Assessment of Airway Wall Thickness by High-Resolution Computed Tomography in Patients With Asthma of Different Degree of Severity

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Abstract

To measure airway wall thickness at the segmental and subsegmental levels, HRCT scanning was performed in 30 patients with asthma and in 10 normal controls.

The subjects were prospectively divided into four groups: 10 normal controls (group 1), 10 patients with mild asthma (group 2), 10 patients with moderate asthma (group 3), and 10 patients with severe asthma (group 4). HRCT (1.5 mm collimation) scans of the chest were done at five different levels. The ratio of airway wall thickness to outer diameter (T/D) and the percentage wall area (WA %) defined as [(wall area/total airway area) x 100] were used to compare airway wall thickness between the groups.

Mean (SD) forced expiratory volume in one second (FEV_1) was 102.10 (5.47) % for group 1, 95.10 (13.40) % for group 2, 68.50 (19.67) % for group 3, and 45.0 (15.30) % for group 4. Mean (SD) T/D and WA% were 0.23 (0.05) and 70.28 (10.28) % for group 1, 0.26 (0.05) and 75.14 (9.95) % for group 2, 0.27 (0.05) and 78.09 (10.40) % for group 3, and 0.29 (0.04) and 81.72 (7.49) % for group 4. Groups 2, 3, and 4 had higher T/D and WA% values than the control group ($p<0.001$). Differences between asthma patients of different severity were also demonstrated. Group 3 had a higher T/D and WA% than group 2 ($p=0.002$, $p=0.003$) and Group 4 had a higher T/D and WA% than group 3 ($p<0.001$). The differences between the groups were noted both for small airways (with a luminal diameter of >2 mm) and for the larger airways (with a luminal diameter of ≤2 mm).

The results of the study indicate that, as assessed by HRCT scanning, all patients with asthma had some degree of airway wall thickening compared to normal subjects. The methodology described in this study may be useful in assessing airway wall thickness in asthma.

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Introduction

Asthma is characterized with bronchial hyper-responsiveness and develops as a result of a state of chronic inflammation of the bronchial system caused by allergic and non-allergic factors. It can improve either spontaneously or with treatment. Narrowing of the bronchial tree due to bronchospasms occurs during the course of this disease (1,2). A state of chronic inflammation regulated by T cells and in which mast cells and eosinophils also participate is characteristic of asthma (3,4). Post-mortem studies performed on patients who died during acute attacks have shown that airways of small and moderate caliber were closed with secretion plaques and contained abundant numbers of eosinophils and epithelial cells. As a result of this remodeling of airways, bronchial hyperactivity develops, which in turn causes asthma

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Table 1. Demographic characteristics, lung function and medications used by the patients

	Group 1 (n:10)	Group 2 (n:10)	Group 3 (n:10)	Group 4 (n:10)
Sex (M/F) (n)	5/5	-/10	2/8	5/5
Mean age (SD)[a] (years)	38.40 (2.37)	42.80 (14.23)	43.40 (8.92)	44.80 (10.60)
Mean (SD) duration of asthma (years)[b]	-	9.40 (8.30)	8.0 (5.75)	13.40 (10.61)
Inhaled steroids*	-	3	All	All
Theophylline*	-	3	5	7
Systemic steroids*	-	-	1	6
FEV_1 (% predicted) Mean (SD)[c]	102.10 (5.47)		68.50 (19.67)	45.0 (15.30)

FEV_1: Forced expiratory volume in one second.
M/F: Male/female ratio.
[a]No significant differences between the groups.
[b]No significant difference between group 2, 3 and 4.
[c]No significant differences between group 1 and 2 in FEV_1. However, FEV_1 was lower in group 3 than group 2 ($p<0.001$). It was also lower in group 4 than group 3 ($p=0.001$).
*Number of patients using this medication.

symptoms (5). A thickening of the airway walls, involving all layers including the muscle membrane and the adventitia, was also demonstrated in asthmatics (6,7). High-resolution computed tomography (HRCT) scanning has been used to study the abnormalities of the parenchyma and of the airways in patients with asthma. In these studies, bronchial dilatation, mucoid impaction and bronchial thickening were frequent findings (8,9). Although HRCT has been used to study the mechanism and site of airway narrowing in experimental models (10), there are few studies which provide actual airway dimensions in patients with different degrees of asthma severity (11). We therefore undertook this study to measure the airway wall thickness in patients with asthma and evaluated the bronchi at the segmental and subsegmental levels, using a modified HRCT technique.

