

# Frequency Dependence of Compliance as a Test for Obstruction in the Small Airways

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**ABSTRACT** We selected five bronchitics and four asthmatics in remission, whose routine lung function tests were not significantly abnormal. Dynamic compliance was measured at different respiratory frequencies and the results compared with those obtained from a normal control group. In all patients compliance was frequency dependent and remained so after the administration of bronchodilator aerosols. Compliance was frequency dependent in only one normal subject, and this was completely reversed by bronchodilators. Because the elastic properties of the patients' lungs were normal, and because pulmonary resistance was normal or only minimally increased, we interpret these results as indicating obstruction in peripheral airways.

## INTRODUCTION

Obstruction in peripheral airways (2 mm diameter and less) occurs naturally in human disease (1) and may be produced experimentally in the excised lung<sup>1</sup> and in the intact animal (2, 3). Mechanical studies have confirmed that conventional methods of detecting obstruction in the lung, such as measurement of pulmonary resistance ( $R_L$ ), are too insensitive and may fail to detect peripheral airway obstruction (footnote 1 and references 2 and 3). This is because these airways contribute only 10–30% of the total resistance of the tracheobronchial tree (1). If the upper airway is included in measurements of airway resistance or  $R_L$ , then the contribution of the small airways is even less.

It is probable, however, that obstruction in small airways affects ventilation distribution and gas exchange adversely (footnote 1 and reference 2) and may, in the

final stages of human disease, result in death from respiratory failure (4). The peripheral airways may therefore be regarded as a "silent zone" within the lung, in that obstruction within them causes little abnormality in tests designed specifically to detect it until the obstruction becomes far advanced. Thus, a means of detecting obstruction in peripheral airways is essential, both for the diagnosis of human disease and the interpretation of experimentally produced changes in  $R_L$ .

In 1966 Macklem and Mead (5) showed that the time constants or (RC) of the lung units distal to airways smaller than about 2 mm were in the order of 0.01 sec. Under these circumstances they concluded that a four-fold difference in RC between these units would be sufficient to cause dynamic compliance ( $C_{dyn}(1)$ ) to fall with increasing respiratory frequency. This raised the possibility that frequency dependence of compliance could be used as a test for obstruction in peripheral airways. In order for widespread time constant discrepancies to occur it would be necessary for the obstruction to be irregularly distributed, that is, some airways would have to remain unobstructed while others would be severely narrowed. Additionally, it would be necessary to meet other criteria in order to establish that frequency dependence of compliance was due to obstruction in peripheral airways rather than to lesions within other parts of the lung. We have reasoned that if the static pressure-volume (P-V) curve were normal, then it would be most unlikely that frequency dependence would result from abnormalities in the elastic properties of lungs. In analyzing the theoretical framework by which frequency-dependent behavior is explained (6), regional differences in elastic properties sufficient to cause a detectable fall in  $C_{dyn}(1)$  at rapid respiratory rates should result in a markedly abnormal static P-V curve. Similarly, time constant discrepancies due to obstruction in central airways should lead to a significant increase in  $R_L$ . Thus, we feel that if patients with normal values for  $R_L$  and elastic recoil pres-

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tures exhibited a fall in  $\dot{C}_{a\gamma n}$  (1) with increasing respiratory frequency, then it would be reasonable to conclude that there was peripheral airway obstruction.

## METHODS

The group of bronchitic subjects was chosen from a number of veterans already participating in long-term function studies (7, 8). All were cigarette smokers and had a productive daily cough. They were included in our study only if their lung function in the routine laboratory was within, or close to, the limits predicted for their age.

The subjects in the second group had bronchial asthma but were asymptomatic at the time of the study. They also were only included in the study if their lung function was close to the normal range.

The control group was composed of normal subjects, drawn from the medical and laboratory staff, in the same age range as the asthmatic and bronchitic subjects. Although some were smokers, none had a chronic cough. One normal subject was studied before, during, and after an attack of acute bronchitis.

The lung function tests in the routine laboratory in-

cluded measurement of lung volume and mixing efficiency, using helium dilution, measurements of maximal mid-expiratory flow rate, and indirect maximum breathing capacity and steady-state diffusing capacity for carbon monoxide (7). The predicted values used were those of Goldman and Becklake (9).

$\dot{C}_{a\gamma n}$  (1) was measured from simultaneous recordings of transpulmonary pressure ( $P_L$ ) and volume on a 4-channel Sanborn polyviso.  $P_L$  was obtained from a Sanborn 268 B transducer to which catheters from an esophageal balloon and the mouth were attached. Volume was obtained from a volume displacement plethysmograph the signal from which was corrected so that it remained exactly 90 degrees out of phase with flow at the mouth at all frequencies used. The subject was asked to inspire fully, expire to his normal resting level, and then breathe at a constant tidal volume, being careful not to go below his resting end-expiratory level which was displayed in front of him by a marker that moved with the spirometer bell. The subject breathed at increasing frequencies up to a maximum of 120 breaths/min. A constant volume history of inflation to total lung capacity (TLC) preceded the measurement of  $\dot{C}_{a\gamma n}$  (1) at each new frequency. Great care was taken to ensure that  $\dot{C}_{a\gamma n}$  (1) was measured under similar conditions at each frequency.

