JCI The Journal of Clinical Investigation

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J Clin Invest. 1973;52(8):1994-2006. https://doi.org/10.1172/JCI107384.

Research Article

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Interrelation between Alterations in Pulmonary Mechanics and Hemodynamics in Acute Myocardial Infarction

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ABSTRACT Pulmonary mechanics were evaluated in 30 patients with acute myocardial infarction by measuring forced expiratory flow rates and total pulmonary resistance (R_T) with the oscillometric method at the resonant frequency of the chest (6–8) cycle/s). During the first 3 days after infarction, forced expiratory volume (FEV) and forced mid-expiratory flow rate ($FEF_{25-75\%}$) were 69% and 60% of predicted values, respectively. 10 or more wk later these values were 95% and 91%. Initially, R_T was 52% greater than predicted, but was only 4% greater 10 or more wk later. In 11 patients R_T was measured at both resonant frequency and at 3 cycle/s. Five of these patients had no clinical signs of heart failure, but nine had abnormally high values of pulmonary artery pressure, "wedge" pressure and pulmonary extravascular water volume. All of these patients recovered. Initially, R_T at resonance was 50% and R_T at 3 cycle/s was 130% greater than predicted values. 2–3 wk later these figures were -3% and $+6\%$ of those predicted, respectively. At 10 wk or more, significant frequency dependence of R_T had disappeared (R_T at 3 cycle/s was 7% greater than R_T at resonance). Isoproterenol inhalation in six patients caused no change in flow rates, R_T at resonance, or R_T at 3 cycle/s. R_T at resonance and at 3 cycle/s, FEV, and $FEF_{25-75\%}$ correlated significantly with the pulmonary vascular pressures. Patients with more marked arterial hypoxia and larger values for extravascular water volume had greater elevations of R_T and depression of $FEF_{25-75\%}$, but linear correlations were not significant. Clinical signs of congestive heart failure significantly correlated with a fall in FEV and $FEF_{25-75\%}$, the development of frequency dependence of R_T, and elevation of the pulmonary wedge pressure. The initial elevation of R_T and low flow rates indicate a modest degree of airway obstruction in acute myocardial infarction. Lack of response to isoproterenol suggests that bronchial muscular constriction is not a major factor. Frequency dependence of R_T accompanied by elevated pulmonary vascular pressures and extravascular water volume indicates that pulmonary congestion causes the development of uneven time constants in the airways. Vascular engorgement and interstitial edema from elevated vascular pressures causing narrowing of the peripheral airways and closure of collateral airways could account for the above findings.

INTRODUCTION

Hypoxemia is a common finding in patients after acute myocardial infarction (1–6). Determination of arterial oxygen pressure (P_{O_2}) while patients breathe air or 100% O_2, as well as measurements of the physiological dead space, indicate that this hypoxemia results from shunting of blood past unventilated alveoli and uneven distribution of pulmonary ventilation to pulmonary perfusion (7–10). In contrast, alveolar hypoventilation is uncommon and, in fact, arterial P_{CO_2} is frequently lower than normal. These patients show little or no impairment in carbon monoxide-diffusing capacity, so that hypoxemia usually cannot be attributed to "alveolar-capillary block" (11).

The present study was undertaken to define more clearly changes in pulmonary mechanics in patients with acute myocardial infarction. Alterations in lung mechanics

This work was presented in part at the jointly sponsored Pulmonary Meeting of the American Federation for Clinical Research and the American Society for Clinical Investigation in Atlantic City, New Jersey, on 30 April 1972.

This work was performed during Dr. Interiano's tenure as a Pulmonary Fellow of the Finger Lakes Tuberculosis and Respiratory Disease Association, and Dr. Hyde's tenure as an Established Investigator of the American Heart Association, with partial support from the Southern Tier Heart Association.

Received for publication 27 September 1972 and in revised form 15 March 1973.

were correlated with clinical status, roentgenograms of the chest, arterial blood gas analyses, hemodynamic alterations, and measurements of the pulmonary extravascular water volume. The data indicate that moderate alterations in pulmonary mechanics coincide with subclinical abnormalities in pulmonary hemodynamics. More marked pulmonary function abnormalities were seen in patients with clinical, hemodynamic, and radiological evidence of pulmonary congestion.

METHODS

Selection of patients. 32 patients admitted to the Myocardial Infarction Research Unit at the University of Rochester Medical Center were studied. The diagnosis of acute myocardial infarction was established on the basis of history, serial enzyme changes, and characteristic electrocardiographic changes. All patients showed the development of pathological Q waves accompanied by evolutionary changes in the ST segments and T waves. To avoid confusion of abnormalities secondary to chronic obstructive lung disease with changes caused by myocardial infarction, two patients with evidence of more than moderate airway obstruction 3–10 wk after infarction were excluded. Forced expiratory volume in one s (FEV_1) [1] of 55% of the predicted value, or less, was used to identify these patients. Mean age of the patients accepted for study was 56 yr with a range from 34 to 72 yr. Eight of the subjects (29%) did not smoke. Three of the subjects (10%) were women. Four patients died 20–180 days after onset of symptoms. None of the patients died while in the Myocardial Infarction Research Unit.

Each patient was placed into one of four clinical classes with respect to left ventricular function, as follows: class I, no signs of left ventricular dysfunction; class II, a third heart sound ("gallop") and basal pulmonary rales; class III, pulmonary edema; class IV, shock. Signs of left ventricular failure observed on roentgenograms of the chest were classified by the method described by McHugh, Forrester, Adler, Zion, and Swan (12), namely, absent, labeled class 0; minimal, labeled class I, showing increased blood flow to the upper zones, pulmonary vascular blurring, and hilar haze; moderate, labeled class II, showing marked increase in the outer zone vessels and periacinal rosette formation; and severe, labeled class III, showing diffuse pulmonary infiltrates.

All the patients were studied during the first 3 days after myocardial infarction (acute studies); 19 patients had studies of pulmonary mechanics performed 2–3 wk later (early follow-up); and 8 patients were again studied 10 or more wk later (late follow-up). In order to appraise the validity of using the normal values for forced expiratory flow rates (FEF) recently published by Morris, Koski, and Johnson (13), measurements were obtained from 10 normal subjects, 30–58 yr old (mean 43 yr), and from 5 patients, 37–62 yr old (mean 50 yr) who had been hospitalized with documented myocardial infarction 1 or more yr previously. Initial measurements were obtained with subjects in bed in the sitting position. Follow-up studies were obtained while subjects sat in a chair with the feet elevated by an additional chair of equal height. FEF was

[1] *Abbreviations used in this paper:* ASHD, arteriosclerotic heart disease; FDI, frequency dependence index; FEF, forced expiratory flow rate; $FEF_{25-75\%}$, forced mid-expiratory flow rate; FEV, forced expiratory volume; FEV_1, FEV in one s; FRC, functional residual capacity; pO_2, oxygen pressure; R_T, total pulmonary resistance; R_{RES}, R_T observed at the resonant frequency; R_3, R_T at 3 cycle/s.

