Right and left ventricular performance in ambulatory young adults with cystic fibrosis*

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SUMMARY Although cystic fibrosis is noted primarily for pronounced abnormalities in pulmonary function, a substantial number of patients die as a result of cardiac complications. Nevertheless, little is known about cardiac performance in this disease. The cardiac pathophysiological consequences of cystic fibrosis were investigated non-invasively by measuring right and left ventricular performance using radionuclide angiocardigraphy. Studies were performed in 22 ambulatory young adults with cystic fibrosis and clinically evident pulmonary disease. Right ventricular ejection fraction was abnormal ($<45\%$) in nine patients, while left ventricular ejection fraction was normal ($\geq 55\%$) in all 22 patients. Within one year of radionuclide evaluation, four patients with depressed baseline right ventricular function developed acute cor pulmonale and died. The presence of abnormal right ventricular performance was related to the severity of cystic fibrosis. Arterial oxygen tension, forced expiratory volume in one second, and forced vital capacity were significantly less in patients with abnormal right ventricular ejection fraction than in those with normal function. All six patients with severe disease (Schwachman clinical score ≤ 40) had abnormal right ventricular ejection fraction, while none of 10 with good to excellent scores had abnormal right ventricular function. Radionuclide angiocardigraphy allows non-invasive detection of right ventricular dysfunction at a time when it would not be appreciated by conventional clinical methods. This approach provides pathophysiological insights into the haemodynamic abnormalities associated with this disease and may also allow the response to treatment to be monitored.

Cor pulmonale and respiratory failure are common in cystic fibrosis, particularly at the time of death.¹⁻⁸ Unfortunately, right ventricular hypertrophy and right heart failure frequently are difficult to identify before overt cardiopulmonary decompensation.^{5 6 9-11} Because of a lack of accurate non-invasive techniques, the relation between the severity of cystic fibrosis and right and left ventricular performance has not been determined. In fact, relatively little is known about the early pathophysiological abnormalities in cardiac performance which commonly are undetected before the development of cor pulmonale.

Non-invasive techniques suitable for the study of cardiac performance are needed for assessment of functional status in patients with cystic fibrosis. Echocardiography previously has been used to measure right ventricular wall thickness and cavity dimensions.⁹⁻¹¹ However, this technique is limited theoretically by geometric assumptions not necessarily appropriate for the right ventricle and technically by difficulties encountered in studying patients with thoracic hyperinflation caused by lung disease. Quantitative radionuclide angiocardigraphy is an alternative non-invasive method which allows evaluation of both right and left ventricular ejection fractions from regional radionuclide time-activity curves. This technique is free of assumptions concerning the geometric configurations of the two ventricles and technically is unaffected by the presence of concomitant lung

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disease. A previous study from this laboratory has shown that this radionuclide technique allows detection of right ventricular dysfunction before development of clinically evident cor pulmonale in patients with chronic bronchitis and emphysema.¹² In addition, intravenous aminophylline has been found to improve biventricular performance determined by this technique in the same patient population.¹³ This radionuclide method has also been used to evaluate a broad spectrum of patients with coronary and congenital heart disease.¹⁴⁻¹⁸ The present report describes the application of quantitative radionuclide angiography to the assessment of right and left heart performance in cystic fibrosis.

Patients and methods

PATIENT SELECTION

Twenty-two young adults (13 male and nine female) with cystic fibrosis were included in this study. The mean age was 20 years (range 14 to 27 years) and all had clinically apparent pulmonary disease. The diagnosis was established from conventional clinical findings and sweat electrolyte tests.² The severity of cystic fibrosis was assessed, without knowledge of cardiac or pulmonary function data, by one investigator (TD) using the Schwachman clinical scoring system.² Briefly, this system assigns a maximum of 25 points to each of four categories: general activity, physical examination, nutrition, and chest radiograph. The grading system is divided as follows: severe (≤ 40 points), mild to moderate (41 to 70 points), and good to excellent (71 to 100 points). According to these criteria, six patients were severe, six were mild to moderate, and 10 were good to excellent. All patients were ambulatory and fully compensated without evidence of right or left heart failure.

At the time of entry into the study, a radionuclide angiogram, pulmonary function tests, arterial blood gases, and a 12 lead electrocardiogram were obtained. Three patients (cases 7, 10, and 16) refused arterial blood gas tests. All patients were followed clinically for at least two years or until death. Informed consent was obtained from each patient or, if necessary, from a parent, according to procedures established by the Human Investigation Committee of Yale University School of Medicine.