TABLE I  
Physical Characteristics and Lung Function of Patients Studied

Subject No.	Age	Sex	VC	FRC	TLC	RV	MBC	MMF	Dco	R <sub>1</sub> cm H <sub>2</sub> O/ liters per sec		R <sub>1</sub> × FRC cm H <sub>2</sub> O × sec	
										Before broncho-dilator	After broncho-dilator	Before broncho-dilator	After broncho-dilator
% predicted													
Chronic bronchitis													
1	42	M	89	72	90	93	102	150	98	2.4	2.0	5.3	4.4
2	49	M	112	112	104	88	98	80	71	2.7	2.4	9.2	8.2
3*	57	M	40	58	50	68	53	57	71	3.3	3.0	6.5	5.9
4	49	M	95	79	89	76	117	134	130	1.8	1.2	6.1	4.1
5	58	M	122	131	129	140	120	100	106	2.0	1.2	8.8	5.3
Asthma													
6	21	M	103	112	115	119	83	66	85	3.3	2.2	11.2	7.5
7	21	M	85	80	85	84	88	75	—	2.0	1.6	7.2	5.8
8	22	M	100	103	105	121	85	73	—	3.0	—	8.8	—
9	44	F	116	131	124	142	85	56	116	3.8	2.4	13.6	8.6
Normal													
10	47	M	96	95	101	112	101	96	—	1.4	1.2	5.2	4.5
11	49	M	110	82	106	97	113	107	101	1.9	1.4	6.7	4.9
12	46	M	103	93	122	99	99	85	101	1.8	1.3	5.1	3.7
13	50	M	84	87	89	147	93	127	97	2.1	1.6	6.3	4.8
14	33	M	98	90	89	67	104	98	—	1.5	1.2	5.6	4.5
15	32	M	109	87	99	74	99	100	116	1.3	1.0	4.5	3.4
16	29	F	112	86	102	128	134	124	110	2.0	1.5	5.8	4.3
17	36	M	107	91	105	101	100	97	87	1.5	1.1	5.2	3.8

VC, vital capacity; FRC, functional residual capacity; TLC, total lung capacity; RV, residual volume; MBC, maximum breathing capacity; MMF, maximal mid-expiratory flow rate; Dco, steady-state diffusing capacity for carbon monoxide; R<sub>L</sub>, pulmonary resistance.

\* Postpneumectomy.

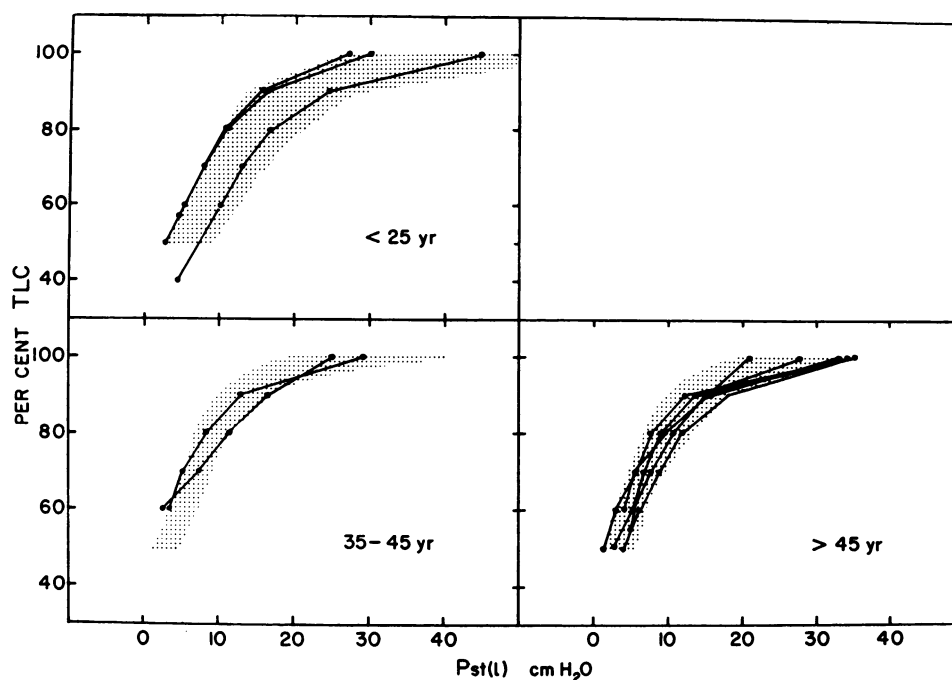


FIGURE 1 Static deflation pressure-volume curves for five bronchitic and four asthmatic subjects, divided into different age groups. The shaded area is the range of normal values given by Turner et al. (12).