Materials and Methods

Study Groups

This prospective study was done in the Department of Chest Diseases of the Fırat University Faculty of Medicine. Forty subjects, 30 were asthma patients and 10 were healthy controls, participated in the research.

Asthma was defined according to American Thoracic Society criteria (12). Asthma patients were recruited from our clinic. All subjects were lifetime nonsmokers. Patients who were stable during the two weeks before the evaluation were included in the study. Patients who had any evidence of other concurrent pulmonary or systemic disease or of any upper or lower respiratory tract infection were excluded from the study.

The subjects were divided into 3 groups according to the severity of their asthma (13):

Group 1 (the control group, n=10) consisted of normal healthy subjects. All subjects were randomly selected from amongst the hospital staff. Inclusion criteria were absence of a history of respiratory or allergic disease, normal baseline spirometric parameters for age, sex and height, no smoking history, no history of upper respiratory tract infection in the preceeding 6 weeks, and not taking any regular medication.

Group 2 (patients with mild persistent asthma, n=10) consisted of patients who had symptoms more frequently than twice a week (3-6), had nocturnal symptoms more often than twice a month (3-4), who were using bronchodilators with or without inhaled steroids intermittently and who had FEV_1 values ≥80% of predicted value.

Group 3 (patients with moderate asthma, n=10) consisted of patients who had symptoms daily, had nocturnal symptoms more frequently than twice a week, who needed bronchodilators daily, who were on moderate or high doses of inhaled steroids and whose had FEV_1 were 60 to 80%.

Group 4 (patients with severe asthma, n=10) consisted of patients who had daily symptoms, frequent nocturnal attacks, needed daily high doses of inhaled steroids and long acting bronchodilators and who had FEV_1 values <60%.

All subjects were given information about the study and were asked for their written informed consent.

Clinical and demographic data including information on age, sex, duration of asthma, frequency of asthma exacerbations, admissions to hospital or to an intensive care unit, and current treatment were obtained using a standardized interview form.

Baseline data including spirometric findings and bronchodilator response were obtained for all asthma patients. In normal subjects only spirometric measurements were performed. HRCT was done within one week of the pulmonary function tests.

Spirometric tests were performed according to standard tech-

Table 2. Results of bronchial wall measurements by HRCT scanning

	Group 1	Group 2	Group 3	Group 4
Number of bronchi evaluated per patient[a] Mean (SD)	16.3 (3.34)	17.8 (10.42)	17.8 (10.42)	16.20 (9.32)
Total number of bronchi per group	163	178	178	162
T Mean (SD) (mm)[b]	1.31 (0.37)	1.38 (0.37)	1.38 (0.37)	1.52 (0.42)
T/D ratio Mean (SD)[c]	0.23 (0.05)	0.26 (0.05)	0.26 (0.05)	0.29 (0.04)
WA% Mean (SD)[d]	70.28 (10.28)	75.14 (9.95)	75.14 (9.95)	81.72 (7.49)

T: thickness , D: outer diameter, WA%: percentage wall area.
[a]No significant differences between the groups.
[b]No significant difference between groups 1 and 2 or between groups 3 and 4, but values in both groups were significantly greater than group 1 ($p<0.001$). There was also significant increase in group 3 when compared to group 2 ($p=0.002$).
[c]There were significant increases in all asthma groups when compared to group 1 ($p<0.001$). Group 4 had significantly greater values than group 3 ($p<0.001$) and group 3 had significantly greater values than group 2 ($p<0.001$).
[d]Significantly higher values were noted in all asthma groups when compared to group 1 ($p<0.001$). Group 4 had significantly higher values than group 3 ($p<0.001$) and group 3 higher values than group 2 ($p=0.003$).

niques (14) using "Fukuda Denshi Spirosift 500" equipment.