RADIONUCLIDE TECHNIQUE

Patients were studied supine in the anterior position using a computerised multicrystal scintillation camera (Cordis-Baird System-77, Bedford, Massachusetts). Twenty mCi technetium-99m per tech-

netate were injected in the right antecubital vein. The initial transit of radioactivity through the central circulation was recorded at 20 frames/second for approximately 25 seconds. Right ventricular and left ventricular ejection fractions were determined in a standardised and reproducible manner from quantitative radionuclide angiograms using techniques developed and validated in this laboratory.¹²⁻¹⁴ Individual ejection fractions from each ventricle are obtained readily with this technique, since there is anatomical and temporal separation of the radionuclide bolus as it traverses the central circulation. The multicrystal camera as present commercially available allows accumulation of high count rate data (up to 450 000 counts/s) without dead-time losses, such that statistical uncertainty is minimised. In 50 normal subjects without cardiopulmonary disease, right ventricular ejection fraction was 55 ± 5 per cent (mean ± 1 SD).¹² The normal range, expressed as the mean ± 2 standard deviations, was 45 to 65 per cent. Normal left ventricular ejection fraction is 55 per cent or more.

PULMONARY FUNCTION TESTS AND ARTERIAL BLOOD GASES

Forced expiratory volume in one second and forced vital capacity were measured using a computerised flow-volume system.¹⁹ Data were also expressed as a percentage of predicted value based upon age and sex.²⁰ Arterial blood gases were obtained while patients were breathing room air.

STATISTICAL DATA

Data are expressed as the mean $\pm$ standard error. Comparisons between two groups were made by Student's *t* test and between three groups by analysis of the variance (*F* test) using conventional techniques.²¹

Results

Right ventricular ejection fraction was abnormal ($< 45\%$) in nine patients (range 39 to 44%) and normal in the remaining 13 patients (range 49 to 64%) (Table, and Fig. 1). Left ventricular ejection fraction was normal in all 22 patients, with a range of 56 to 80 per cent. During the first year of follow-up, four patients (cases 1, 2, 4, and 6) developed cor pulmonale with acute respiratory failure²² and right-sided heart failure. One additional patient (case 7) developed acute respiratory failure without right-sided heart failure. Right ventricular ejection fraction determined six to 12 months (mean eight months) before clinical decompensation was moderately abnormal in all five cases (range 39 to

44%). All four patients with cor pulmonale subsequently died as a result of cardiorespiratory failure. Necropsy data were available in two patients (cases 1 and 4), and both had evidence of right ventricular hypertrophy and dilatation.⁶⁻²³ The left ventricle was normal in both cases. No other patient in the study died within the follow-up period. Of the 22 patients in the study, only two patients (cases 4 and 6) had electrocardiographic evidence of right ventricular hypertrophy²⁴ (right ventricular ejection fractions, 39 and 41%). At the time of data analysis, four patients (cases 3, 4, 9, and 11) have radionuclide evidence of right ventricular dysfunction but are clinically stable. None of these four patients or the 13 with normal right ventricular ejection fraction have signs or symptoms of cor pulmonale.

The presence of right ventricular dysfunction was related to the severity of cystic fibrosis as determined by the Schwachman clinical score. Right ventricular ejection fraction was 42 ± 1 per cent (mean $\pm$ SEM) in patients with severe cystic fibrosis, compared with 49 ± 3 per cent in those with mild to moderate clinical scores, and 56 ± 2 per cent in those with good to excellent scores ($p < 0.001$ for between group means) (Fig. 2). All six patients with severe disease had abnormal right ventricular ejection fraction (range 39 to 44%), while none of 10 with good to excellent scores had

Fig. 2 Right ventricular ejection fraction compared with Schwachman clinical score in 22 patients with cystic fibrosis. Right ventricular ejection fraction is abnormal ($< 45\%$) in all six patients with a Schwachman score ≤ 40 , in three of six with a score of 41 to 70, and in none of 10 with a score of > 70 . The differences between groups were significantly greater than within groups ($p < 0.001$). N, number of patients; SE, standard error of the mean.