$C_{dyn}(1)$  was calculated by dividing the volume change by the pressure change between points of zero flow on the tracing. Inspiratory values for 10 breaths were calculated, and the average was taken. The value was then expressed as a percentage of the static value ( $C_{st}(1)$ ).

$C_{st}(1)$  was found as the slope of the inspiratory static P-V curve over the tidal volume range. This curve was plotted by asking the subject to inflate his lungs to TLC. Then, after several tidal breaths, the airway opening was closed briefly at the end-expiratory level. As the subject inspired slowly to TLC and back to residual volume, the opening was closed repeatedly for periods of approximately 1 sec.

The maximal static  $P_L$  was found by asking the subject to inspire maximally while holding his glottis open.  $R_L$  was measured by plotting  $P_L$  against flow (obtained from a Fleisch pneumotachygraph at the mouth connected to a Sanborn 270 transducer) on a display oscilloscope to form a loop and subtracting elastic pressure until the loop was closed (10). The slope of the line was read directly by an overlying grid as the resistance. Lung volumes were measured in a volume displacement plethysmograph by the technique described by Mead (11).

Measurements of  $C_{dyn}(1)$  and  $R_L$  were repeated after two doses of isoproterenol, administered as an aerosol spray.

## RESULTS

Results obtained in the lung function tests for the three groups of subjects are given in Table I. The values shown for lung volumes are those obtained with the plethysmograph. All the normal subjects came within

20% of the predicted values for lung volumes, expiratory flow rate,  $R_L$ , and diffusing capacity. The asthmatic and bronchitic subjects also came within normal limits, except for subject Nos. 6 and 10 whose residual volume and functional residual capacity seemed abnormally high.

The static P-V curves of the bronchitic and asthmatic subjects are shown in Fig. 1. They have been subdivided into age groups, and only the expiratory curves are shown. The shaded areas indicate the predicted values for each group from the data of Turner et al. (12). The static elastic properties of all the subjects fell within normal limits. The data for the normal subjects are not illustrated, but they were also all within normal limits.

Fig. 2 shows  $C_{dyn}(1)$  expressed as a percentage of  $C_{st}(1)$  and plotted as a function of frequency for bronchitic subjects and normal subjects of a comparable age (see Table I). The numbers at the end of each line in Figs. 2-6 represent the value of  $R_L$  at the time of the measurement. Frequency dependence of compliance was demonstrated in all of the bronchitic subjects but in only one normal subject. The  $C_{dyn}(1)$  of the lungs of all the bronchitic subjects fell to less than 80% of  $C_{st}(1)$  at the highest frequency attained.

Fig. 3 shows the results of the same experiment repeated in the asthmatic subjects and the younger normal subjects. The asthmatic subjects had marked fre-

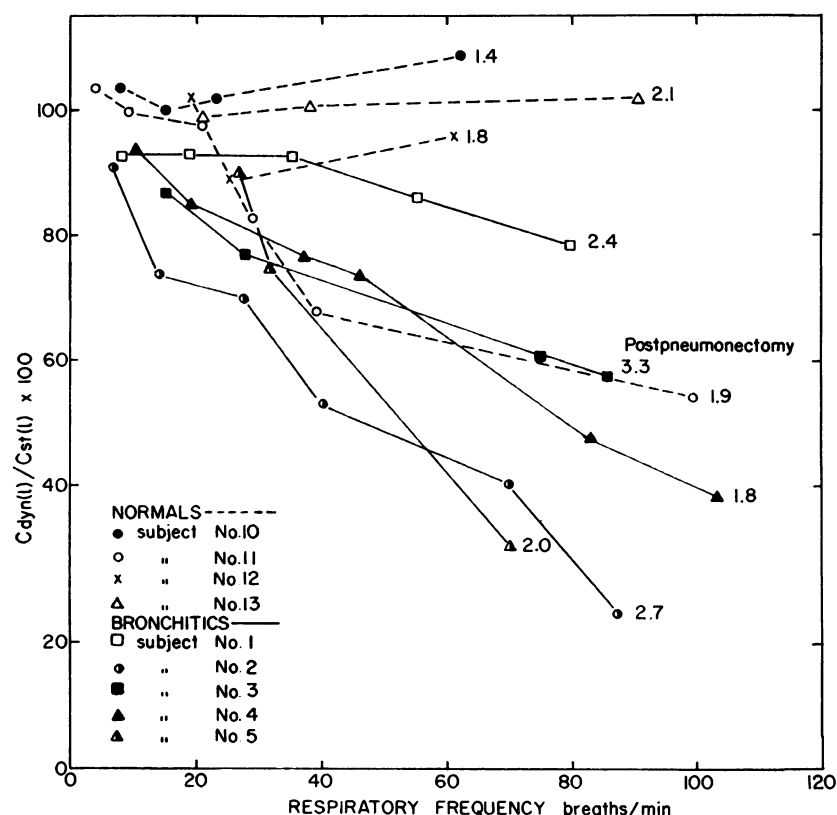


FIGURE 2 Dynamic compliance ( $C_{dyn}(1)$ ) as a percentage of static compliance ( $C_{st}(1)$ ) at different frequencies in five bronchitic subjects (—) and four normal subjects (---) of similar age. The number at the right of each graph is the value obtained for pulmonary resistance ( $R_L$ ) at the time of the study.

quency dependence. There was no overlap between the two groups.