HRCT: A modified HRCT images were taken using a Hitachi (Japan) 1000 W CT machine. Oral and inhaled long acting bronchodilators and oral-inhaled short acting bronchodilators were stopped before 24 hours and 12 hours prior to the application of the HRCT, respectively. Thin section (1.5 mm collimation), 120 KV, 100 mA, 1.95 sc segment time images, taken in high spatial bone algorithm, were used. The images at the end of the inspiration were taken at 5 different levels: the superior edge of the aortic arch, the tracheal carina, the site 1 cm inferior to the carina, inferior pulmonary veins and the site 2 cm superior to the diaphragm.

The window level for the images was adjusted to –450 HU and the window space was adjusted to 1500 HU. The CT images were magnified (magnification x 5). In all of the segmental and subsegmental bronchi with lumen diameters larger than 1 mm, measurements of the bronchus wall thickness (T) and of the short axis lumen diameter (L) were performed. Only bronchi seen in cross section were analyzed. The measurements were done by two chest radiologists who had no knowledge about the patients.

The total diameter of every airway was calculated using D=L+2T. Lumen area (A_1) and total airway area (A_0) as mm^2 were calculated from L and D values using the formula $A=pr^2$. The formulae $A_1=p(L/2)^2$ and $A_0=p(D/2)^2$ were used for the calculation of the areas. According to these values the airway wall area (WA) was calculated by "A_0-A_1". We used both the ratio of airway wall thickness to total diameter (the T/D ratio) (11), and the percentage wall area (WA %=WA/A_0x100) (15,16) to compare airway wall thickening among the four groups.

Statistical Analysis

All groups were compared between themselves about age and gender. Asthmatic patients were compared with each other about the duration of asthma.

All statistical analyses were done using SPSS V10.0 packet program. Results were expressed as means (SD). The ANOVA test was used to compare all HRCT scan measurements and the pulmonary function tests data between the groups. P values of ≥0.05 were considered significant. Kruskall Wallis and Mann Whitney-U test were used when we repeated the statistical analysis after getting the mean T/D ratio and the mean WA % for each subject.

Results

Patient characteristics, lung function data, and current medications are shown in Table 1. There were no statistically significant differences between group 1 and 2 regarding FEV_1 values. Mean FEV_1 value was lower in group 3 than in group 2 ($p<0.001$). Mean FEV_1 value was lower in group 4 than in group 3 ($p=0.001$).

Representative HRCT images of subjects from the four groups are shown in Figure 1.

The results of HRCT scan measurements are presented in Table 2. There were no statistically significant differences between the groups in the mean number of bronchi measured per patient, but statistically significant differences were noted in thickness/outer diameter (T/D) values. T/D values were significantly increased in the moderate asthma group when compared to the mild asthma group ($p=0.002$), and also significantly increased in the severe asthma group when compared to the moderate asthma group ($p<0.001$).

The percentage of the wall areas (WA) were also found to be significantly increased in all asthma groups when compared to the control group ($p<0.001$). In addition, when asthma groups were compared with one another there was again a significant increase in the moderate asthma group when compared to the mild group ($p=0.003$) and the same was true for the severe group when compared to the moderate group ($p<0.001$).