Fig. 1 Left ventricular (LV) and right ventricular (RV) ejection fraction in 22 patients with cystic fibrosis. RV ejection fraction is abnormal ($< 45\%$) in nine, while LV ejection fraction is abnormal ($< 55\%$) in none. N, number of patients.

abnormal right ventricular function (range 49 to 64%). In addition, three of six with mild to moderate cystic fibrosis also had abnormal right ventricular function. When approached in an alternative way, patients with abnormal right ventricular ejection fraction had a Schwachman score of 42 ± 4 points, which was significantly less than in those with normal right ventricular function (73 ± 3 points, $p < 0.001$).

Arterial oxygen tension was significantly less in patients with abnormal right ventricular ejection fraction than in those with normal function (45 ± 2 vs. 73 ± 3 mmHg, $p < 0.001$) (Fig. 3). All eight patients with severe arterial hypoxaemia (oxygen tension ≤ 50 mmHg) had abnormal right ventricular ejection fraction (range 39 to 44%). Similarly, arterial carbon dioxide tension was significantly greater in patients with abnormal right ventricular ejection fraction than in those with normal function (46 ± 4 vs. 35 ± 1 mmHg, $p < 0.01$). All five patients with hypercapnia (carbon dioxide tension ≥ 45 mmHg) had abnormal right ventricular ejection

fraction (range 39 to 44%) (Table).

Forced expiratory volume in one second was 32 ± 5 per cent of predicted in patients with abnormal right ventricular performance, compared with 68 ± 6 per cent of predicted in those with normal ejection fraction ($p < 0.01$) (Fig. 4). Seven of nine patients with abnormal right ventricular ejection fraction demonstrated a forced expiratory volume in one second less than 35 per cent of predicted and less than 1 litre, indicative of pronounced obstructive ventilatory impairment (Table). Forced vital capacity was 46 ± 7 per cent of predicted in patients with depressed right ventricular function, compared with 84 ± 6 per cent of predicted in those with normal ejection fraction ($p < 0.001$).

Discussion

This non-invasive study has evaluated right and left heart performance in cystic fibrosis and defined the pathophysiological relation between compromise in right ventricular performance and disease severity. Right ventricular dysfunction was present in nine of 22 ambulatory young adults with cystic fibrosis and clinical evidence of pulmonary disease. An abnormal right ventricular ejection fraction was noted in all six with severe disease, in three of six with mild to moderate disease, and in none of 10 with good to excellent Schwachman score. Presence

Fig. 3 Arterial oxygen tension in 19 patients with cystic fibrosis. Arterial oxygen tension is significantly lower in patients with an abnormal right ventricular ejection fraction (RVEF) than in those with a normal right ventricular ejection fraction. Arterial oxygen tension is ≤ 50 mmHg in all patients with an abnormal right ventricular ejection fraction and in none with a normal right ventricular ejection fraction. N, number of patients; SE, standard error of the mean; p, probability.

Table Clinical characteristics, pulmonary function data, and radionuclide ventricular performance data

Case no.	Age (y) and sex	Schwachman clinical score	Arterial blood gases			Pulmonary function tests					Radionuclide data	
			pH	PCO ₂	PO ₂	FEV ₁ (litres)	FEV ₁ (% pred.)	FVC (litres)	FVC (% pred.)	FEV ₁ /FVC (%)	LVEF (%)	RVEF (%)
1	22 F	25	7.35	56	50	0.93	30	1.83	52	51	69	44
2	21 F	33	7.46	55	40	0.65	24	0.98	32	66	67	44
3	18 M	36	7.47	39	50	0.80	20	0.88	20	91	66	42
4	25 M	37	7.38	57	35	0.50	13	1.45	33	35	80	39
5	21 F	40	7.40	47	50	0.75	24	1.98	56	38	63	42
6	23 F	40	7.40	54	44	0.66	23	0.91	27	73	72	41
7	17 M	44	—	—	—	0.90	32	1.29	42	70	71	41
8	23 F	49	7.41	40	53	0.78	27	1.63	49	48	63	55
9	18 M	57	7.46	36	46	2.65	59	3.49	67	76	74	43
10	17 M	65	—	—	—	1.50	43	2.15	54	70	56	55
11	17 M	65	7.46	24	44	2.50	59	4.00	81	63	70	44
12	21 M	68	7.46	30	71	3.33	74	4.53	86	74	72	54
13	14 F	71	7.45	32	74	1.05	51	1.54	71	68	70	52
14	15 F	72	7.43	35	78	2.20	75	3.09	97	71	70	64
15	17 M	72	7.46	37	76	2.35	69	3.35	91	70	63	54
16	19 M	76	—	—	—	2.95	67	4.50	87	66	80	52
17	25 F	77	7.46	30	63	1.68	54	2.25	62	75	71	60
18	27 F	78	7.44	34	67	1.96	63	3.10	86	63	73	57
19	17 M	79	7.49	35	76	4.16	92	4.83	92	86	66	52
20	15 M	79	7.41	43	81	2.96	89	3.80	100	78	57	55
21	20 M	83	7.49	35	69	3.16	73	4.52	91	70	66	62
22	20 M	86	7.44	30	95	4.84	112	6.40	128	76	57	49