Fig. 4 shows the individual results of the bronchitics subjects illustrated in Fig. 2, before and after isoproterenol was administered. The bronchodilator caused the degree of frequency dependence of compliance to improve in subject No. 2, while in subject Nos. 3 and 5 it was not changed. It was made worse in subjects Nos. 1 and 4, in spite of the fact that  $R_L$  (the figure given at the end of each line) decreased in all of the subjects.

Conversely, the lungs of all three asthmatic subjects given isoproterenol became less frequency dependent after therapy (Fig. 5). In no case, however, did the compliance become independent of frequency. Three of the four normal subjects of comparable age to the bronchitic subjects were also given isoproterenol. The results are shown in Fig. 5. The one subject who was frequency dependent became frequency independent and the other subjects remained unchanged. Subject No. 14 was not given isoproterenol.

Compliance as a function of frequency was measured

before, during, and after an attack of acute bronchitis in subject No. 17. The results are shown in Fig. 6.  $C_{dyn}(1)$  is expressed as a percentage of  $C_{st}(1)$ . In spite of virtually no change in  $R_L$ , the compliance of his lungs fell with increasing frequency at the time when he had a productive cough.

## DISCUSSION

Frequency dependence of compliance indicates that some regions of the lung are moving out of phase with others. At times of zero flow at the mouth, air is flowing within the lung from one region to another (6). The resulting Pendelluft will affect ventilation distribution adversely. In addition, "slow" regions will have a smaller tidal volume than the "fast" ones, which results in an additional abnormality of ventilation distribution (6). It should be stressed that under these circumstances, abnormalities of ventilation distribution will only occur at those respiratory frequencies at which compliance is significantly less than the static value. Furthermore, as Ingram and Schilder have shown the distribution will be worse as breathing frequency increases (13).

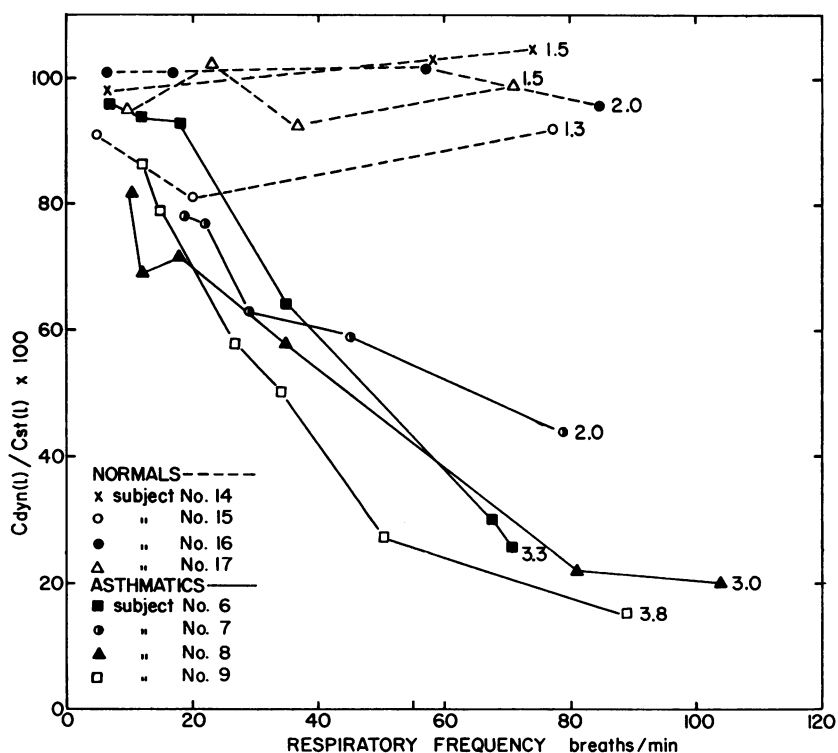


FIGURE 3  $C_{dyn}(t)$  as a percentage of  $C_{st}(t)$  at different frequencies in four asthmatic subjects (—) and four normal subjects (----) of similar age. The number at the right of each graph is the value obtained for  $R_L$  at the time of the study.