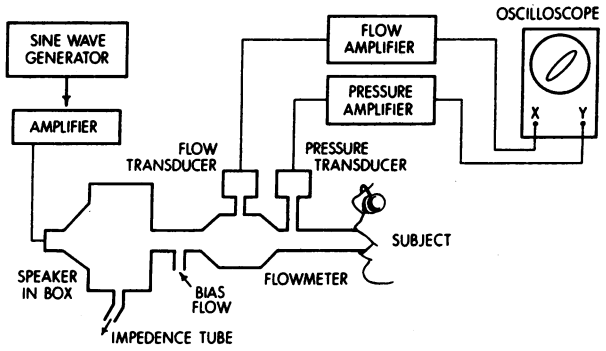

FIGURE 1 Diagram of apparatus used to measure pulmonary resistance with the forced oscillometric technique. The speaker generates bidirectional sine wave airflow at frequencies that can be varied from 3 to 9 cycle/s. This airflow is superimposed on the subject's normal breathing pattern. Flow and pressure at the mouth are recorded on the x and y axes of the oscilloscope. Resistance is then a function of the slope of the line connecting the extremes of the loop on the flow axis. Support of the cheeks with the hands did not significantly alter the observed value of R_T so that this procedure was not used in this study.

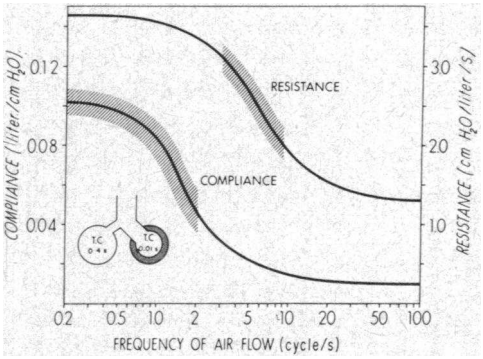

FIGURE 2 Diagram of effect of uneven distribution of airway time constants upon measured values of pulmonary compliance and resistance. In this model one airway was assumed to have a compliance of 0.1 liter/cm H_2O and a resistance of 4 cm/liter/s. Values in the other airway were 0.005 liter/cm H_2O and 2 cm/liter/s. Since the time constant of an airway is the product of its resistance and compliance, one airway would have a time constant of 0.4 s and the other 0.01 s. From the equations published by Otis and co-workers (18) the compliance and resistance at any frequency of airflow can be calculated. Note that both values fall with increasing frequency but resistance falls at a higher frequency. The true value of compliance is approached at low frequencies while the minimum value of resistance is reached at high frequencies. The shaded areas represent the approximate frequencies at which it is practical to make measurements in man. (TC = time constant).

TABLE I

FEF and Pulmonary Resistance in Patients with Acute Myocardial Infarction (MI)

Patient	Day post-MI	Age	FEV	% predicted FEV	FEV_1	% FEV_1/FEV	$FEF_{25-75\%}$	% predicted $FEF_{25-75\%}$	R_T
			ml		*ml*		*liter*		*cm H_2O/liter/s*
H. G.	2	55	2,990	77	2,380	80	2.0	66	2.5
	19		3,880	98	3,050	79	3.3	106	2.7
	1 yr		3,470	92	2,920	80	4.1	130	1.2
W. J.	4	55	2,370	57	1,720	77	1.5	50	
	19		2,820	60	2,170	76	2.0	67	
	1 yr		3,270	84	2,400	80	2.2	73	2.0
C. P.	3	68	3,240	83	1,950	60	1.4	46	
R. R.	3	54	3,560	89	2,470	73	2.4	80	2.7
	23		4,080	102	2,980	73	2.7	90	2.9
	8 mo		4,270	106	3,080	73	2.6	86	1.6
D. L.	2	46	4,070	95	3,040	74	3.6	100	
	20		4,300	100	3,430	80	5.0	138	
H. Mc.	3	52	2,800	80	2,080	74	1.3	50	2.8
	21		3,020	86	2,170	71	1.6	62	3.1
D. D.	2	65	2,260	58	1,700	75	1.4	46	
F. B.	2	68	3,490	89	2,320	66	1.3	43	2.3
S. L.	3	67	3,185	82	2,250	70	1.7	56	2.4
	18		3,670	89	2,600	73	2.2	73	
	7 mo		3,640	88	2,780	76	2.1	70	1.9
C. B.	3	57	1,990	65	1,400	70	1.2	46	2.5
E. S.	2	58	3,620	93	2,590	71	2.3	76	3.0
I. S.	4	64	1,510	57	1,120	74	1.5	57	1.8
J. H.	3	63	4,360	86	2,890	66	1.8	50	
G. D.	3	52	3,560	72	2,590	73	2.0	66	2.4
F. J.	3	56	3,530	74	2,530	75	1.9	63	
	21		3,920	83	2,770	75	1.8	60	
J. R.	4	57	2,160	54	1,490	69	1.4	46	
	21		3,080	77	2,100	68	1.8	60	
A. L.	2	62	3,520	86	2,450	70	1.6	53	
J. M.	4	57	2,590	70	1,620	63	1.2	40	
H. B.	3	50	3,510	83	2,260	64	1.6	53	
V. W.	3	50	3,420	67	2,690	78	2.7	75	1.5
	15		3,920	77	3,250	83	4.3	126	1.0
	90		5,000	98	3,800	76	3.4	100	1.3
H. O.	3	72	3,060	66	2,440	80	2.1	60	1.9
	15		3,380	74	2,620	77	2.0	58	1.0
E. H.	3	49	4,210	81	3,450	82	3.7	100	2.2
	17		4,430	85	3,530	80	3.3	90	1.7
	72		4,560	88	3,650	80	3.7	100	1.7
D. R.	3	34	3,560	69	2,700	76	2.4	57	1.6
	19		4,300	84	3,660	85	3.8	90	1.8
	86		5,080	100	4,000	80	4.3	100	1.6
C. St.	1	64	1,510	42	1,200	80	1.2	47	4.1
	19		2,290	64	1,980	86	2.7	100	2.2
F. M.	2	44	4,430	94	3,670	83	4.0	100	1.5
	20		4,450	94	3,700	85	4.0	100	1.4
	120		4,480	95	3,700	79	4.0	100	1.6

TABLE I—(*Continued*)

Patient	Day post-MI	Age	FEV	% predicted FEV	FEV_1	% FEV_1/FEV	FEF_{25-75}%	% predicted FEF_{25-75}%	R_T
			ml		*ml*		*liter*		*cm H_2O/liter/s*
S. S.	3	59	2,480	55	1,940	78	2.1	67	3.6
	18		4,000	89	3,140	78	3.0	98	1.5
E. W.	3	48	3,220	58	2,380	74	1.7	46	3.7
	17		4,540	83	3,420	75	2.5	68	1.2
J. G	3	66	2,380	69	1,940	81	1.8	65	2.1
	19		3,320	97	2,700	81	2.8	100	1.7
M. S.	2	64	1,990	59	1,540	83	1.5	60	2.4
	20		2,700	80	2,240	83	2.2	88	1.8
R. B.	3	68	1,700	50	940	55	1.2	45	2.9
	19		2,800	80	1,700	69	1.8	68	2.0
Mean values	1–4 days	57	2,900	69	2,120	73	1.9	60	2.5
	2–3 wk	51	3,860*	84*	2,830*	74	2.8*	88*	1.8‡
	10 wk or more	55	4,220*	95*	3,290*	77	3.3*	91*	1.6‡

Predicted values for FEV and FEF_{25-75} were obtained from reference 13. %FEV_1/FEV, percent of FEV during first second.
* $P < 0.01$ (compared to 1–4 days values).
‡ $P < 0.05$ (compared to 1–4 days values).

obtained with a Stead-Wells spirometer[2] and calculated by the methods described by Morris, Koski, and Johnson (13).