Definitions of abbreviations: FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; LVEF, left ventricular ejection fraction (normal $\geq 55\%$); PCO₂, arterial carbon dioxide tension, mmHg; PO₂, arterial oxygen tension, mmHg; pred., predicted; RVEF, right ventricular ejection fraction (normal $\geq 45\%$); Schwachman clinical score: severe (0 to 40), mild to moderate (41 to 70), good to excellent (71 to 100).

of abnormal right ventricular performance was related to the severity of cystic fibrosis as assessed by Schwachman clinical score, the presence of arterial hypoxaemia and hypercapnia, and the degree of ventilatory impairment. These data suggest that in cystic fibrosis normal resting right ventricular performance is maintained in most cases until clinically severe disease is present. The abnormalities in right ventricular performance generally were not severe at the time of preclinical detection and were more modest than those noted in adult patients with long-standing chronic bronchitis.¹²

Most patients with an abnormal right ventricular ejection fraction will have a Schwachman clinical score ≤ 40 points (severe disease), arterial oxygen tension ≤ 50 mmHg, arterial carbon dioxide tension ≥ 45 mmHg, and a forced expiratory volume < 1 litre. In a cardiac catheterisation study of 34 patients with cystic fibrosis, these findings were associated with conspicuously raised mean pulmon-

ary artery pressure (≥ 38 mmHg) and severe cor pulmonale.⁵ These correlations are not surprising in view of the pathophysiology of cystic fibrosis which involves hypoventilation caused by mucous obstruction of the airways, recurrent infections, and progressive multilobar bronchiectasis. Chronic hypoxia results, leading to pulmonary artery hypertension. Since the right ventricle is highly afterload dependent, this sustained increase in afterload ultimately results in hypertrophy and failure.^{4 6 8 25-27}

Although all patients were clinically compensated at the time of the study, within one year of follow-up, five of nine patients with an abnormal right ventricular ejection fraction developed respiratory failure and four of these five died with decompensated cor pulmonale. Radionuclide angiocardigraphy allowed identification of right ventricular dysfunction at a time when it was not appreciated by conventional clinical evaluation. Even though the abnormalities in right ventricular function were not particularly obvious, they still were a harbinger of subsequent decompensation. Thus, this technique may provide potential prognostic information. This may be particularly important because overt right heart failure usually occurs late in the course of cystic fibrosis and has been found to be a warning of imminent death. Moss *et al.*²⁸ reported a median survival of less than three months once right heart failure was clinically apparent. The sensitivity of radionuclide angiocardigraphy for detection of preclinical right ventricular dysfunction in cystic fibrosis is similar to that previously reported in patients with chronic bronchitis and emphysema. Four of nine patients with severe airways obstruction and an abnormal right ventricular ejection fraction developed decompensated cor pulmonale within one year of their original study, though none died.¹²

The electrocardiogram has not been found to be a sensitive technique for determining right ventricular hypertrophy or for following patients with cystic fibrosis.^{5 9 26} Echocardiography has been applied to patients with cystic fibrosis,^{9 11 29} and mild increases in right ventricular wall thickness and cavitory diameter have been shown. However, measurements of right ventricular dimensions with M-mode echocardiography, particularly in patients with obstructive lung disease, are technically difficult and unreliable in many patients.^{9 30 31} As the severity of lung disease increases, the usefulness of this approach appears to decrease, making it a less desirable technique in this patient population.