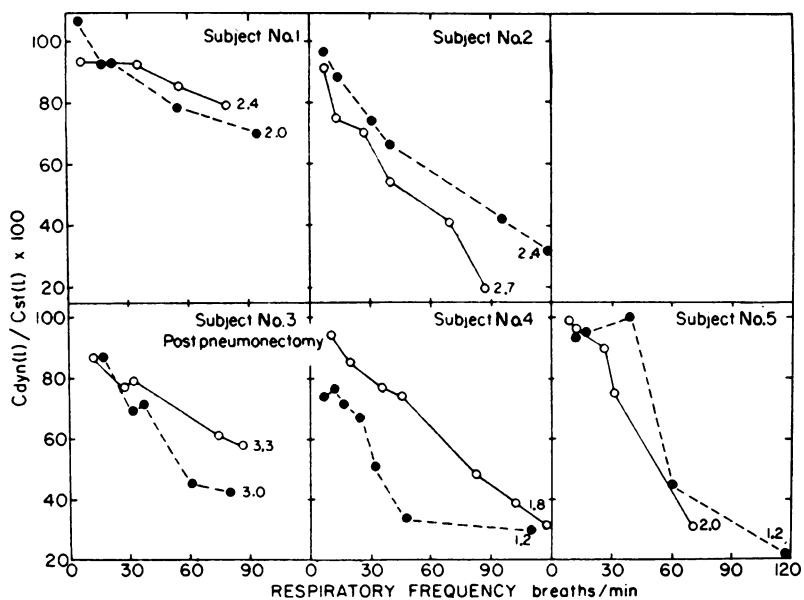


FIGURE 4  $C_{dyn}(t)$  as a percentage of  $C_{st}(t)$  at different respiratory frequencies in the bronchitic subjects before ( $\circ$ — $\circ$ ) and after ( $\bullet$ --- $\bullet$ ) bronchodilator aerosol. The number at the right of each graph is the subject's  $R_L$ .

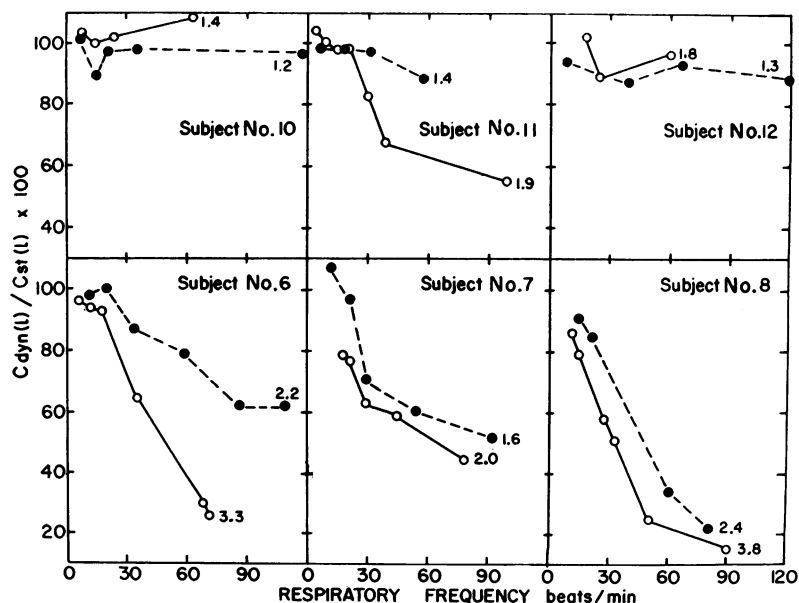


FIGURE 5  $C_{dyn}(l)$  as a percentage of  $C_{st}(l)$  at different respiratory frequencies in three of the four asthmatic subjects (lower panels) and in three normal subjects (upper panels) before (○—○) and after (●---●) bronchodilator aerosol. The number at the right of each graph is the subject's  $R_L$ .

Phase differences resulting in frequency dependence of compliance are generally thought to occur within lobes. Although this may be so in the patients we have studied, the obstruction of airways by insufflation of

beads into excised dog lobes failed to produce such phase differences.<sup>1</sup> This result was attributed to the presence of extensive collateral channels in the dog lung. In the pig collateral channels are apparently less abun-