A subgroup analysis was done by grouping the bronchi as lar-

Table 3. Ratio of wall thickness to bronchial diameter (T/D) and wall area (WA%) in small and large airways				
	Group 1	Group 2	Group 3	Group 4
Small airways ≤2 mm				
n	32	50	76	86
T/D ratio-Mean (SD)	0.29 (0.03)	0.30 (0.04)	0.30 (0.05)	0.31 (0.03)
WA% -Mean (SD)	80.94 (6.42)	83.62 (5.72)	83.81 (10.87)	85.84 (4.63)
Large airways >2 mmn				
n	131	128	116	77
T/D ratio-Mean (SD)	0.22 (0.04)	0.24 (0.04)	0.25 (0.04)	0.26 (0.04)
WA% -Mean (SD)	67.67 (9.33)	71.83 (9.26)	74.34 (8.16)	77.12 (7.43)

ge (L>2mm) and small (L≥2mm) airways (15) (Table 3). When compared according to T/D ratio; in the *small airways group*, there were no significant differences between mild asthma and control groups. In moderate and severe asthma groups the values were significantly higher when compared to the control group ($p=0.016$ and $p<0.001$, respectively). When asthma groups were compared with one another, the severe asthma group had significantly higher values when compared to the mild asthma group ($p=0.045$). There was no difference between the moderate and severe groups. Regarding WA % values, a significant increase was only found in the severe asthma group when compared to the control group ($p=0.002$). In the *large airways group*, the T/D ratio was found to be significantly high in mild, moderate and severe asthma groups when compared to the controls ($p<0.001$), high in the moderate asthma group in comparison with the mild group ($p=0.024$) and also high in the severe asthma group when compared to the moderate group ($p=0.018$). WA % was found to be significantly higher in all asthma groups ($p<0.001$). Also in the moderate group significantly higher values were found when compared to the mild group ($p=0.025$); the same was true for the severe group when compared to the moderate group ($p=0.031$).

A statistical analysis of the groups regardless of airway caliber showed that all asthma groups had significantly higher T/D and WA % values than the control group ($p<0.05$). Amongst the asthma groups, the severe asthma group had significantly higher values when compared to the moderate asthma group ($p<0.05$), but the difference between moderate and mild asthma groups did not reach statistical significance (respectively $p=0.267$ for T/D, and $p=0.292$ for WA %).

Discussion

In this study, airway dimensions were evaluated by using modified HRCT techniques. In asthma patients of different degrees of severity, T/D ratio and WA % values were higher compared to the control group. Also between the asthma groups, these values increased significantly with the degree of severity of the asthmatic state. Airway wall thickening was especially notable in small airways in the moderate and severe asthma groups.

In all asthma types, a relationship between the clinical severity of the disease and presence or severity of inflammation of the airway has been reported (17,18). It is reported that inflammation is present both in central and peripheral airways (19). Airway wall thickening is secondary to chronic inflammatory changes. The importance of airway wall thickening in the mechanism of airway narrowing has been discussed (6). The same degree of bronchial smooth muscle contraction in an airway with a thickened wall will result in a greater degree of narrowing than an airway of normal thickness (15).

Airway dimensions were measured by HRCT in experimental models (10) and human subjects (20). These studies were done using a HRCT protocol similar to that used in this study. In previous studies, HRCT images were digitized and internal and external perimeters were outlined in order to measure bronchial cross sectional areas. Okazawa et al showed that smaller airways (of 1.5-6 mm luminal diameters) of asthma patients were significantly thickened when compared with normal controls (20). Boulet et al found no difference between asthma patients and normal controls in the T/D ratio of the bronchus intermedius, but smaller bronchi were not evaluated in this study (11). Awadh and coworkers found no difference in T/D ratios and WA % values between severe and moderate asthma groups, nor between mild asthma and control groups. However, in moderate and severe asthma groups there was a significant increase in T/D ratio and WA % values when compared to mild asthma and control groups (15). Moreover, in this study, the T/D ratio and WA % values of large (L>2mm) and small (L≥2mm) airways in moderate and severe asthma groups were significantly higher than that of mild asthma and control groups. In asthma, airway wall thickening can be seen in both large and small airways and this, in turn, causes excess narrowing of the airways (6,21). In our study, we demonstrated that T/D and WA % values increased with the severity of the disease. A marked thickness in small airways was observed especially in moderate and severe groups, and the thickness of

