Mucociliary transport in trachea of patients with cystic fibrosis

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Yeates, D. B., Sturgess, J. M., Kahn, S. R., Levison, H., and Aspin, N. (1976).
Archives of Disease in Childhood, **51**, 28. **Mucociliary transport in trachea of
patients with cystic fibrosis.** Mucociliary tracheal transport rates were measured
in 20 patients with cystic fibrosis, in whom these rates ranged from 0 to 12·8 mm/min.
The patients were divided into 3 roughly equal groups on the basis of their transport
rates. (1) Those in whom no abnormality in mucociliary transport was detected in the
trachea; (2) those in whom normal transport rates were measured but in whom
abnormalities such as cessation, or reversal of bolus movement were observed; (3)
those in whom no normal transport rates were observed. In the first group the rates
were similar to those observed in a population of healthy adults. These normal rates
were observed in some patients who had a productive cough. The mean mucociliary
tracheal transport rate increased with increasing maximum midexpiratory flow. Those
patients with a low Shwachman score and poor arterial oxygen tension tended to fall
into groups 2 and 3. In the ciliary dyskinesia assay in rabbit trachea the serum from
the patients with the higher transport rates tended to initiate more rapid discharge
of material from the epithelium and ciliary dyskinesia.

A defect in the mucociliary transport mechanism
has been implicated in the pathogenesis of lung
disease in cystic fibrosis (CF). This hypothesis has
resulted from several observations. Patients with
CF secrete more mucus than normal subjects, as
indicated by gland hypertrophy (Zuelzer and New-
ton, 1949; Reid and de Haller, 1967; Esterly and
Oppenheimer, 1968), and frequently retain secre-
tions in the lung (Zuelzer and Newton, 1949;
Esterly and Oppenheimer, 1968). This mucus has
been reported to have altered biochemical (Mat-
thews *et al.*, 1963; Potter *et al.*, 1963) and rheological
(Denton, 1960) properties. While the physio-
chemical properties of mucus are altered in lung
disease, little difference has been shown in histo-
chemical (Lamb and Reid, 1972) or rheological
(Sturgess and Reid, 1969; Charman and Reid,
1972; Feather and Russell, 1970) studies between
mucus from patients with CF and patients with
other hypersecretory conditions such as chronic
bronchitis or bronchiectasis. A factor in the serum

of CF patients inhibits normal ciliary activity in
explants of ciliated epithelium (Spock, Heick, and
Logan, 1967; Conover *et al.*, 1973). In addition,
poor mucociliary transport could result from infec-
tion (Camner, Jarstrand, and Philpson, 1973a, b;
Sakakura *et al.*, 1973) which damages human ciliated
epithelium in culture (Hoorn and Tyrrell, 1966).
Recent studies report conflicting results regarding
the transport of particles from the lungs of CF
patients (Sanchis *et al.*, 1973; Thomson *et al.*, 1974;
Wood, Wanner, and Hirsch, 1974).

This study was designed to determine whether an
abnormality in mucociliary transport was present in
the trachea of CF patients and to investigate whether
the measured transport rates were related to the
ciliary dyskinesia factor in their serum.

Methods

Mucociliary tracheal transport rates (MTTRs) were
measured on 20 CF patients (12 males, 8 females) aged
11–20 years. Informed consent to perform these
studies was obtained both from the patients and their
parents. The experimental protocol was approved by

the Human Experimentation Committee at the University of Toronto. MTTR was measured by two methods: 4 subjects were measured in the upright position and 18 in the supine position.

MTTRs. The first group of patients was studied in the upright position using the method of Yeates *et al.* (1975). By this method an aqueous aerosol containing albumin microspheres ($0·5 \mu m$ count median diameter) labelled with ^{99}Tcm (Yeates, Warbick, and and Aspin, 1974a) was inhaled so that it was deposited in local concentrations in the large airways. 15 minutes before the study each subject was given potassium perchlorate (8 mg/kg) to inhibit the uptake of free pertechnetate by the thyroid gland. The bolus of radioactive microspheres was transported up the trachea and its position recorded with a gamma camera. The MTTR of each bolus was determined from these measurements.