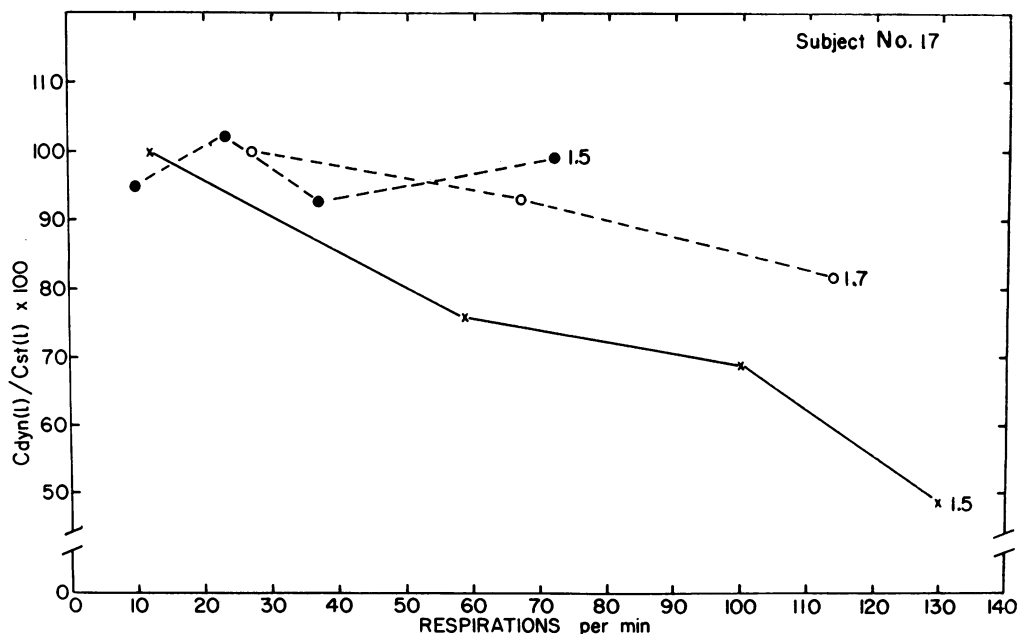


FIGURE 6  $C_{dyn}(l)$  as a percentage of  $C_{st}(l)$  at different respiratory frequencies in subject No. 17 before (●---●), during (×—×), and after (○---○) an attack of acute bronchitis. The number at the right of each graph is the subject's  $R_L$ .