The Committee on Human Investigation of this institution had reviewed and approved the research proposal. Written informed consent for these studies was obtained from each patient.

Total pulmonary resistance (R_T) was measured with the forced oscillometric technique previously described by Fisher, DuBois, and Hyde (14), with the following modifications: mechanical design of the apparatus closely followed the specifications reported by Hyatt, Zimmerman, Peters, and Sullivan (15), thereby permitting the patient to breathe comfortably during the procedure (Fig. 1). An additional volume of 18 ml of air contained in ¼-inch rubber tubing was connected with a "T" to the smaller-sized chamber of the differential pressure manometer[3] attached to the pneumotachygraph in order to give adequate frequency response at 9 cycle/s. R_T was measured at the patient's resonant frequency (5–8 cycle/s) and in 11 of these patients at 3, 5, 7, and 9 cycle/s. At 3 and 9 cycle/s the display of mouth pressure and flow on the two axes of the x-y storage oscilloscope frequently showed considerable "looping." If looping was present, a line was drawn between the extremes of flow of the individual loop and the angle determined. As described by Frank, Mead, and Whittenberger (16), the tangent of this line is proportional to R_T. Theoretical aspects of this method have been discussed in detail elsewhere (Fig. 2 [14–18]). At each frequency the mean of 3–7 determinations obtained at functional residual capacity or early in inspiration during normal breathing was recorded. Power to the loudspeaker supplying the oscillating airflow was adjusted to give a flow rate at the mouth that oscillated between +0.5 and −0.5 liter/s. Narrowing of the glottis could be readily detected by a sudden increase in R_T. Control values for R_T were obtained from the 15 subjects previously mentioned.

In six patients, spirometry and pulmonary resistance were measured before and after inhalation of 0.5% isoproterenol in four deep breaths over a 10-min period delivered by a replica of a Dautrebande D-30 nebulizer.[4] This method of administration of isoproterenol produces improvement in FEF in patients with asthma (19). Arterial blood gases were analyzed by previously described methods (19). Right ventricular, pulmonary artery, and pulmonary wedge pressures were monitored with a Swan-Ganz catheter (20). Cardiac outputs were performed by the indocyanine green dye dilution technique, with injection into the main pulmonary artery and sampling from the brachial artery. From the same injection and sampling site, pulmonary extravascular water volume was determined by the double isotope dilution technique using radio-iodinated serum albumin and tritiated water as indicators (21). Details of the techniques for measuring cardiac output, vascular pressures, and pulmonary extravascular water volume will be reported separately.

RESULTS

Spirometry. During the first 4 days after acute myocardial infarction, FEF was reduced in the majority of patients (Table I). The mean forced expiratory volume (FEV) was 69% of predicted, compared to 95% in 10 normal subjects ($P < 0.01$) and 90% in 5 patients with stable arteriosclerotic heart disease (ASHD) ($P <$

[2] Warren E. Collins, Inc., Braintree, Mass.

[3] Statham model PM-5 TC±0.15–350, Statham Instruments, Inc., Hato Rey, Puerto Rico. Because gas volume on the inner side of the sensing membrane of this gauge is much larger than the volume on the outer side, the latter volume must be increased to obtain a flat frequency response up to 10 cycle/s.

[4] Manufactured by the R. E. Reynolds Co., Rochester, N. Y.

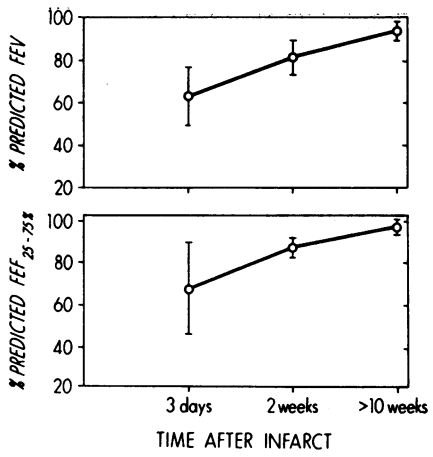

FIGURE 3 Mean values and standard deviation for the percent of FEV and $FEF_{25-75}\%$ measured 3 days, 2–3 wk, and more than 10 wk after acute myocardial infarction.

TABLE II

Pulmonary Resistance at Different Frequencies in Patients with Acute Myocardial Infarction (MI)

Patient	Day post-MI	fRES	RT	R5	R7	R9	FDI
		cycle/s		*cm H_2O/liter/s*			
V. W.	3	6	1.5	2.0	1.5	1.5	0.17
	15	6	1.0	1.2	1.0	0.9	0.10
	90	6	1.3	1.4	1.3	1.2	1.1	0.03
H. O.	3	6	1.9	2.4	1.9	1.9	0.17
	15	7	1.1	1.5	1.1	0.9	0.13
E. H.	3	6	2.2	3.2	2.7	2.2	2.2	0.33
	17	7	1.7	2.3	1.8	1.7	1.6	0.15
	71	7	1.7	1.9	1.8	1.6	1.6	0.05
D. R.	3	6	1.6	3.2	1.9	1.6	1.5	0.53
	19	6	1.8	1.9	1.8	1.8	1.7	0.03
	86	7	1.6	1.6	1.5	1.5	1.5	0.00
C. St.	2	7	4.1	7.9	5.5	3.9	3.5	0.95
	19	7	2.2	2.4	2.2	2.0	1.9	0.05
F. M.	2	6	1.5	2.4	2.0	1.6	1.5	0.30
	20	6	1.4	1.8	1.5	1.4	1.4	0.13
	120	7	1.5	1.6	1.6	1.4	1.4	0.02
S. S.	3	7	3.6	4.9	4.0	3.5	3.2	0.33
	18	7	1.5	1.6	1.5	1.4	1.4	0.02
E. W.	3	6	3.7	5.5	4.1	3.6	3.1	0.56
	17	6	1.2	1.5	1.3	1.2	1.1	0.10
J. G.	3	7	2.1	3.5	2.3	2.1	1.8	0.35
	19	7	1.7	2.0	1.8	1.7	1.6	0.08
M. S.	2	7	2.4	4.9	2.7	2.4	2.3	0.62
	20	7	1.8	2.2	1.9	1.8	1.6	0.10
R. B.	3	7	2.9	4.9	3.5	2.9	2.8	0.50
	19	7	2.0	2.5	2.1	2.0	1.9	0.12
Mean	2–3 days		2.5	4.1	2.9	2.5	2.4	0.44
	2–3 wk		1.6*	1.9*	1.6*	1.5*	1.6‡	0.09‡
	10–17 wk		1.5*	1.6*	1.6*	1.4*	1.4‡	0.03*

fRES frequency during resonance. R5, R5, R7, R9, resistance measured at 3, 5, 7, and 9 cycles.
* $P < 0.05$. ‡ $P < 0.01$ (compared to 2–3 days values).