In the second group of patients, MTTR was measured in the supine position using a scanning scintillation probe. The patients inhaled the labelled aerosol as described by Yeates *et al.* (1975) until a pair of scintillation probes positioned behind the subject's lungs indicated that sufficient radioactivity had been deposited. Then the subject immediately washed his mouth with water and lay on his back under the scintillation probe. The position of the trachea with respect to the scanner was determined using a point source of radioactivity placed over the carina (position determined from a chest x-ray) and the larynx. The alignment of the subject with respect to the probe was checked at regular intervals using markers on the subject's skin and on the scanning probe. To ensure that the activity measured by the probe was in the trachea and not in the oesophagus the subject was asked to drink water at regular intervals. The probe, which had a parallel slit collimator, scanned back and forth along the trachea at a rate of 19 cm/min. The activity measured by this probe was recorded using a rate meter connected to a chart recorder. The time of occurrence and the forcefulness of every cough was recorded. Each subject was scanned for a period of 2 hours.

The position of each radioactive bolus in the trachea was plotted as a function of time and the transport rate determined using the method of least squares fit. A significant MTTR resulted when the position of the bolus was measured on at least four tracings of the profile of the radioactivity over the trachea. These must also represent movement of the bolus over at least $2·5$ cm of the trachea or observation of the bolus for at least 15 minutes in time. Transport rates were analysed only during periods when the patient did not cough. An abnormal MTTR was defined as one which was zero or negative. When calculating the average MTTR a negative value was considered as a zero transport rate.

Clinical history. The following data were recorded for each subject: Shwachman score, chest x-ray, extent of cough and sputum production, and assessment of clinical condition at the time of the study together with the lung history over the past 2–5 years. Before each study static lung volumes were measured by plethysmography (DuBois *et al.*, 1956), functional residual capacity, and total lung capacity, and maximal midexpiratory flow (MMEF) by water spirometry. Oxygen tension (Pao_2) and carbon dioxide tension ($Paco_2$) were measured in duplicate specimens of arterialized capillary blood 10 minutes after the application of a vasodilator cream. Sputum cultures were made before and after the study.

Serum factor assay. Blood samples were collected from 14 patients about one year after completion of the MTTR study. The serum was separated and assayed for the ciliary dyskinesia factor using the method of Spock, Heick, and Logan (1967) as modified by Conover *et al.* (1973). These sera were measured in such a way that the observer was not aware of the magnitude of each patient's MTTR.

Explants of rabbit tracheal epithelium were incubated in tissue culture medium at 37°C in 5% carbon dioxide/ 95% oxygen for 24–48 hours. Each explant was incubated with $0·2$ ml serum from a CF patient or from a control subject. The amount of the discharge of material from its surface and the alterations in ciliary activity were recorded at 5-minute intervals over a period of 35 minutes.

Results

The patients' MTTRs, lung function tests, and results of serum factor assays are shown in the Table. The patients are listed according to their transport rates, the mean MTTRs ranging from 0–12·8 mm/min. The patients are divided into three roughly equal groups: (1) those in whom no abnormal transport rate was detected (Cases 1–10), (2) those in whom positive tracheal transport rates were measured but who also showed abnormalities such as a radioactive bolus residing at one spot in the trachea for more than 15 minutes or a bolus moving distally in the trachea (Cases 11–16b), and (3) those in whom no normal tracheal transport was observed (Cases 16a–20). Cases 3 and 16 who had repeated tests one year apart, gave similar results on both. Of the patients with the three fastest rates, Cases 2 and 3 had essentially normal values of all parameters measured and did not cough up any mucus, and Case 1, though his values were below normal, had normal results in his function tests at other times. It was remarkable that in Cases 4–8 and 10, who had productive coughs normal MTTRs were measured. In some patients the boli remained stationary or slid slowly backwards in the trachea, but were cleared subsequently by coughing.

The clinical factor with the highest correlation to mean MTTR was the MMEF ($0·1 < P < 0·5$).

