severe and more difficult to treat^{7-9,11}.

Our previous studies have shown that spa therapy is effective on bronchial asthma¹²⁻¹⁵, particularly on steroid-dependent intractable asthma (SDIA)¹⁻³. The efficacy of sp therapy is considerably different among patients with bronchial asthma^{12,15}. More effective and less effective cases are observed in the treatment of bronchial asthma with spa therapy. More effective were patients over the age of 41, those over the age of 31 at onset of the disease, those with type Ib (bronchoconstriction + hypersecretion) and with type II (bronchiolar obstruction) of asthma¹⁵. Furthermore, it has been suggested that spa therapy improves ventilatory function of asthma patients, particularly ventilatory dysfunction in the small airways^{4,16,17}.

In the present study, efficacy of complex spa therapy was evaluated in patients with SDIA, and the direct action on the airways was analyzed by observing ventilatory function and cellular composition in BAL fluid. Regarding ventilatory function, the complex spa therapy was assessed to be effective in patients with low values of FEV_{1.0%} and %PEFR. The low value of % \dot{V}_Z which is considered to represent ventilatory dysfunction in the small airways, is not always related to efficacy of the complex spa therapy. The data from the present study show that the complex spa therapy is more effective in patients showing low value of % \dot{V}_Z (less than 10%) accompanied by BAL neutrophilia. This might depend on different pathophysiology of the small airways between the patients with and without BAL neutrophilia. It might be suggested that the

complex spa therapy is more effective in patients with airway inflammation

References

1. Tanizaki Y, Komagoe H, Sudo M, Ohtani J, Kimura I. Intractable asthma and swimming training in a hot spring pool. *J J A Phys M Baln Clim.* 47 : 115-122, 1984.
2. Tanizaki Y, Komagoe H, Sudo M, Morinaga H. Clinical effect of spa therapy on steroid-dependent intractable asthma. *Z Physiother.* 37 : 25-430, 1985.
3. Tanizaki Y, Komagoe H, Sudo M, et al. Swimming training in a hot spring pool as therapy for steroid-dependent asthma. *Jpn J Allergol.* 33 : 389-395, 1984.
4. Tanizaki Y. Improvement of ventilatory function by spa therapy in patients with intractable asthma. *Acta Med Okayama* 40 : 55-59, 1986.
5. Tanizaki Y, Sudo M, Kitani H, Araki H. Spa therapy for bronchial asthma. Clinical effect of inhalation of iodine salt solutions. *Papers of the Institute for Environmental Medicine, Okayama University Medical School.* 60 : 19-24, 1989.
6. Tanizaki Y, Komagoe H, Morinaga H, et al. Classification of asthma based on clinical symptoms : Asthma type in relation to patient age and age at onset of disease. *Acta Med Okayama* 38 : 471-477, 1984.
7. Tanizaki Y, Sudo M, Kitani H, et al. Characteristics of cell components in bronchoalveolar lavage fluid (BALF) in patients with bronchial asthma, classified by clinical symptoms. *Jpn J Allergol.* 39 : 75-81, 1990.
8. Tanizaki Y, Sudo M, Kitani H, et al. Clinical characteristics of bronchial asthma in the elderly in relation to cell component

- in the airways. *Jpn J Geriat.* 27 : 589-594, 1990.
9. Tanizaki Y, Kitani H, Okazaki M, et al. Cellular composition of fluid in the airways of patients with house dust sensitive asthma, classified by clinical symptoms. *Jpn J Med.* in press.
 10. Tanizaki Y, Kitani H, Okazaki M, et al. Effect of fango therapy on steroiddependent intractable asthma. *Medicine and Biology* 122 : 105-108, 1991.
 11. Tanizaki Y, Sudo M, Kitani H, et al. Clinical studies on steroid-dependent intractable asthma. Comparison between early and late onset of asthma. *Jpn J Allergol.* 38 : 6873, 1989.
 12. Tanizaki Y, Komagoe H, Sudo M, Morinaga H, Kimura I. Clinical effects of spa therapy on patients with bronchial asthma and characteristics of its action mechanisms. *J J A Phys M Baln Clim.* 48 : 99-103, 1985.
 13. Tanizaki Y, Sudo M, Kitani H, et al. Clinical effects of spa therapy on patients with bronchial asthma. Comparison between immediate and distant effects of spa therapy. *J J A Phys M Baln Clim.* 53 : 146-152, 1990.
 14. Tanizaki Y. Spa therapy for bronchial asthma. *J J A Phys M Baln Clim.* 54 : 197-204, 1991.
 15. Tanizaki Y, Kitani H, Okazaki M, et al. Clinical effects of spa therapy on bronchial asthma. 1. Relationship to clinical asthma types and patient age. *J J A Phys M Baln Clim.* 55 : 77-81, 1992.
 16. Tanizaki Y, Kitani H, Okazaki M, et al. Clinical effects of spa therapy on bronchial asthma. 2. Relationship to ventilatory function. *J. J. A. Phys M Bal Clim.* 55 : 82-86, 1992.
 17. Tanizaki Y, Kitani H, Okazaki M, et al. Spa therapy improves ventilatory function in the small airways of patients with steroid-dependent intractable asthma (SDIA). *Acta Med Okayama.* in press.

ステロイド依存性重症難治性喘息に対する複合温泉療法の作用機序

谷崎勝朗, 貴谷 光, 岡崎守宏, 御船尚志, 光延文裕, 高取明正¹⁾, 奥田博之¹⁾, 越智浩二²⁾, 原田英雄²⁾, 木村郁郎³⁾

岡山大学医学部附属病院三朝分院内科, ¹⁾産婦人科, ²⁾医学部臨床検査医学, ³⁾医学部第二内科

ステロイド依存性重症難治性喘息を対象に, 温泉プール水泳訓練, ヨードゾル吸入療法, 鈹泥湿布療法からなる複合温泉療法の臨床効果の解析を行った。1. 複合温泉療法は, FEV_{1.0%}および%PEFR 値の低い症例により有効であった。2. 複

合温泉療法は, 細気管支領域の換気障害を示すと考えられる% \dot{V}_E 値が低い症例に対して, 必ずしも有効ではなかった。3. 複合温泉療法の効果は, BAL 液中好中球増多(10%以上)が見られ, かつ% \dot{V}_E 値が低い症例により有効であったが, 同様に% \dot{V}_E 値が低くても, BAL 液中に好中球増多が見られない症例に対しては, 有効ではなかった。

以上の結果より, 複合温泉療法はFEV_{1.0%}や%PEFR値の低く, またBAL 液中好中球増多が見られ, かつ% \dot{V}_E 値が低いようなステロイド依存性重症難治性喘息に対して有効性が高いことが示唆された。

キーワード: 複合温泉療法, 換気機能, BAL 好中球増多, 気管支喘息