◎原　著

A patient with pulmonary emphysema treated by diet therapy with α-linolenic acid-enriched perilla seed oil.

Hirofumi Tsugeno, Kozo Ashida, Fumihiro Mitsunobu, Takashi Mifune, Makoto Okamoto, Yasuhiro Hosaki, Yoshiro Tanizaki and Takao Tsuji[1)]

Division of Medicine, Misasa Medical Branchi,
[1)]First Department of Medicine, Okayama University Medical School

Abstract: An effective treatment for the advanced stages of chronic obstructive pulmonary disease (COPD) has not been established yet. We report our recent experience of one patient with pulmonary emphysema treated by dietary supplementation of n-3 fatty acid for two months. He presented improvements in clinical symptoms and pulmonary function, and suppression of leukotriene B_4 generation by peripheral leukocytes. We consequently suppose that dietary treatment with n-3 fatty acids (perilla seed oil) may offer benefits for the treatment of pulmonary emphysema by competitively inhiabiting the conversion of arachidonicacid to leukotrienes and prostanoids.

key words: pulmonary emphysema, n-3 fatty acid, leukotriene, diet therapy

Introduction

An effective treatment for the advanced stages of chronic obstructive pulmonary disease (COPD) has not been established yet. Several modalities for COPD treatment such as medical treatment (1), pulmonary rehabilitation (2,3) and surgical treatment (4) have been employed, but these are merely symptomatic therapy, inefficient, and frequently limited by the side effects of medication and the risk of surgical treatment (5-7).

In this study, we reported our recent experience of one patient with pulmonary emphysema, who received dietary treatment with supplementation of n-3 fatty acid for two months, and presented improvements in clinical symptoms, pulmonary function and suppression of leukotriene B_4 (LTB_4) generation by peripheral leukocytes.

Case Report

A 67-year-old man (height 157 cm, weight 42 kg) with COPD was admitted to our hospital for the first time in September 1995. He was a previous smoker with smoking history of 69 pack-years. He had experienced wheezing and slight dyspnea on exertion since he was 65 years old, and consulted doctor because his symptoms were gradually worsening (Hugh-Jones IV). He was diagnosed with pulmonary

emphysema and treated unsuccessfully with bronchodilators and expectorants.

At the time of the first admission, a physical examination revealed a decrease in breath sound over both lung fields on auscultation. The findings of blood chemistry and urinalysis were normal. The serum IgE level was 139.4 IU/ml and no specific antibodies for inhaled allergens were detected by the radioallergosorben test (RAST)(Table 1).

Table 1. Laboratory data on first admission

Hematology		IgE(RAST)	House dust (-)
WBC	7700 /mm^3		Mite (-)
Seg	29 %		Candida (-)
Stab	24 %		
Lym	33 %	Blood chemistry	
Mo	11 %	T-CHO	190 mg/dl
Eo	3 %	TP	6.7 mg/dl
Ba	1 %	AST	24 IU/L
RBC	545 ×10^4/mm^3	ALT	5 IU/L
Hb	16.4 g/dl	ALP	74 IU/L
Hct	49.5 %	BUN	15.6 mg/dl
PLT	29.0 ×10^4/mm^3	Cr	1.0 mg/dl
Serology		Arterial blood gas(room air)	
CRP	0.1 mg/dl	pH	7.40
ESR	3 mm/h	PO_2	75.0 mmHg
IgG	1036 mg/dl	PCO_2	39.0 mmHg
IgA	197 mg/dl	HCO_3^-	24.7 mEq/L
IgM	60 mg/dl	BE	-0.2
IgE	139.4 IU/ml	SaO_2	94.9 %

RAST: radioallergosorben test

A chest X-ray revealed a hyperlucent lung and descent of the diaphragm (Fig.1). CT scans of the nasal cavity and sinuses showed normal findings.

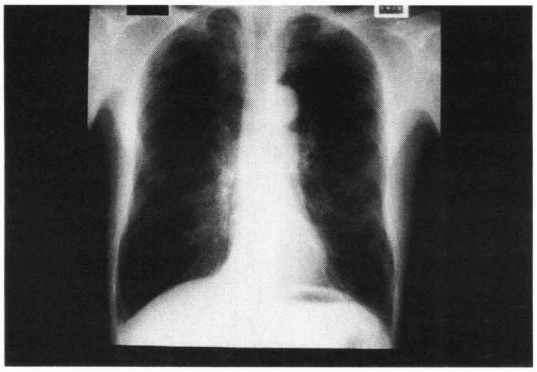


Figure 1. Chest radiograph on admission showing a hyperlucent lung and descent of the diaphragm.