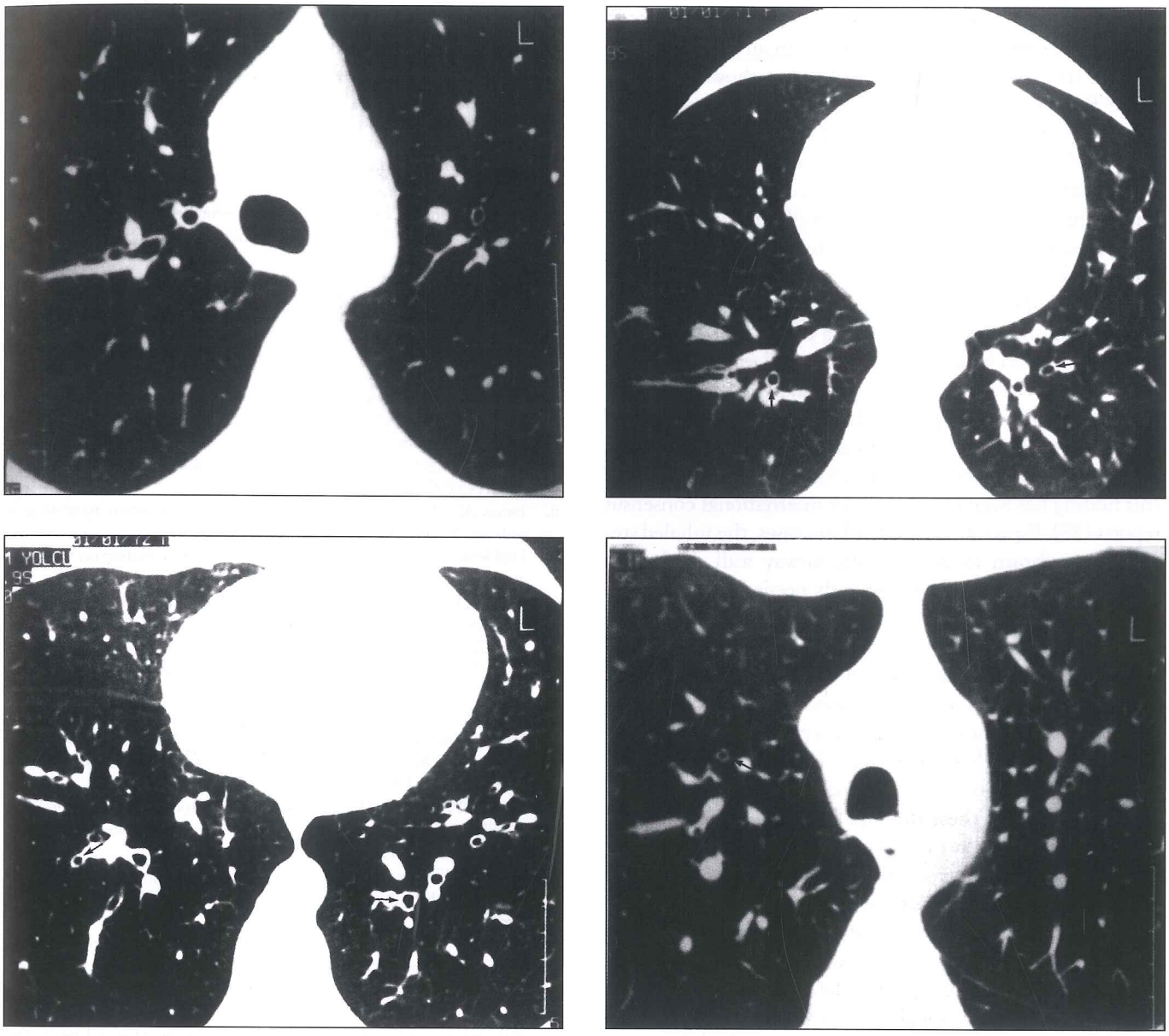

Figure 1. *HRCT images of a control subject (A), a patient with a mild asthma (B), a patient with moderate asthma (C) and of a patient with a history of near fatal asthma (D).*

large airways increased with the severity of the asthma.