In the present study, left ventricular performance was normal in all patients and at necropsy the left ventricle was normal in two patients dying with

Fig. 4 Forced expiratory volume in one second (FEV_1), expressed as a percentage of predicted in patients with cystic fibrosis. FEV_1 is significantly lower in patients with an abnormal right ventricular ejection fraction (RVEF) than in those with a normal right ventricular ejection fraction. N, number of patients; SE, standard error of the mean; p, probability.

decompensated cor pulmonale. These findings are in agreement with most studies in adults with severe chronic obstructive pulmonary disease.^{12 13 32-34} However, there are isolated reports of left ventricular hypertrophy and mild functional impairment in cystic fibrosis.^{9 35 36}

Studies from this laboratory have established the value of radionuclide angiocardigraphy for assessing the response to treatment in obstructive lung disease. After aminophylline infusion, significant increases in right and left ventricular ejection fractions have been shown in patients with chronic bronchitis and emphysema.¹³ With a similar technique, others have shown that right ventricular performance improves with chronic oxygen treatment.³⁷ Clinical trials of similar therapeutic regimens in cystic fibrosis have been hindered by a lack of sensitive, reliable, and non-invasive means of quantifying right ventricular performance. Radionuclide angiocardigraphy may provide a means, in addition to conventional clinical methods, for selecting appropriate patients with cystic fibrosis for treatment and for following their haemodynamic responses.

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References

- ¹Royce SW. Cor pulmonale and early childhood. Report on 34 patients with special reference to the occurrence of pulmonary heart disease in cystic fibrosis of the pancreas. *Pediatrics* 1951; **8**: 255-74.
- ²Schwachman H, Kulczycki LL. Long-term study of 105 patients with cystic fibrosis. *Am J Dis Child* 1958; **96**: 6-15.
- ³Golding RM, Fishman AP, Turino GM, Cohen HI, Derming CR, Andersen DH. Pulmonary hypertension and cor pulmonale in cystic fibrosis of the pancreas. *J Pediatr* 1964; **65**: 501-24.
- ⁴di Sant'Agnese PA, Talamo RC. Pathogenesis and physiopathology of cystic fibrosis of the pancreas (concluded). Fibrocystic disease of the pancreas (mucoriscidosis). *N Engl J Med* 1967; **277**: 1399-408.
- ⁵Siassi B, Moss AJ, Dooley RR. Clinical recognition of cor pulmonale in cystic fibrosis. *J Pediatr* 1971; **78**: 794-805.
- ⁶Ryland D, Reid L. The pulmonary circulation in cystic fibrosis. *Thorax* 1975; **30**: 285-92.
- ⁷Fink RJ, Doershuk CF, Tucker AS, Stern RC, Boat TF, Matthews LW. Pulmonary function and morbidity in 40 adult patients with cystic fibrosis. *Chest* 1978; **74**: 643-7.
- ⁸di Sant'Agnese PA, Davies PB. Cystic fibrosis in adults: 75 cases and a review of 232 cases in the literature. *Am J Med* 1979; **66**: 121-32.
- ⁹Liebman J, Lucas RV, Moss A, Rosenthal A. Cor pulmonale and related cardiovascular effects of cystic fibrosis. In: Mangos JA, Talamo RC, eds. *Cystic fibrosis: projection into the future*. New York: Stratton International Book Corporation, 1976: 41-80.
- ¹⁰Rosenthal A, Tucker CR, Williams RG, Khaw KT, Strider D, Schwachman H. Echocardiographic assessment of cor pulmonale in cystic fibrosis. *Pediatr Clin North Am* 1976; **23**: 327-44.
- ¹¹Ryssing E. Assessment of cor pulmonale in cystic fibrosis by echocardiography. *Acta Paediatr Scand* 1977; **66**: 753-6.
- ¹²Berger HJ, Matthay RA, Loke J, Marshall R, Gottschalk A, Zaret BL. Assessment of cardiac performance with quantitative radionuclide angiocardigraphy: right ventricular ejection fraction with reference to findings in chronic obstructive pulmonary disease. *Am J Cardiol* 1978; **41**: 897-905.
- ¹³Matthay RA, Berger HJ, Loke J, Gottschalk A, Zaret BL. Effects of aminophylline upon right and left ventricular performance in chronic obstructive pulmonary disease. *Am J Med* 1978; **65**: 903-10.
- ¹⁴Marshall RC, Berger HJ, Costin JC, et al. Assessment of cardiac performance with quantitative radionuclide angiocardigraphy: sequential left ventricular ejection fraction, normalized left ventricular ejection rate, and regional wall motion. *Circulation* 1977; **56**: 820-9.
- ¹⁵Steele PP, Kirch D, Ellis J, Vogel R, Battock D. Prompt return to normal of depressed right ventricular ejection fraction in acute inferior infarction. *Br Heart J* 1977; **39**: 1319-32.
- ¹⁶Reduto L, Berger HJ, Cohen L, Gottschalk A, Zaret BL. Sequential radionuclide assessment of left and right ventricular performance after acute transmural myocardial infarction. *Ann Intern Med* 1978; **89**: 441-7.
- ¹⁷Reduto L, Berger HJ, Johnstone D, et al. Radionuclide assessment of exercise right and left ventricular performance following total correction of tetralogy of Fallot (abstract). *Circulation* 1978; **57** and **58** Suppl II: 45.
- ¹⁸Berger HJ, Johnstone D, Sands M, Gottschalk A, Zaret BL. First-pass radionuclide assessment of right ventricular performance during exercise in coronary artery stenosis. *Circulation* 1979; **60**: 1292-9.
- ¹⁹Bouhuys A, Littner M. Computer graphics and lung function tests. *Biosci Communications* 1975; **1**: 330-8.
- ²⁰Higgins MW, Keller JB. Seven measures of ventilatory lung function. *Am Rev Respir Dis* 1973; **108**: 258-72.
- ²¹Snedecor G, Cochran W. *Statistical methods*. 6th ed. Ames, Iowa: Iowa State University Press, 1973: 91-6 and 258-68.
- ²²Pontoppidan H, Gelfan B, Lowenstein E. Acute respiratory failure in the adult. Part I. *N Engl J Med* 1972; **287**: 690-8.
- ²³Mitchell RS, Stanford RE, Silvers GW, Dart G. The right ventricle in chronic airway obstruction: a clinicopathologic study. *Am Rev of Respir Dis* 1976; **114**: 147-54.
- ²⁴Marriott HJL. *Practical electrocardiography*. 6th ed. Baltimore: Williams & Wilkins, 1977: 51-61.
- ²⁵Bowden DH, Fischer VW, Wyatt JP. Cor pulmonale in cystic fibrosis: a morphometric analysis. *Am J Med* 1965; **38**: 226-32.
- ²⁶Moss AJ, Harper WH, Dooley RR, Murray JF,