Pulmonary function tests showed severe reduction in FVC (2.32L, 72.8%pred), FEV_1 (0.82L), FEV_1 /FVC (37.6%) and $\dot{V}25$ (0.19L, 13.4%pred), suggesting severe airflow obstruction especially in the peripheral airway (Table 2). Blood gas analysis revealed hypoxemia (Table 1).

Table 2. Pulmonary function tests on first admission

		on admission	at discharge
FVC	L	2.32	2.30
%FVC	%	73.4	72.8
FEV_1	L	0.82	0.72
FEV_1/FVC	%	37.6	31.3
MMF	L /S (%)	0.32 (10.6)	0.30 (9.9)
PEFR	L /S (%)	2.86 (38.1)	2.89 (38.5)
$\dot{V}_{50}$	L /S (%)	0.35 (8.0)	0.34 (7.7)
$\dot{V}_{25}$	L /S (%)	0.19 (13.4)	0.17 (12.0)
$\dot{V}_{25}$/HT	L/S/M	0.18	0.11
PEF	L /M	210	200

MMF : maximal midexpiratory flow
PEFR : peak expiratory flow rate
PEF : peak expiratory flow
HT : height

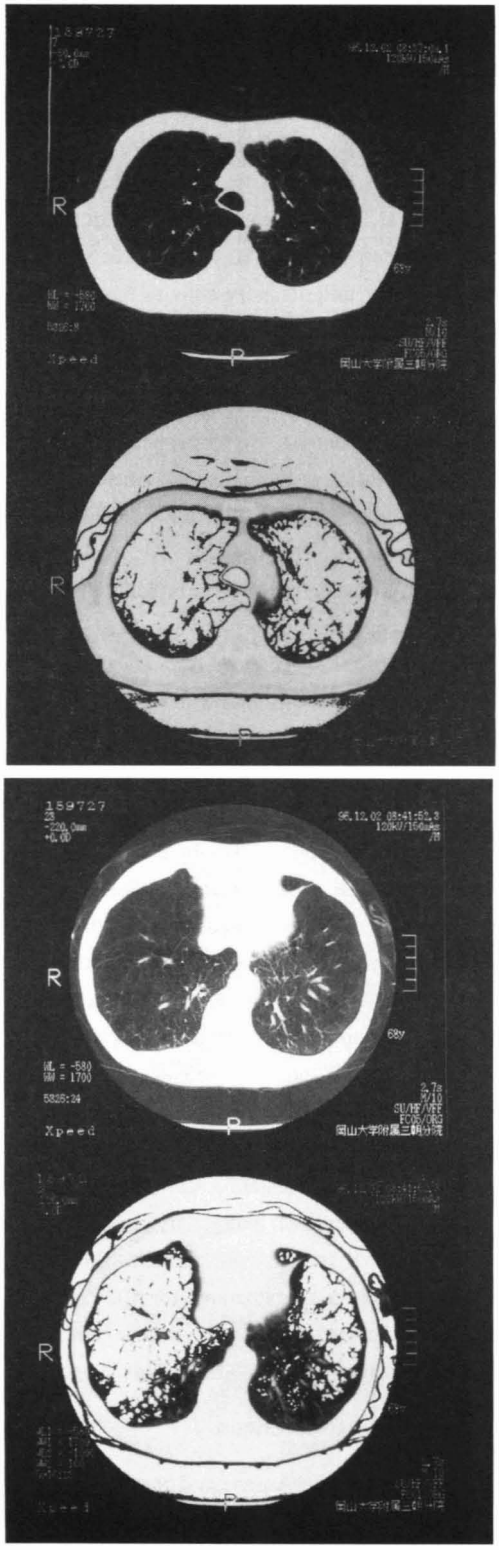
After admission, the patient underwent complex spa therapy (swimming training in hot spring pool, inhalation of iodine salt solution, fango therapy)(8) with glucocorticoid inhalation (200μg/day of beclomethasone dipropionate) and bronchodialators for two months. No apparent improvement was found in pulmonary function (Table 2), including the peak expiratory flow (PEF)(190-230L/min) in the early morning despite gradual improvement of dyspnea (Hugh-Jones III). After discharge from our hospital, he was monitored by his home doctor for eight months.