0.05). The mean forced mid-expiratory flow rate ($FEF_{25-75}\%$) was 60% of that predicted, compared to control values of 95% in normal ($P < 0.01$) and 86% in ASHD ($P < 0.02$).

When spirometric studies were repeated 2–3 wk later in 19 patients, mean FEV increased from 69% to 84% of that predicted. This change was significant ($P < 0.01$). Mean $FEF_{25-75}\%$ increased from 60% to 88% of predicted ($P < 0.01$) (Fig. 3). In the eight patients studied 10 or more wk after acute infarction, mean FEV was 95% and $FEF_{25-75}\%$ was 90% of the predicted values. When compared to results obtained during the first 4 days, these changes were significant at the 1% level.

FEV and $FEF_{25-75}\%$ measured 2–3 wk after acute myocardial infarction did not significantly differ from the control values ($P < 0.3$ and 0.2, respectively).

Total pulmonary resistance (R_T). R_T was measured at the resonant frequency of the thorax (5–7 cycle/s) in 21 patients during the first 4 days after acute infarction. Mean R_T at resonance was 2.5 cm H_2O/liter/s compared to values in the control patients of 1.6 cm H_2O/liter/s ($P < 0.02$). 3 wk later, mean R_T at resonance was 1.8, and 10 wk after acute infarction, 1.7 cm H_2O/liter/s. Compared to the initial values determined in these subjects, these changes were significant ($P < 0.05$). In 11 of these patients the pulmonary resistance was also measured at frequencies of 3, 5, 7, and 9 cycle/s (Table II). No significant difference was seen between the resistance measured at resonant frequency and 9 cycle/s ($P > 0.2$), but a striking elevation of resistance at a frequency of

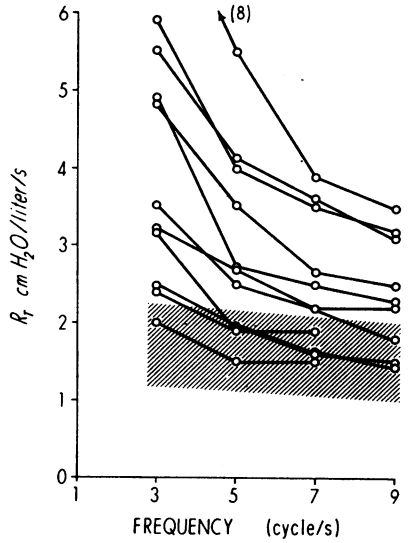

FIGURE 4 R_T measured at 3, 5, 7, and 9 cycle/s 1–3 days after acute myocardial infarction. The shaded area represents the range observed in control subjects. Note that most of the patients show an increased resistance at 3 cycle/s.

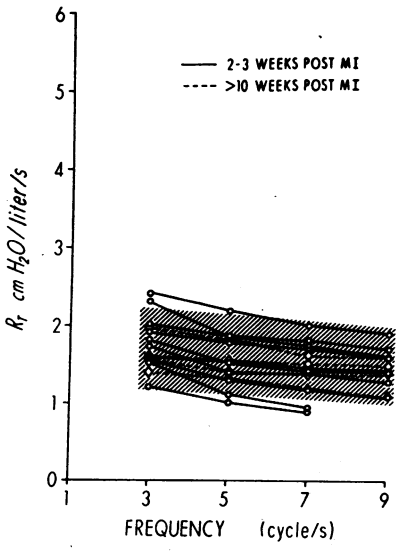

FIGURE 5 R_T measured at 3, 5, 7, and 9 cycle/s 2–3 wk and over 10 wk after acute myocardial infarction. The shaded area is the range observed on control subjects. Note that the frequency dependence of the resistance has almost completely disappeared.

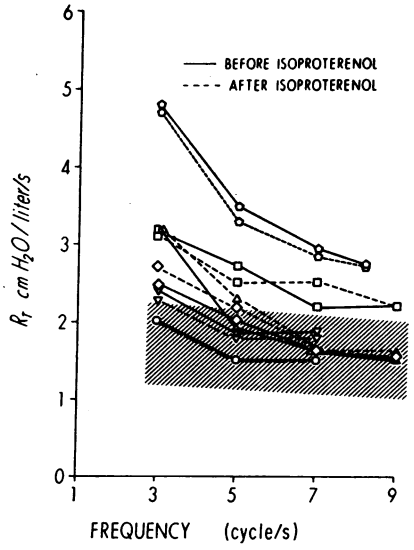

FIGURE 6 R_T measured at 3, 5, 7, and 9 cycle/s before (continuous line) and after (broken line) isoproterenol inhalation. Each symbol represents a different patient. Note the absence of change in frequency dependence of the resistance after inhalation of isoproterenol.

3 cycle/s was observed. The mean R_T at 3 cycle/s was 4.1 cm H_2O liter/s compared to 2.5 for the R_T at resonance ($P < 0.02$) (Fig. 4).

2–3 wk later, R_T at 3 cycle/s fell to 1.9 cm H_2O/liter/s ($P < 0.01$) and did not differ significantly from the resistance measured at higher frequencies ($P > 0.2$). 10 or more wk after acute infarction the mean R_T at 3 cycle/s was 1.6 cm H_2O/liter/s, almost identical to the predicted value of 1.7 cm H_2O/liter/s ($P > 0.3$) (Fig. 5).

Effect of isoproterenol on pulmonary mechanics. After the inhalation of isoproterenol, no consistent change in FEF, R_T at resonance, or R_T at other frequencies was observed in any patient (Fig. 6, Table III).

Frequency dependence index. In order to have a single numerical expression of the frequency dependence of resistance that could be readily compared to other data obtained in these patients, a frequency dependence index (FDI) was devised. It is defined as the difference be-

TABLE III
Isoproterenol Studies

Patient		Predicted % FEV	Predicted % FEV_1	% Predicted FEF_{25-75}%	R_T	R_3	R_5	R_7	R_9	FDI
V. W.	Control	67	72	75	1.5	2.0	1.5	1.5		0.17
	Isoproterenol	70	73	75	1.5	2.0	1.5	1.5		0.25
H. O.	Control	66	80	60	1.8	2.4	1.9	1.9		0.20
	Isoproterenol	70	80	58	1.8	2.3	1.8	1.8		0.25
E. H.	Control	81	90	100	2.2	3.2	2.7	2.2	2.2	0.33
	Isoproterenol	77	88	100	2.3	3.1	2.5	2.5	2.2	0.26
D. R.	Control	69	67	57	1.6	3.2	1.9	1.6	1.5	0.53
	Isoproterenol	67	67	53	1.6	3.2	2.3	1.6	1.6	0.53
F. M.	Control	94	100	100	1.5	2.4	2.0	1.6	1.5	0.29
	Isoproterenol	90	100	100	1.6	2.7	2.2	1.5	1.5	0.34
R. B.	Control	50	55	45	2.9	4.9	3.5	2.9	2.9	0.50
	Isoproterenol	48	54	40	2.8	4.8	3.2	2.8	2.8	0.50

R_3, R_5, R_7, R_9, resistance measured at 3, 5, 7, and 9 cycle/s.
FDI = $(R_3 - R_r) \div (\nu_r - 3)$ where ν_r = resonant frequency of the chest. For details see text.