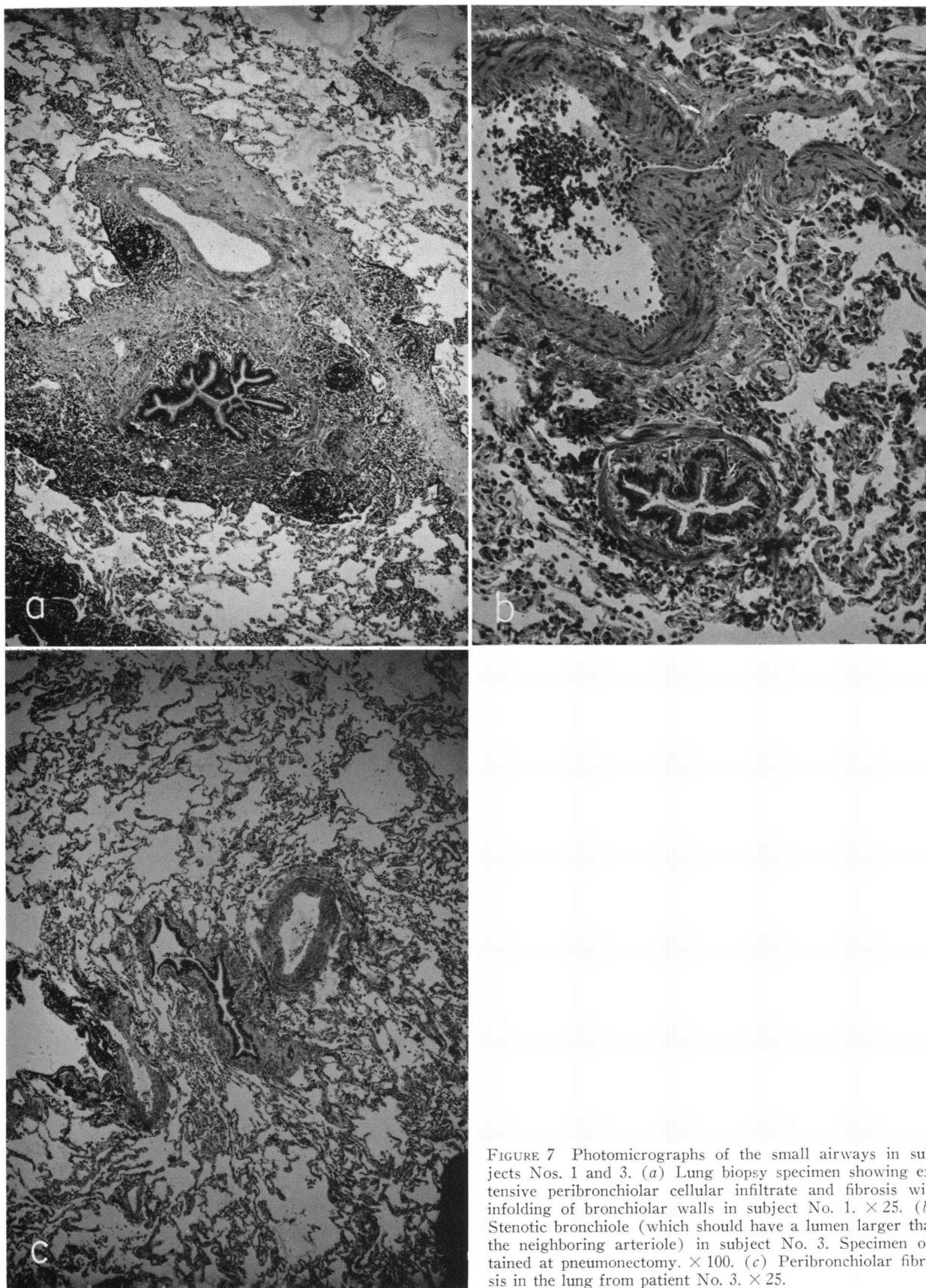


FIGURE 7 Photomicrographs of the small airways in subjects Nos. 1 and 3. (a) Lung biopsy specimen showing extensive peribronchiolar cellular infiltrate and fibrosis with infolding of bronchiolar walls in subject No. 1.  $\times 25$ . (b) Stenotic bronchiole (which should have a lumen larger than the neighboring arteriole) in subject No. 3. Specimen obtained at pneumonectomy.  $\times 100$ . (c) Peribronchiolar fibrosis in the lung from patient No. 3.  $\times 25$ .

dant, and frequency-dependent behavior was observed in this species. It appears likely that collateral ventilation in the human lung lies somewhere between that of the dog and pig. If this is true, frequency-dependent behavior within lobes of human lungs, resulting from unequally distributed airways obstruction, will depend on the rapidity of collateral ventilation. Although our experiments suggest that it is sufficiently slow in patients with obstructive airway disease, the phase differences we observed could just as well be between lobes or lungs rather than within a lobe. Phase differences might also occur between dead space and parenchyma (14).

Regardless of where the phase shifts are occurring within the lung, it is apparent that they *are* present in bronchitics and asthmatics in spite of routine lung function tests being normal or only minimally deranged. As shown in Fig. 1, these patients' lungs had normal elastic recoil.  $R_L$  was normal or slightly increased in the bronchitics, ranging from 1.8 to 2.7 cm H<sub>2</sub>O/liters per sec, except for one individual whose  $R_L$  was 3.3 cm H<sub>2</sub>O/liters per sec after pneumonectomy. This is probably a normal value for a patient with one lung. It would be difficult to prove that any of these values were abnormally high. As a group they are higher than the normal values, which ranged from 1.3 to 2.1 cm H<sub>2</sub>O/liters per sec, but the overlap is considerable. Thus, this test was not sufficiently discriminating to enable us to distinguish between the two groups. Bronchodilators reduced resistance in the bronchitic group to values ranging from 1.2 to 2.4 cm H<sub>2</sub>O/liters per sec and in the patient with one lung to 3.0 cm H<sub>2</sub>O/liters per sec. These values for the group as a whole are higher than the normals, which ranged from 1.0 to 1.6 cm H<sub>2</sub>O/liters per sec, but again there is considerable overlap. A more sensitive method of assessing  $R_L$  is to multiply it by the functional residual capacity (FRC). However, as seen in Table I there is still overlap between the bronchitics and the normals, both before and after bronchodilators. Even this test failed to distinguish clearly between the two groups.

Figs. 2-5 reveal that assessment of compliance at different breathing frequencies before and after bronchodilators does discriminate between the two groups. Compliance was frequency dependent in all bronchitics studied, falling to less than 80% of the static value at the highest respiratory rates. Bronchodilators had a variable effect on this measurement, leading to an apparent improvement in subject No. 2 but a deterioration in subject Nos. 3 and 4. In subject Nos. 1 and 5 there appears to be no significant change. In normal subjects,  $C_{dyn}(1)$  remained above 80% of  $C_{st}(1)$  in all subjects except one. Previous reports on measurements of  $C_{dyn}(1)$  as a function of frequency in "normal" subjects have noted several subjects whose lungs were fre-

quency dependent (13, 15, 16). As Ingram and Schilder (13) point out in their series, the subjects who had frequency dependence were all cigarette smokers, and it is possible that they had disease in their small airways. The frequency-dependent behavior observed in our one normal subject was reversed by bronchodilators. This subject was a nonsmoker with neither cough nor sputum. The response to bronchodilators may therefore be important in that it may distinguish between the occasional normal subject whose compliance is frequency dependent and those in whom frequency dependence reflects underlying disease.

The bronchitic group all met the three criteria we established for determining obstruction in peripheral airways, i.e., static recoil pressures and  $R_L$  were not significantly different from normal values, yet  $C_{dyn}(1)$  was frequency dependent. In subject Nos. 1 and 3, peripheral airway obstruction was proven by lung biopsy in one and pneumonectomy in the other. As shown in Fig. 7 there is inflammatory cell infiltration and fibrosis around the small airways, and the airways appear smaller than normal. These abnormalities occurring in subjects with advanced peripheral airway obstruction have been described previously (17).

Measurements of  $R_L$  and  $R_L \times FRC$  were sufficiently sensitive to distinguish between the asthmatic and the normal subjects. The asthmatic patients had the greatest degree of frequency dependence.  $C_{dyn}(1)$  fell to 25% or less of the static value at the highest frequency. Thus, the lungs were behaving as if only 25% of the parenchyma was ventilating at the most rapid respiratory rates. Although it is an oversimplification to state that the lung was behaving in this manner, the obstruction of airways must have been extremely widespread to cause such low values for  $C_{dyn}(1)$ . In the central airways such widespread obstruction would probably increase  $R_L$  markedly. Since this did not occur it seems likely, as in the bronchitics, that the peripheral airways were the site of the obstruction. Dunhill's demonstration of mucous plugging in the peripheral airways of asthmatic subjects who died from other causes supports this hypothesis (18).