In August 1996, the patient was admitted to our hospital a second time, due to gradual aggravation of exertional dyspnea (Hugh-Jones IV). Again, the findings of blood chemistry and urinalysis were normal, pulmonary function tests revealed severe airflow obstruction, especially in the peripheral small airway, and blood gas analysis showed hypoxemia (Table 3). The values of FEV_1 and PEF improved, but did not exceed 15% fluctuation, after inhalation of a β-

Table 3. Pulmonary function tests and arterial blood gas analysis on 2nd admission

		on admission	at discharge
Pulumonary function tests			
FVC	L	2.24	2.58
%FVC	%	71.3	82.6
FEV_1	L	0.88	0.97
FEV_1/FVC	%	39.3	37.6
MMF	L/S (%)	0.36 (12.1)	0.38 (13.0)
PEFR	L/S (%)	2.68 (35.8)	3.18 (42.6)
$\dot{V}_{50}$	L/S (%)	0.35 (8.0)	0.38 (8.8)
$\dot{V}_{25}$	L/S (%)	0.20 (14.5)	0.20 (14.9)
$\dot{V}_{25}$/HT	L/S/M	0.38	0.13
PEF	L/M	190	290
%FRC			104.5
%TLC			118.5
%RV			199.4
RV/TLC	%		126.9
%DLCO			68.0
DLCO/VA			1.61
Arterial blood gas(room air)			
pH		7.43	7.45
PO_2	mmHg	75.0	76.0
PCO_2	mmHg	33.9	34.3
HCO_3^-	mEq/L	23.1	23.9
BE		-1.3	-0.3
SaO_2	%	95.6	95.7

MMF : maximal midexpiratory flow
PEFR : peak expiratory flow rate
PEF : peak expiratory flow
HT : height



(a)

(c)

Figure 2. HRCT scan showing emphysematous change such as many low attenuation areas (LAAs) in the lung fields (a,b). HRCT findings were also analyzed quantitatively, defining lung areas with CT numbers less than -950 Hounsfield Units (HU) as LAAs. The percentages of LAAs on HRCT were 72.6% at the top of the aortic arch (c), and 49.3% at a level of 2 cm above the diaphragm (d).

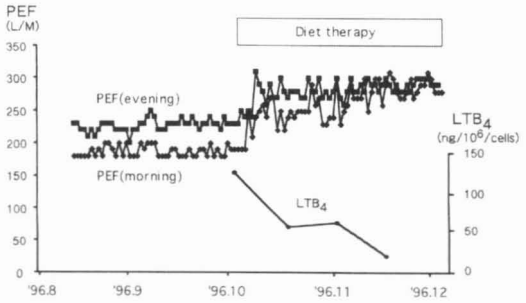


Figure 3. Clinical course of the patient during the second admission. Changes of peak expiratory flow (PEF) in the early morning (◆) and in the evening (■), and synthesis of LTB_4 (●) by peripheral leukocytes stimulated by Ca^{2+} ionophore.

(b)

(d)

dietary supplementation with α-Linolenic acid (α-LNA), the n-3 parent fatty acid, is beneficial to bronchial asthma patients with regard to symptoms, inhibiting the production of LTB_4 and C_4 from arachidonic acid in leukocytes (8,13) as well as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)(14).

There are a few retrospective studies of COPD which have focused primarily on the effects of fish oil or EPA. With a dietary questionnaire, Sharer et al. studied the relationship between dietary intake of fish containing n-3 polyunsaturated fatty acids, principally EPA acid and DHA, and COPD in smokers (15). A high dietary intake of n-3 fatty acids was inversely related to the risk of COPD in a quantity-dependent

fashion, and may protect cigarette smokers against COPD. The pathogenesis of chronic bronchitis, emphysema and deterioration of lung function in smokers is likely to involve inflammatory processes resulting from an accumulation of neutrophils in the lung (16), increased production of LTB_4 by leukocytes (17), a potent inflammatory metabolite of arachidonic acid, and enhanced release of reactive oxygen metabolite (e.g.superoxide anions) by alveolar macrophages (18). Both LTB_4 and reactive oxygen metabolite may stimulate mucus secretion in the airways, and have also been implicatied in the proteinase-antiproteinase theory of emphysema (19).