Clinical data, lung function, MTTRs,

Case no.	Age (yr)	Shwachman score	MMEF (% predicted	FRC/ TLC (%)	Paco₂ (mmHg)	Pao₂ (mmHg)
1	11	85	46	47	38	76
2*	15	80	124	37	38	90
3*a	12	95	137	45	36	81
3b	13	95	88	47		
4	18	80	13		42	66
5	14	80	49	25		
6	16	65	18	38	40	71
7	16	80	116		35	89
8	16	50	51	30	43	57
9	13	95	67	27		
10	12	80	52	48	40	83
11	20	45	23	31	44	59
12	15	30	8	140	40	57
13	13	75	19	56	43	67
14	19	45	14	43	38	59
15	15	50	9	39	43	68
16a*	16	80	66	49	39	74
16b	17	80	41	40	38	68
17*	14	40	13	58	40	68
18	16	85	27	54	34	70
19	13	80	84	37	39	83
20	17	70	41	52	40	63

Note: The rates are given in the order in which they were measured
a and b refer to the 1st and 2nd studies which were conducted one year apart.
Numbers in parentheses are rates of transport of the same bolus.
*Studies conducted in the upright position.
†Refers to the transport rate of the least squares fit through all points contributing to the rates in the preceeding brackets.
FRC/TLC, functional residual capacity/total lung capacity.

and results of serum assay

Chest x-ray	Sputum	Transport rates (mm/min)	Average transport rates (mm/min)	Start of discharge (min)	Start of dyskinesia (min)
Mild peribronchial thickening	0	12·8	12·8	10	15
Minimal peribronchial infiltration	0	10·4	10·4	5	10
Mild peribronchial thickening	0	10	10		
As above	0	2·2, 1·7	2·0		
Moderate interstitial changes, subsegmental atelectasis, peribronchial thickening, and air trapping	+	5·3, 5·8	5·6	—	—
Moderate patchy consolidation, bronchial thickening, and air trapping	+	5·3, 4·4, 7·2, 3·4	5·1	5	10
Moderate bronchial thickening, patchy consolidation, emphysema	+	6·3, 4·8 4·6, 4·5, 4·1, 5·1	4·9	10	15–20
Mild peribronchial thickening and air trapping	+	4·5, 3·3, 3·1	3·6		
Marked peribronchial thickening, patchy consolidation, and air trapping	+ + +	4·6, 2·3	3·5	10	10
Minimal thickening of bronchovascular markings	0	1·7, 1·0, 1·2	1·3	10–15	25
Moderate emphysema, peribronchial thickening	+ +	4·8, 1·1 1·9, 0·8 1·9, 1·2	2·0	5	10
Severe changes of CF, diffuse bronchiectasis, patchy consolidation	+ + +	7·9, 1·1, 0	3·0	10	15
Severe changes; extensive bronchiectasis, peribronchial thickening, patchy atelectasis, emphysema	+	(13·7, 1·8), 11·4, 11·8 −0·3, 3·3†	6·6		
Moderate patchy infiltration and air trapping	+ +	3·2, (2·0, −0·8) 0·32†	1·8		
Moderate bronchial wall thickening, patchy atelectasis, and air trapping	+ +	1·60, 0, 4·3	1·5	15	20–25
Moderate emphysema, widespread peribronchial thickening, and patchy atelectasis	+ + +	0, (4·9, 0), −1·6, 1·3†	0·4		
Mild emphysema, peribronchial thickening, and patchy atelectasis	+	0	0		
As above	+	(0·9, 0, −0·9), −0·9, 0†	0		
Bronchial wall thickening, patchy atelectasis, air trapping	+ +	0	0	10	15
Moderate peribronchial thickening, and patchy infiltration	0	0	0	15	20
Mild peribronchial thickening, and patchy atelectasis	+	0·−0·8	0	20	20
Moderate patchy atelectasis and increased bronchovascular markings	+	0	0	5	10

Those patients with a higher arterial oxygen tension and Shwachman score tended to have faster transport rates. Very little correlation could be detected between the rates and the other clinical parameters.