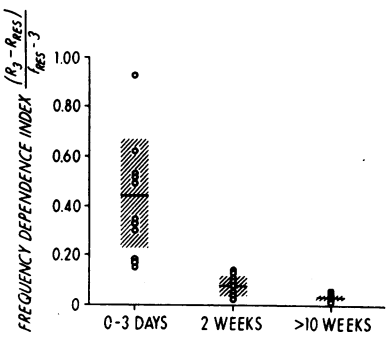

FIGURE 7 FDI during the first 3 days, 2 wk, and more than 10 wk after acute myocardial infarction. Each circle represents a patient. The horizontal line is the mean value and the shaded area the standard deviation. Note the significant fall in the index, 2 and 10 wk after the infarction.

tween R_T at 3 cycle/s (R_3) and R_T observed at the resonant frequency (R_{RES}), divided by the difference in the number of cycles between the resonant frequency (f_{RES}) and 3 cycle/s or: $FDI = (R_3 - R_{RES}) \div (f_{RES} - 3)$. During the first 4 days after acute myocardial infarction, all 11 patients studied had an abnormally elevated FDI. Its value was 0.44 compared to 0.05 obtained in 15 control subjects ($P < 0.01$). 2–3 wk later the FDI had fallen to 0.09 and did not significantly differ from control values ($P > 0.2$) (Fig. 7).

Correlation of alterations in pulmonary mechanics with other findings. The measurements of pulmonary mechanics obtained during the first 3 days after acute myocardial infarction in the 11 patients studied in detail were correlated with measurements of arterial blood gases, pulmonary extravascular water volume, mean pulmonary artery pressure, pulmonary wedge pressure, and pulmonary vascular resistance (Table IV). The FDI showed a significant correlation ($P < 0.01$) to pulmonary artery pressure but not to pulmonary vascular resistance or pulmonary wedge pressure (Table V). Pulmonary resistance measured at 3 cycle/s correlated with pulmonary artery pressure and pulmonary wedge pressure ($P < 0.01$), but not with pulmonary vascular resistance. FEV showed a similar correlation with the pulmonary vascular pressures ($P < 0.01$), while $FEF_{25-75\%}$ showed a less striking correlation ($P < 0.05$).

Although nine patients had abnormally high pulmonary extravascular water volume (> 120 ml/m^2), and six patients had an arterial oxygen tension less than 70 mm Hg while breathing air, no significant linear correlation could be established between these parameters and the degree of abnormality in pulmonary mechanics (Table V).

Clinical and radiological findings. Four patients were in clinical class I, six in class II, and one in class III. 10 of the 11 patients studied in detail during the first 3 days after acute myocardial infarction had roentgenograms of the chest available for study. One patient showed no radiological evidence of left ventricular failure, two patients had minimal changes, five had moderate changes, and two had severe changes. The correlation of the clinical classification with FEV,

TABLE IV

FEV, R_3, FDI, Arterial Oxygen Tension, Hemodynamic Measurements, Pulmonary Extravascular Water Volume, Clinical Class, and Radiological Class in Patients with Acute Myocardial Infarction

Patients	% FEV	R_3	FDI	Pa_{O_2}	PWP	PAP	CI	PVR	PEV	Clinical class	Radiological class
				mm Hg	*mm Hg*	*mm Hg*	*liter/min/m²*	*dyn·s·cm⁻⁵*	*ml/m²*		
V. W.	67	2.0	0.17	78	12	20	2.53	124	105	1	—
H. O.	66	2.4	0.17	62	7	11	2.30	65	180	1	III
E. H.	81	3.2	0.33	69	5	15	3.52	106	209	1	0
D. R.	69	3.2	0.53	77	9	17	4.29	69	80	2	I
C. St.	42	7.9	0.95	53	—	50	2.84	—	116	2	III
F. M.	94	2.4	0.30	61	3	10	3.02	95	177	1	I
S. S.	55	4.9	0.33	69	18	24	2.21	114	132	2	II
E. W.	58	5.5	0.56	67	17	23	2.91	74	159	2	II
J. G.	57	3.5	0.35	73	14	29	4.24	143	152	2	II
M. S.	54	4.9	0.62	63	17	22	2.49	93	183	3	II
R. B.	50	4.9	0.50	72	14	30	2.30	294	153	2	II

% FEV, percent of predicted FEV; Pa_{O_2}, arterial oxygen tension; PWP, pulmonary capillary wedge pressure; PAP, mean pulmonary artery pressure; CI, cardiac index; PVR, pulmonary vascular resistance; PEV, pulmonary extravascular water volume (normal = 120); Clinical class, clinical classification of severity, as explained in the text; Radiological class, radiological evidence for pulmonary congestion, as explained in the text.

TABLE V

Correlation Coefficients

	Chest X-ray	Clinical class	PVR	CI	PEV	PAP	PWP	Pa_{O_2}	FDI	R_3	R_T	$FEF_{25-75}\%$	% FEV_1/FEV
% Predicted FEV	−0.72‡	−0.68*	−0.40	+0.27	+0.32	−0.81‡	−0.89‡	+0.14	−0.60*	−0.76‡	−0.71‡	+0.86‡	+0.37
% FEV_1/FEV	−0.12	−0.16	−0.82‡	+0.26	+0.19	−0.23	−0.29	−0.32	−0.12	−0.21	−0.24	+0.52	
$FEF_{25-75}\%$	−0.72‡	−0.62*	−0.26	+0.19	+0.42	−0.59*	−0.70*	+0.06	−0.56*	−0.62*	−0.56*		
R_T	+0.48	+0.46	+0.21	−0.34	−0.05	+0.73‡	+0.72‡	−0.45	+0.66*	+0.92‡			
R_3	+0.49	+0.63*	+0.28	−0.20	−0.14	+0.85‡	+0.78‡	−0.53	+0.89‡				
FDI	0.31	+0.65*	+0.12	+0.07	−0.24	+0.77‡	+0.48	−0.49					
Pa_{O_2}	−0.48	−0.08	+0.30	+0.34	−0.37	−0.32	+0.20						
PWP	+0.50	+0.77‡	+0.23	−0.29	−0.25	+0.81‡							
PAP	+0.52	+0.48	+0.65*	−0.05	−0.36								
PEV	−0.23	−0.16	−0.01	−0.20									
CI	−0.50	+0.01	−0.23										
PVR	+0.08	+0.14											
Clinical class	+0.31												

Legends as in Tables I, II, and IV. Chest X-ray: radiological evidence for pulmonary congestion as explained in the text.
* = $p < 0.05$.
‡ = $p < 0.01$.