Although the net in vivo effect of n-3 fatty acids might be difficult to predict from in vitro studies, some workers have reported that supplementing the diet with n-3 fatty acids interferes with all of these pathogenic mechanisms, because n-3 fatty acids reduce the chemotactic responsiveness of neutrophils (20), inhibit the production of LTB_4 from arachidonic acid in leukocytes (21), and decrease the production of superoxide anions in leukocytes (22,23). n-3 fatty acids also decrease the production of other putative mediators of pulmonary inflammation, including platelet-activating factor (24), interleukin-1 (25-27), and tumor neurosis factor (25,26). n-3 fatty acids have been also reported to influence the kinds of bacteria (28-30) that might be able to survive in a chronic infection, and these findings might have implications for n-3 fatty acid enrichment of any organ with a normal bacterial flora or where microbial host interactions are involved in disease processes. It has been reported that n-3 fatty acids can reduce blood viscosity on red cell flexibility in animal models (31, 32), offering improvement in the pulmonary hemodynamic function.

Leukotrienes (LTs) are one of the most important chemical mediators from inflammatory cells. Peptic leukotrienes (LTC_4, D_4, and E_4) have a bronchoconstricting action and LTB_4 is known as a strong chemotactic factor. These LTs are generated from arachidonic acid (AA), which is a product from membrane phospholipids during cell activation through the 5-lipoxygenase pathway. Sulfidopeptide LTs of the 'five series' (LTC_5 and E_5) from EPA have relatively similar properties to those of the 'four series' (LTC_4, D_4 and E_4) from arachidonate (33). In contrast, the generation of LTB_4 which is chemotactic and recruits many inflammatory cells to the focus of inflammation, and both LTB_4 from AA and LTB_5 from EPA have similar biological activities. The action of LTB_5 is, however, very weak compared with that of LTB_4. In contrast, cyclcoxygenase products from EPA have different biological activities to those from AA. Thromboxane A_3 does not stimulate platelets, in contrast to thromboxane A_2. LTB_5 and thromboxane A_3 made from n-3 fatty acids differ in the degree and character of their biological activities to LTB_4 and thromboxane A_2 dericed from arachidonate.

The clinical course of this case with the diet therapy using α-LNA-enriched perilla seed oil supplementation showed an apparent improvement of exertional dyspnea and pulmonary function accompanied by a decrease in the generation of LTB_4 by leukocytes. The findings may suggest a mechanism for dietary supplementation with n-3 fatty acids for COPD. We consequently suppose that competitively inhibiting the conversion of arachidonic acid (AA) to leukotrienes (LTs) and prostanoids, forming fewer active metabolites such as LTB_5 and thromboxane A_3, may be the most important effect of dietary supplementation with n-3 fatty acids.

Perilla seed oil supplementation seems to be beneficial in the treatment of pulmonary emphysema. Further prospective studies with more subjects are needed to develop a diet therapy for COPD, and further studies are needed to investigate the effects of dietary supplementation with n-3 fatty acids.

References

1. The statement of the American Thoracic Society: Standards for the diagnosis and care of patients with

chronic obstructive pulmonary disease. American Jounal of Respiratory and Critical Care Medicine 152:S44-S120, 1995.

2. American Thoracic Society. Pulmonary rehabilitation. American Review of Respiratory Disease 124:663, 1981.

3. Position Paper of the American Association of Cardiovascular and Pulmonary Rehabilitation: Scientific bases of pulmonary rehabilitation. Journal of Cardiopulmonar Rehabilitation 10:418, 1990.

4. Cooper JD, Trulock EP, Triantafillou AN, Patterson GA, Pohl MS, Deloney PA, Sundaresan RS and Roper CL: Bilateral pneumectomy (volume reduction) for chronic obstructive pulmonary disease. J Thoric Cardiovasc Surg 109:106-16; discussion 116-119, 1995.

5. Bagley PH, Davis SM, O'Shea M and Coleman AM: Lung volume reduction surgery at a community hospital: program development and outcomes. Chest 111:1552-1559, 1997.