Other sensitive techniques for studying lung function have revealed significant abnormalities in groups of bronchitics and asthmatics in remission who were similar to the subjects in the present study. Using radioactive xenon, Anthonisen et al. (19) demonstrated regional abnormalities of ventilation-perfusion ratios ( $\dot{V}_A/\dot{Q}$ ) in subjects with chronic bronchitis (some of these subjects were also included in our series). Both abnormal ventilation and abnormal perfusion were demonstrated in one or more of six zones of the lung in all the subjects they studied. The abnormal zones were not uniform in that there were large variations in  $\dot{V}_A/\dot{Q}$



within zones as well as between zones. This finding is quite compatible with peripheral airway obstruction. In fact, Anthonisen et al. (19) concluded that it was the most likely explanation of their data.

Radioactive xenon techniques have also shown abnormalities in the ventilation distribution of subjects with asthma in remission. Bentivoglio et al. (20) and Heckscher et al. (17) demonstrated abnormal regions of the lung in half the asthmatics in each series. Heckscher et al. (17) analyzed the washout curves for <sup>133</sup>xenon after rebreathing and infusion, but failed to demonstrate any intraregional variations of  $\dot{V}_A/\dot{Q}$ . This contrasted with the findings in the bronchitics. Ledbetter, Bruck, and Farhi (21) also found abnormal  $\dot{V}_A/\dot{Q}$  in asthmatics in remission. The most likely explanation of these findings in asthmatics is that within the regions of lung with lower than normal ventilation there is a general bronchoconstriction at the level of the small airways, causing phase shifts between larger regions of lung tissue than exist in subjects with chronic bronchitis. McFadden and Lyons (22) studied the response of asthmatic patients to bronchodilators and found no direct relationship between the severity of airway obstruction as determined by airway resistance and uneven ventilation as determined by nitrogen washout and frequency dependence of compliance. They showed that even when resistance had been brought into the normal range by bronchodilatation, considerable inequality of ventilation distribution persisted. They concluded that this was probably due to obstruction in peripheral airways.

Our results indicate that there is a difference between bronchitics and asthmatics in their response to bronchodilators. In the three asthmatics  $C_{dyn}(1)$  became less frequency dependent, whereas in four or five bronchitics it was unchanged or became more frequency dependent. This suggests that ventilation distribution was improved in asthmatics, a rather surprising result in view of the reports of worsening of arterial blood gas tensions in asthmatic patients after administration of an isoproterenol aerosol (23). The findings in the bronchitics suggest that bronchodilators made ventilation distribution worse. This might occur if the smooth muscle tone in small airways was acting to reduce the variations in time constants between different units, thereby reducing the phase differences between them. Bronchodilatation would then remove this protective mechanism leading to greater phase shifts and increased frequency dependence of  $C_{dyn}(1)$ .

The finding of frequency dependence of  $C_{dyn}(1)$  in an otherwise normal subject during an attack of "acute bronchitis" suggests that this illness might more aptly be named "acute bronchiolitis." If, in fact, every episode of "acute bronchitis" results in inflammation of periph-

eral airways it would not be surprising if a certain percentage of patients failed to resolve completely and went on to develop chronic inflammatory changes. It is possible that the chronic bronchitics studied in our experiments represent such a group. Because peripheral airways must be severely obstructed before an increase in  $R_L$  is readily detectable, such a disease might smoulder for years before dyspnoea or symptoms other than a chronic cough and sputum production become apparent. Yet because ventilation distribution is affected, gas exchange is presumably abnormal as well, particularly during rapid respiration such as may occur in exercise. This statement must be made tentatively, as we have been unable to find any reported measurements of gas exchange made in patients similar to ours during exercise. The idea, however, has some intriguing implications. Abnormalities in ventilation distribution and gas exchange might preexist the onset of dyspnoea and the increase in  $R_L$  by years. There is strong evidence both from our own experiments and those of Anthonisen et al. (19) that this is the case.

A reasonable question to ask is whether or not the disease is irreversible at this stage and whether progression may be prevented? If so, will it prove necessary to treat a large segment of the population in order to prevent end-stage disease in a few? The answers to these questions may prove difficult to obtain but they are of obvious importance. Indeed, a new approach to the management and control of chronic airway obstruction is possible if the diagnosis can be established at an earlier stage. Although the use of radioactive gas techniques (19) and the measurement of  $C_{dyn}(1)$  as a function of respiratory rate appear to be satisfactory for this purpose, neither method is suitable for wide-scale studies. The development of a simple, accurate test to detect these abnormalities is urgently needed.

## ACKNOWLEDGMENTS

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