$FEF_{25-75}\%$, pulmonary resistance at 3 cycle/s, FDI and pulmonary wedge pressure was significant (Table V). The chest X-ray signs of pulmonary congestion had positive correlations with the FEV and $FEF_{25-75}\%$ but not with other parameters.

Control measurements. Values for FEV and its subdivisions obtained in the 15 control subjects were compared to the values reported by Morris, Koski, and Johnson (Table VI). In general, our control subjects tended to have values 3–5 percentage points lower. This difference may be related to the standing position and the exclusion of smokers in the series reported by Morris and co-workers.

DISCUSSION

These studies demonstrate that during the first few days after acute myocardial infarction, most patients

TABLE VI

FEF and Pulmonary Resistance in Control Subjects and Patients with Arteriosclerotic Heart Disease

Subjects	Age	% FEV	$FEF_{25-75}\%$	R_{RES}	R_3	R_5	R_7	R_9	FDI
					cm H_2O/liter/s				
Normals									
R. H.	41	93	100	1.1	1.2	1.1	1.1	1.0	0.03
M. G.	30	100	100	1.4	1.3	1.4	1.4	1.4	0.00
S. D.	37	105	110	1.8	1.9	1.8	1.7	1.6	0.03
V. D.	47	95	100	1.6	1.9	1.6	1.6	1.6	0.08
M. G.	58	92	90	1.6	1.8	1.6	1.6	1.4	0.07
P. B.	43	95	80	2.0	2.1	2.0	1.9	1.9	0.03
D. B.	38	100	90	1.3	1.5	1.3	1.2	1.2	0.05
B. C.	32	90	92	1.4	1.5	1.4	1.4	1.4	0.03
J. C.	54	93	98	1.6	1.8	1.6	1.6	1.6	0.07
J. V.	47	92	90	1.8	1.9	1.8	1.8	1.7	0.03
Mean	43	95	95	1.6	1.7	1.6	1.5	1.5	0.05
ASHD patients									
D. A.	37	87	80	1.6	1.8	1.6	1.6	1.4	0.05
R. K.	42	100	100	1.4	1.5	1.4	1.4	1.2	0.03
J. C.	50	92	88	2.0	2.2	2.2	2.0	2.0	0.05
H. D.	62	82	75	2.0	2.3	2.0	2.0	1.6	0.07
M. F.	62	88	88	1.4	1.6	1.5	1.4	1.4	0.05
Mean	50	90	86	1.7	1.9	1.7	1.7	1.5	0.05

% FEV, percent of predicted FEV; $FEF_{25-75}\%$, percent of predicted $FEF_{25-75}\%$; R_{RES}, pulmonary resistance measured at resonance; R_3, R_5, R_7, R_9, resistance measured at 3, 5, 7, and 9 cycle/s.

have a small but reversible abnormality in pulmonary mechanics. Typically, FEV and FEV_1 are reduced 30%, maximum $FEF_{25-75\%}$ is reduced 40%, and R_{RES} is elevated 50%. Similar findings have been reported by others (1, 6, 22).

An original and more striking finding was the transient development of frequency dependence of R_T (Table III, Fig. 4). For example, compared to measurements 2–3 wk after acute myocardial infarction, R_5 was initially increased 115%, while at 9 cycle/s, resistance was increased only 50%. The following mechanisms deserve special attention as causes for these changes in lung function.

Decrease in lung volume. A decrease in lung volume will produce diminution of flow rates, increased R_T, and frequency dependence of lung compliance (14, 23, 24). Since frequency dependence of compliance and resistance are closely related phenomena (Fig. 2), a decrease in lung volume would explain the development of frequency dependence of resistance in patients with acute myocardial infarction. Previous studies by other investigators have also noted a decrease in vital capacity with acute myocardial infarction and pulmonary congestion, so that this volume loss might explain the decrease in FEF (1, 11). However, R_T is measured at functional residual capacity (FRC) or a volume slightly higher than FRC. Unfortunately, FRC was not measured in these patients, and measurements published by others do not clearly indicate if FRC increases or decreases with pulmonary congestion (25–27). We therefore cannot exclude the possibility that the development of frequency dependence of resistance was secondary to a decrease in lung volume.

According to the data of Fisher, DuBois, and Hyde, the 60% rise in R_T such as observed in our patients would require a 40% decrease in FRC if the change was entirely due to a loss in volume (14). Such a large reduction in FRC seems unlikely. We therefore conclude that the elevated R_T in acute myocardial infarction cannot be attributed solely to volume loss.

Bronchial constriction of major airways. Narrowing of major airways such as seen in bronchial asthma could account for the fall in FEF and the rise in R_T ("cardiac asthma"). Bronchoconstriction of larger airways may increase lung volumes due to air trapped behind the site of constriction and may cause large increments in measured airway resistance, because these airways contain the major share of the resistance of airflow in the lungs (28, 29). This mechanism was not supported by the finding that the rise in R_T was small compared to the changes seen in bronchial asthma (30). In addition, these subjects did not show any change in flow rates or R_T after inhaling isoproterenol. Since the bronchoconstriction of asthma usually responds to this therapy, the lack of response to isoproterenol in our patients suggests that the mechanisms causing bronchoconstriction in patients with asthma does not commonly cause the decrease in flow rates or increase in R_T observed in acute myocardial infarction.

Gravitational changes in pulmonary compliance and resistance. Regional changes in compliance or resistance due to gravitational forces could explain the development of frequency dependence of airway resistance (29). Lung compliance decreases with pulmonary congestion and this decrease is probably greater in dependent zones where pathological changes are more marked (22, 31). However, the degree of change reported in the dependent areas (6, 32) is probably not large enough to explain the degree of frequency dependence of pulmonary resistance observed in our subjects. For example, as shown in Fig. 2, when the time constants of a lung with two compartments differ by a factor of 40, pulmonary resistance increases only twofold when the frequency is decreased from 10 cycle/s to 3 cycle/s. We have made additional calculations using the equations of Otis, et al. (18), and they indicate that time constants of a two-compartment lung must usually differ by more than 10-fold to result in a 15% decrease in pulmonary resistance between 3 and 10 cycle/s. Since external scanning techniques of the lungs after acute myocardial infarction have not demonstrated alterations in ventilation suggestive of this degree of abnormality, additional mechanisms must be contributing to the observed frequency dependence of pulmonary resistance in this disease (6, 32).