6. Howell RE, Muehsam WT, and Kinnier WJ: Mechanism for the emetic side effect of xanthine bronchodilators. Life Sci 46:563-568, 1990.

7. Shane E, Silverberg SJ, Donovan D, Papadopoulos A, Staron RB, Addesso V, Jorgesen B, McGregor C and Schulman L: Osteoporosis in lung transplantation candidates with end-stage pulmonary disease. Am J Med 101:262-269, 1996.

8. Tanizaki Y, Kitani H, Okazaki H, Mifune T and Mitsunobu F: Clinical effects of complex spa therapy on patients with steroid-dependent intractable asthma (SPIA). Jpn J Allergol 42:219-221, 1993.

9. Ashida K, Mifune T, Mitsunobu F, Hosaki Y, Yokota S, Tsugeno H, Tanizaki Y, Yamamoto J and Tsuji T: A pilot study: Effects of dietary supplementation with alpha-linolenic acid-enriched perilla seed oil on bronchial asthma. Allergology International 46:181-185, 1997.

10. Szekekely LA, Oelberg DA, Wright C, Johnson DC, Wain J, Trotman-Dickenson B, Shepard JA, Kanarek DJ, Systrom D and Ginns LC: Preoperative predictors of operative morbidity and mortality in COPD patients undergoing bilaterallung volume reduction surgery. Chest 111:550-558, 1997.

11. Belluzzi A, Brignola C, Campieri M, Pera A, Boschi S and Miglioli M: Effect of an enteric-coated fish-oil preparation on relapses in Crohn's diseases. N Engl J Med 334:1557-1560, 1996.

12. Belch JJ, Ansell D, Madhok R, O'Dowd A and Sturrock RD: Effects of altering dietary essential fatty acids on requirements for non-steroidal anti-inflammatory drugs in patients with rheumatoid arthritis: a double blind placebo controlled study. Ann Rheum Dis 47:96-104, 1988.

13. Ashida K, Mifune T, Mitsunobu F, Hosaki Y, Yokota S, Tsugeno H, Tanizaki Y, Yamamoto J and Tsuji T: Dietary supplementation with n-3 fatty acids in bronchial asthma correlated with the generation of LTB4 and LTC4. Annual Reports of Misasa Medical Branch, Okayama University Meddical School 67:35-42, 1996.

14. Arm JP, Horton CE, Spur BW, Mencia-Huerta JM and Lee TH: The effects of dietary supplementation with fish oil lipids on the airways response to inhaled allergen in bronchial asthma. Am Rev Respir Dis 139:1395-1400, 1989.

15. Shahar E, Folsom AR, Melnick SL, Tockman MS, Comstock GW, Gennaro V, Higgins MW, Sorlie PD, Ko WJ and Szklo M: Dietary n-3 polyunsaturated fatty acids and smoking-related chronic obstructive pulmonary disease. A therosclerosis Risk in Communities Stuby Investigators. N Engl J Med 331:228-233, 1994.

16. McGowan SE and Hunninghake GW: Neutrophils and emphysema. N Engl J Med 321:968-970, 1989.

17. Zakrzewaski JT, Barnes NC, Piper PJ and Costello JF: The detection of 5-lipoxygenase and cyclooxygenase products in sputum of patients with chronic bronchitis and bronchiectasis. Prostaglandins 33:663-674, 1987.

18. Hubbard RC, Ogushi F, Fells GA, Cantin AM,

Jallat S, Courtney M and Crystal RG: Oxidants spontaneousuly released by alveolar macrophages of cigarette smokers can inactivate the active site of alpha 1-antitrypsin, rendering it inffective as an inhibitor of neutrophil elastase. J Clin Invest 80:1289-1295, 1987.