Airway measurements performed by HRCT are a complex method (22,23). Our measurements were taken directly from the HRCT images and bronchial cross sectional areas were calculated. The gradient in airway thickness from normal subjects to subjects with severe disease suggests the validity of our method. Park et al. reported a significant increase in bronchial wall thickness in asthmatic patients compared to control groups, but their study did not show any correlation with the clinical findings or lung function (24).

Studies in phantoms have shown that HRCT scanning allows accurate assessment of hollow cylinders ranging from 1 mm to 5 mm in diameter with a wall thickness ranging from 0.5 mm to 2 mm (10,25). Current studies also support this finding (16). CT scanning was reported to overestimate bronchial wall thickness and underestimate lumen diameter of the airways. This is probably due to mucosal folds and to the interstitium that surrounds the bronchus leaving a relatively low spatial resolution (6). In the entrance of bronchial wall area, the neighboring pulmonary artery often makes the unknown part of the bronchial wall.

In our study, it was demonstrated that airway wall thickening -an indicator of airway inflammation- had increased in mild, moderate and severe asthma groups compared to the controls. Awadh et al. reported no difference between severe and moderate asthma groups, which is an expected finding. This finding is probably due to the fact that the measurements were taken while the patients were taking their routine antiinflammatory treatment (15). In our study, in moderate and severe groups with stable asthma who were taking their regular antiinflammatory medications, there was a significantly higher increase in airway wall thickness in the severe asthmatic

group than in the moderate asthmatics. These data indicate that the severity of disease and increase in airway wall thickness are related. Although the FEV_1 values showed no difference between mild asthmatics and controls, airway wall thickness was greater in mild asthma patients than in the controls. This finding could be explained by the fact that not only inflammation but also the other components of airway remodeling have an effect on airway wall thickness. It can be speculated that even the water content of airway wall can influence T/D ratio.

We found that there was a significant increase in airway wall thickness in mild asthma patients, a finding which suggests that some of the changes in the airway wall start in early stages. The use of inhaled corticosteroids in this period may prevent progression of the process. It has already been reported that chronic airway obstruction can be prevented with early usage of inhaled corticosteroids (26,27). The importance of this finding has been emphasized by international consensus reports (28). Especially in mild asthma cases, the inhaled steroids were shown to decrease the airway wall thickening (29,30). Further studies are obviously needed to explain the pathogenesis of the steroid effect and to explain the relationships between airway inflammation, changes in airway wall structures, and history/ severity of the asthmatic condition. The increase of airway inflammation with the severity and chronicity of the disease lead to a progressive increase in structural changes which in turn lead to an increase in symptoms and to irreversible changes in pulmonary functions (31). Based on these findings and on the results of randomized trials, early introduction of anti-inflammatory treatment is recommended in patients with asthma (32-34).

The dominant aspect of the airway thickening in asthma patients is not clear. It is reported that in fatal asthma, the airway wall thickening is both in big cartilaginous and small membranous bronchi (6) and that, especially in non-fatal cases, this thickening is seen in small airways (35). In the study by Awadh et al, a significant increase was seen in both large and small airways when compared with the control group (15). Similar findings were reported by Okazawa et al. (16). In our study, in airways smaller than 2 mm, no difference was observed between mild asthmatics and controls, but the airway wall thickening had increased in the moderate and severe groups as compared to the controls, and the large airways had increased in all groups when compared to the controls.

Exposure to radiation is a possible concern with HRCT, but the use of the methodology described here would give a radiation exposure equivalent to six chest radiographs per assessment. We believe that the methodology described in this study would be useful for assessment of airway wall thickness as well as of the effect of early anti-inflammatory therapy. Although this technique is time consuming and relatively expensive, it offers the opportunity for repeated measurements.

In conclusion, we have shown that HRCT scanning of patients with asthma of different degrees of severity showed a thickening in airway wall compared to healthy controls. This was especially true for moderate and severe asthma groups. HRCT is a relatively expensive but non-invasive technique that can be used to show the bronchus wall changes in asthmatic patients.

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