Peripheral airway disease. Macklem and Mead have shown that in human and canine lungs, airways smaller than 2 mm in diameter contribute less than 20% of the resistance to air flow in the lungs (28). This anatomical relationship permits considerable obstruction to air flow in the peripheral airways with little effect on R_T. Airway obstruction in this location has been called disease in the "silent zone" of the lung, because there can be extensive peripheral airway obstruction with little change in total airway resistance or pulmonary resistance (33). Measurements other than airway or pulmonary resistance may be more sensitive in detecting peripheral airway obstruction. The development of frequency dependence of pulmonary resistance during acute myocardial infarction with only moderate rise in total pulmonary resistance is highly suggestive of alterations in peripheral airways (29, 34). Other techniques that would be expected to detect peripheral airway obstruction include fractionation of pulmonary resistance with catheters placed in airways of various sizes (28), partitioning the distribution of ventilation using nitrogen washout curves (35), measurement of the lung volume at which airways close (36), and

demonstration of uneven time constants in the airways by determining the change in lung compliance at different frequencies (37). If the frequency dependence of resistance observed in this study is due to peripheral airway obstruction, these methods would probably demonstrate abnormalities in many patients with acute myocardial infarction. However, at the present time, to our knowledge, detailed studies of this nature have not been performed.

Factors resulting in changes in the mechanical properties of the peripheral airways have recently been reviewed in detail (29, 38). In addition to regional alterations in ventilation, pulmonary congestion has been shown to result in closure of collateral channels of ventilation between pulmonary segments in dogs (39). Anatomic studies show that pulmonary congestion widens the alveolar walls so that the pores of Kohn would probably be closed (31). Therefore, partially obstructed airways dependent upon collateral channels for adequate ventilation may become underventilated in the presence of pulmonary congestion due to closure of these collateral channels. The resultant alteration in airway time constants could account for the frequency dependence of pulmonary resistance seen in our subjects.

Recent studies in dogs with developing pulmonary edema, in which peripheral airway resistance was measured, demonstrated a rise in peripheral resistance which was most marked at low lung volumes (40). Morphological studies in the same animals suggested that competition for space between arteries and small airways in the bronchovascular sheath accounted for the rapidly reversible increase in peripheral resistance observed at elevations of left atrial pressure up to 15 mm Hg. At higher left atrial pressures, elevation in peripheral resistance was "irreversible" and was attributed to interstitial and alveolar edema. Peribronchial edema with resultant narrowing of the airways in the bronchovascular sheath is a likely additional mechanism. These pathophysiological processes would be expected to result in uneven time constants in the peripheral airways and would cause the alterations in pulmonary mechanics seen in pulmonary congestion after acute myocardial infarction.

Interdependence of airways. Recent studies have demonstrated that the uniform distribution of airflow within the lungs is assisted by interdependence of airways, so that a unit with compromised structure maintains reasonably normal ventilation because of the tethering effects of its normal neighbors (41). Pulmonary congestion and pulmonary edema could alter interdependence and thereby produce frequency dependence of pulmonary resistance. However, we are unaware of any attempt to determine the effect of pulmonary congestion on interdependence of airways.

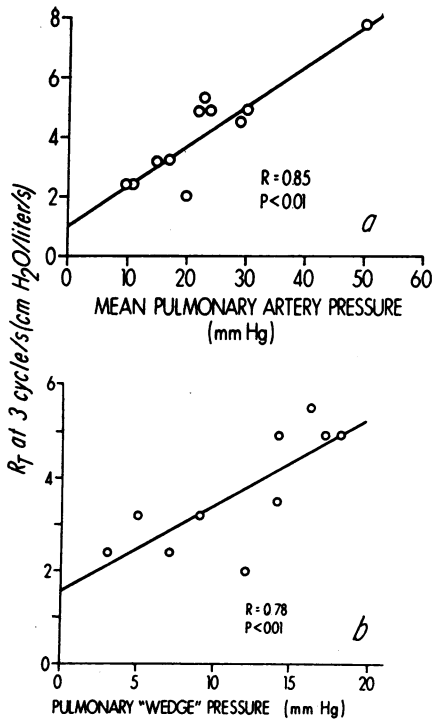

FIGURE 8 Correlation between R_s and (*a*) mean pulmonary artery pressure and (*b*) pulmonary wedge pressure.

Relationship between alterations in hemodynamics and pulmonary function. Table V and Fig. 8 show that the development of elevated values of both R_s and R_{RES} had a highly significant correlation with elevation of the pulmonary artery pressure and pulmonary capillary wedge pressure. The FDI significantly correlated with pulmonary artery pressure but not with the wedge pressure. These findings support the conclusion that the elevated vascular pressures account at least in part for the abnormal values of R_T. It is tempting to recommend determination of R_s and R_{RES} or the FDI as a noninvasive method of detecting elevations of pulmonary vascular pressures. Such an application would be limited by the fact that early chronic obstructive pulmonary disease, hypoalbuminemia, and acute bronchiolitis are among diseases that show or would be expected to show elevated value of R_T at 3 cycle/s and an abnormal amount of frequency dependence of resistance (34, 37, 42). These diseases would therefore give false positive results. However, normal values for resistance and the FDI may be of value in excluding the diagnosis of elevated pulmonary vascular pressures. Studies in a larger series of patients with different causes of elevated pulmonary vascular pressures would be required in order to determine the usefulness of this application of resistance measurements.

Pulmonary extravascular water volume. The poor correlation between pulmonary extravascular water volume and other pulmonary and hemodynamic data was somewhat surprising. Determinations of pulmonary extravascular volume in animals indicate that the percent of total lung water measured by this method varies considerably with the mechanism used to induce pulmonary congestion (43). Also, occlusion of pulmonary vessels decreases the observed pulmonary extravascular water volume (44). Since patients with acute myocardial infarction and pulmonary congestion may stop perfusing parts of their lungs due to perivascular cuffing or other mechanisms, it is not surprising that the values of pulmonary extravascular water volume are at times lower than expected.

Hypoxia and R_T. The development of frequency dependence of resistance and elevated values of R_T in acute myocardial infarction would be expected to cause uneven distribution of ventilation to perfusion and arterial hypoxia. The arterial P_{O_2} should, therefore, closely correlate with R_T and the FDI. However, even though R_T and pulmonary vascular pressures tended to be higher in the more hypoxic patients, significant correlations between arterial P_{O_2} and these parameters could not be demonstrated (Table V). Studies by Kazemi, Parsons, Valencia, and Strieder (6) may partly explain the failure to find a significant correlation between arterial hypoxia and these parameters. They performed regional studies of pulmonary ventilation and perfusion, and showed that regional ventilation-to-perfusion ratios are actually more uniform in patients with acute myocardial infarction than in normal subjects, because of diminished pulmonary blood flow in the dependent zones of the lung. Since hypoxia is an extremely common finding in acute myocardial infarction, this mechanism must only modify rather than prevent arterial hypoxia. Mismatching of ventilation to perfusion may still be present within the gross zones analyzed by external scanning techniques. In addition, regional hypoxia, acidosis, or currently unidentified humoral or reflex mechanism may alter the airways and the pulmonary vasculature in a manner that tends to preserve normal distribution of ventilation to perfusion and thereby minimize arterial hypoxia (45).