19. Janoff A: Biochemical links between cigarette smoking and pulmonary emphysema. J Appl Physiol 55:285-293, 1983.
20. Lee TH, Mencia-Huerta JM, Shih C, Corey EJ, Lewis RA and Austen KF: Effects of exogenous arachidonic, eicosapentaenoic, and docosahexaenoic acids on the generation of 5-lipoxygenase pathway products by ionophore-activated human neutrophils. J Clin Invest 74:1922-1933, 1984.
21. Prescott SM: The effect of eicosapentaenoic acid on leukotriene B production by human neutrophils. J Biol Chem 259:7615-7621, 1984.
22. Harats D, Dabach Y, Hollander G, Ben-Naim M, Schwartz R, Berry EM, Stein O and Stein Y: Fish oil ingestion in smokers and nonsmokers enhances peroxidation of plasma lipoproteins. Atherosclerosis 90:127-139, 1991.
23. Burns A, Lin YG, Gibson R and Jamieson D: The effect of a fish oil enriched diet on oxygen toxicity and lipid peroxidation in mice. Biochem Pharmacol 42:1353-1360, 1991.
24. Weber C, Aepfelbacher M, Lux Zimmer B and Weber PC: Docosahexaenoic acid inhibits PAF and LTD4 stimulated [Ca2+]i-increase in differentiated monocytic U937 cells. Biochim Biophys Acta 1133:38-45, 1991.
25. Endres S, Ghorbani R, Kelley VE, Georgilis K, Lonnemann G, vander Meer JW, Cannon JG, Rogers TS, Klempner MS and Weber PC: The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. N Engl J Med 320:265-271, 1989.
26. Endres S: n-3 polyunsaturated fatty acids and human cytokine synthesis. Lipids 31:S239-242, 1996.
27. Caughey GE, Mantzioris E, Gibson RA, Cleland LG and James MJ: The effect on human tumor necrosis factor alpha and interleukin 1 beta production of diets enriched in n-3 fatty acids from vegetable oil or fish oil. Am J Clin Nutr 63:116-122, 1996.
28. Knapp HR and Melly MA: Bactericidal effects of polyunsaturated fatty acids. J Infect Dis 154:84-94, 1986.
29. Lawrence R and Sorrell T: Eicosapentaenoic acid in cysticfibrosis: evidence of a pathogenetic role for leukotriene B4. Lancet 342:465-469, 1993.
30. D'Ambola JB, Aeberhard EE, Trang N, Gaffar S, Barrett CT and Sherman MP: Effect of dietary (n-3) and (n-6) fatty acids on in vivo pulmonary bacterial clearance by neonatal rabbits. J Nutr 121:1262-1269, 1991.
31. Archer SL, Johnson GJ, Gebhard RL, Castleman WL, Levine AS, Westcott JY, Voelkel NF, Nelson DP and Weir EK: Effect of dietary fish oil on lung lipid profile and hypoxic pulmonary hypertension. J Appl Physiol 66:1662-1673, 1989.
32. Knapp HR: Hypotensive effects of omega-3 fatty acids: mechanistic aspects. World Rev Nutr Diet 66:313-328, 1991.
33. Dahlen SE, Hedqvist P and Hammarstrom S: Contractile activities of several cysteine-containing leukotrienes in the guinea-pig lung strip. Eur J Pharmacol 86:207-215, 1982.

n-3 系脂肪酸を強化した食事療法が有効と考えられた肺気腫の一例

○柘野浩史，岡本　誠，原田誠之，芦田耕三，
光延文裕，御舩尚志，保崎泰弘，谷崎勝朗，
辻　孝夫[1)]

岡山大学医学部三朝分院内科，
[1)]医学部第一内科

今回我々は，肺気腫の症例に対して n-3 系脂肪酸を強化した食事療法をおこない，臨床症状，呼吸機能検査所見ともに速やかに改善を認め，同時に白血球のロイコトリエン B4 産生能が著明に減少した一例を経験したので報告する。

症例は 67 歳，男性。主訴は労作時呼吸困難。【第一回目入院】3 カ月間入院し，薬物療法，温泉を用いた理学療法を行った。自覚症状はやや改善が見られたが，呼吸機能検査所見の改善は得られなかった。【第二回目入院】1 年後に再入院。n-3 系脂肪酸強化食事療法も併用した。自覚症状および，呼吸機能検査上，FVC，FEV1.0，PEF などに改善を認めた。n-3 系脂肪酸はアラキドン酸代謝を通してロイコトリエン合成に関与すると推定されるが，経過中に白血球の LTB4 産生能の減少を認めた。

この症例は肺気腫に対する n-3 系脂肪酸強化食事療法の有用性が示唆され，病態を考える上でも興味深いと考えられた。