The sera from 14 patients in this study, except from Case 4, gave a positive reaction in the rabbit tracheal assay. After incubation with the CF serum, the discharge of material from the surface of the explant was followed by ciliary dyskinesia and finally complete loss of ciliary activity. The earliest time at which discharge of material was detected was between 5 and 20 minutes after incubation with different sera, whereas the earliest alterations in ciliary activity occurred between 10 and 20 minutes. In general the sera from which the earliest response was observed resulted in a more rapid course of events. There appeared to be a relation between the transport rates and the times at which changes occurred in the assay (Table). With the higher transport rates, there was an early response both in discharge of material $(0 \cdot 2 < P < 0 \cdot 3)$ and in ciliary dyskinesia $(0 \cdot 2 < P < 0 \cdot 3)$.

Discussion

The wide variation in tracheal transport rates from normal to abnormal observed in this study is consistent with the wide variation in the severity of the clinical manifestations of this disease. The distribution of mean MTTRs in CF patients in whom no abnormalities in tracheal transport were detected (group 1) is similar to that of a population of healthy adults despite the fact that some of these patients habitually coughed and produced purulent sputum. The mean MTTR of these studies was $6 \cdot 6$ mm/min compared to a mean of $4 \cdot 7$ mm/min for the healthy adult population (Yeates et al., 1974b) and both populations had a similar range in transport rates $0 \cdot 85$–$12 \cdot 8$ mm/min). In group 2 were patients who had one or two fast transport rates together with some slow rates (especially Cases 11 and 12). This suggests that their intrinsic rate of transport may have been similar to those of group 1 but was slowed down in certain areas of the trachea either by localized alterations in the ciliated epithelium or in the mucus blanket. In the third group of patients where no positive transport rates were observed, coughing was the major clearance mechanism from the trachea. Cough was not effective as a clearance mechanism in the trachea of healthy adults (Yeates et al., 1975).

As a result of hypersecretion of mucus the mucociliary transport rates in CF patients might be expected to be more rapid than in healthy subjects. This tendency towards rapid MTTRs was evident in Cases 1, 2, 3, 12, and 13. However, Case 9 who had normal pulmonary function and Shwachman score produced no sputum and had a slow transport rate. This was in contrast to Case 18 who had no cough or sputum but had severe lung disease and showed no measurable transport rates.

There were a number of factors which could have contributed to the apparent discrepancy between these results of mucociliary transport and those of Sanchis et al. (1973), Thomson et al. (1974), and Wood et al. (1974). Each group of investigators have used a different tracer of mucociliary activity and therefore may have observed different physiological processes. The results of the first two studies (Sanchis et al., 1973; Thomson et al., 1974) showed an increased tracheobronchial clearance compared to healthy adults which can be attributed not only to normal clearance, but to more proximal deposition of labelled particles, and to coughing.

Using a fibreoptic bronchoscope, Wood et al. (1974) measured the rate of transport of $0 \cdot 68$ mm teflon discs up the trachea. They reported that CF patients had slower tracheal transport rates than healthy subjects studied by this method. It must be emphasized that the clearance rates in the small airways where the pulmonary disease in CF is first evident cannot be inferred from measurements made in the trachea or large airways. However the results reported here indicate that there is not a general mucociliary defect throughout the respiratory tract in all CF patients.

The fact that most of these studies were conducted in the supine position is not expected to significantly influence the findings. The 2 patients studied twice gave similar results in both the upright and supine positions. The slower transport rate in Case 3 in the supine position, may have been due to the fact that she had recently had tracheitis. A healthy adult subject studied in the supine and upright positions gave similar MTTRs in both studies. The effects of posture on mucociliary transport in health and disease require further investigation.

The results suggest that a higher serum factor activity is associated with faster MTTRs. This is contrary to the expectation that derangement in ciliary activity should result in decreased mucociliary function. In the rabbit trachea explant, the discharge of material preceding ciliary dyskinesia leads to the speculation that this discharge might be related to mucus secretion and be the more important of the two effects. The relevance of the relation between hypersecretion and increased transport rates in the human respiratory tract requires further investigation.

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