- Mack JF. Cor pulmonale in cystic fibrosis of the pancreas. *J Pediatr* 1965; **67**: 797-807.
- ²⁷Kelminson LL, Cotton EK, Vogel JHF. The reversibility of pulmonary hypertension in patients with cystic fibrosis: observation on the effect of tolazoline hydrochloride. *Pediatrics* 1967; **39**: 24-35.
- ²⁸Moss AJ, Dooley RR, and Mickey MR. Cystic fibrosis complicated by heart failure. *West J Med* 1975; **122**: 471-3.
- ²⁹Hirschfeld SS, Fleming DG, Doershuk C, Liebman J. Echocardiographic abnormalities in cystic fibrosis. *Chest* 1979; **75**: 351-5.
- ³⁰Feigenbaum H. *Echocardiography*. Philadelphia: Lea & Febiger, 1972: 41.
- ³¹Kline LE, Crawford MH, MacDonald WJ Jr, Schelbert H, O'Rourke RA, Moser KM. Noninvasive assessment of left ventricular performance in patients with obstructive pulmonary disease. *Chest* 1977; **72**: 558-64.
- ³²Steele PP, Ellis JH Jr, Van Dyke D, Sutton F, Creagh E, Davies H. Left ventricular ejection fraction in severe chronic obstructive airways disease. *Am J Med* 1975; **59**: 21-28.
- ³³Matthay RA, Ellis JH Jr, Steele PP. Effect of dextran loading on left ventricular performance in chronic obstructive pulmonary disease. *Am Heart J* 1976; **92**: 730-6.
- ³⁴Matthay RA, Ellis JH Jr, Steele PP. Methoxamine-induced increase in afterload: effect on left ventricular performance in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1978; **117**: 871-7.
- ³⁵Barnes GL, Gwynne JF, Watt JM. Myocardial fibrosis in cystic fibrosis of the pancreas. *Aust Paediatr J* 1970; **6**: 81-7.
- ³⁶Oppenheimer EH, Esterly JR. Myocardial lesions in patients with cystic fibrosis of the pancreas. *Johns Hopkins Med J* 1973; **133**: 252-61.
- ³⁷Ellis JH Jr, Kirch D, Steele PP. Right ventricular ejection fraction in severe chronic airway obstruction. *Chest* 1977; Suppl **71**: 281-2.

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