Correlations with clinical and radiological findings. The clinical classification of the patients showed a significant correlation with pulmonary wedge pressure and many of the tests indicative of airway obstruction. This study, therefore, confirms the value of the physical examination in detecting the physiological abnormalities accompanying pulmonary congestion. Surprisingly, the signs of congestion demonstrated by the roentgenograms of the chest only correlated with FEV and ($FEF_{25-75\%}$). In contrast, McHugh and co-workers (12), in a study of 30 patients, found that the abnormalities on the chest X-rays suggestive of pulmonary congestion had a reasonable correlation with the pulmonary wedge pressure and the arterial P_{O_2}. However, they suggested that the roentgenographic abnormalities may develop and clear more slowly than the hemodynamic changes. The X-ray abnormalities could therefore be out of phase with the hemodynamic data, with a resultant poor correlation. In this study the failure to demonstrate a significant correlation between roentgenographic findings and many of the other parameters may be caused in part by this phase lag. In addition, in this study roentgenograms of the chest in only 10 patients were compared to the other indices, so that the sample size may have been too small to demonstrate a significant correlation.

Detection of peripheral airway disease. Most methods for diagnosing peripheral airway disease, such as radioactive gas techniques and measurements of lung compliance at different ventilatory frequencies, are either too complex or too uncomfortable to be suitable for wide clinical application. Determination of lung closing volumes by inspiring oxygen or a foreign gas circumvents many of the undesirable features of the other methods, but requires a carefully controlled ventilatory maneuver. The technique of determining R_T at different frequencies used in this study avoids the need for special ventilatory maneuvers and uses relatively simple equipment. We have found this test to be a rapid and practical measurement in the study of a large number of ambulatory patients being screened for early obstructive lung disease.[5] Comparative studies with other techniques in man and experimental animals are needed to see if determination of R_T at different frequencies is a reliable method of detecting peripheral airway obstruction.

ACKNOWLEDGMENTS

We are indebted to Dr. Barry A. Gray for critical review of the manuscript.

This research was supported by grants-in-aid HL 03966, HL 05500, HL 10324, Contract no. NIH-PH-43-68-1331-MIRU, National Heart and Lung Institute, National Institutes of Health, and the Atomic Energy Project at the University of Rochester, and has been assigned publication no. UR-3490-340.

REFERENCES

1. McNicol, M. W., B. J. Kirby, K. D. Bhoola, M. E. Everest, H. V. Price, and S. F. Freedman. 1970. Pulmonary function in acute myocardial infarction. *Br. Med. J.* 2: 1270.

[5] Hall, W. J., R. D. Webb, and R. W. Hyde. Unpublished data.

2. McNicol, M. W., B. J. Kirby, K. D. Bhoola, P. M. Fulton, and A. E. Tattersfield. 1966 Changes in pulmonary function 6–12 months after recovery from myocardial infarction. *Lancet.* **2**: 1441.
3. Valentine, P. A., D. C. Fluck, J. P. D. Mounsey, D. Reid, J. P. Shillingford, and R. E. Steiner. 1966. Blood-gas changes after acute myocardial infarction. *Lancet.* **2**: 837.
4. MacKenzie, G. J., S. H. Taylor, D. C. Flenley, A. H. McDonald, H. P. Staunton, and K. W. Donald. 1964. Circulatory and respiratory studies in myocardial infarction and cardiogenic shock. *Lancet.* **2**: 825.
5. Shillingford, J. P., and M. Thomas. 1967. Cardiovascular and pulmonary changes in patients with myocardial infarction treated in an intensive care unit. *Am. J. Cardiol.* **20**: 484.
6. Kazemi, H., E. F. Parsons, L. M. Valencia, and D. J. Strieder. 1970. Distribution of pulmonary blood flow after myocardial ischemia and infarction. *Circulation.* **41**: 1025.
7. Storstein, O., and K. Rasmussen. 1968. The cause of arterial hypoxemia in acute myocardial infarction. *Acta Med. Scand.* **183**: 193.
8. Pain, M. C. F., M. Stannard, and G. Sloman. 1967. Disturbances of pulmonary function after acute myocardial infarction. *Br. Med. J.* **2**: 591.
9. Fillmore, S. J., M. Shapiro, and T. Killip. 1970. Arterial oxygen tension in acute myocardial infarction. Serial analysis of clinical state and blood gas changes. *Am. Heart J.* **79**: 620.
10. Higgs, B. E. 1968. Factors influencing pulmonary gas exchange during the acute stages of myocardial infarction. *Clin. Sci. (Oxf.).* **35**: 115.
11. Valencia, A., and J. H. Burgress. 1969. Arterial hypoxemia following acute myocardial infarction. *Circulation.* **40**: 641.
12. McHugh, T. J., J. S. Forrester, L. Adler, D. Zion, and H. J. C. Swan. 1972. Pulmonary vascular congestion in acute myocardial infarction: Hemodynamic and radiologic correlations *Ann. Intern. Med.* **76**: 29.
13. Morris, J. F., A. Koski, and L. C. Johnson. 1971. Spirometric standards for healthy nonsmoking adults. *Am. Rev. Respir. Dis.* **103**: 57.
14. Fisher, A. B., A. B. DuBois, and R. W. Hyde. 1968. Evaluation of the forced oscillation technique for the determination of resistance to breathing. *J. Clin. Invest.* **47**: 2045.
15. Hyatt, R. E., I. R. Zimmerman, G. E. Peters, and W. J. Sullivan. 1970. Direct writeout of total respiratory resistance. *J. Appl. Physiol.* **28**: 675.
16. Frank, N. R., J. Mead, and J. L. Whittenberger. 1971. Comparative sensitivity of four methods for measuring changes in respiratory flow resistance in man. *J. Appl. Physiol.* **31**: 934.
17. Goldman, M., R. J. Knudson, J. Mead, N. Peterson, J. R. Schwaber, and M. E. Wohl. 1970. A simplified measurement of respiratory resistance by forced oscillation. *J. Appl. Physiol.* **28**: 113.
18. Otis, A. B., C. B. McKerrow, R. A. Bartlett, J. Mead, M. B. McIlroy, N. J. Salverstone, and E. P. Radford. 1956. Mechanical factors in distribution of pulmonary ventilation. *J. Appl. Physiol.* **8**: 427.
19. Gazioglu, K., J. J. Condemi, R. W. Hyde, and N. L. Kaltreider. 1971. Effect of isoproterenol on gas exchange during air and oxygen breathing in patients with asthma. *Am. J. Med.* **50**: 185.
20. Swan, H. J. C., W. Ganz, J. Forrester, H. Marcus, G. Diamond, and D. Chonetti. 1970. Catheterization of the heart in man with use of a flow-directed balloon-tipped catheter. *N. Engl. J. Med.* **283**: 447.
21. Chinard, F. P. 1951. Capillary permeability. *Bull. Johns Hopkins Hosp.* **88**: 489.
22. Sharp, J. T., G. T. Griffith, I. L. Bunnell, and D. G. Greene. 1958. Ventilatory mechanics in pulmonary edema in man. *J. Clin. Invest.* **37**: 111.
23. Hyatt, R. E., D. P. Schilder, and D. L. Fry. 1958. Relationship between maximum expiratory flow and degree of lung inflation. *J. Appl. Physiol.* **13**: 131.
24. Mills, R. J., G. Cumming, and P. Harris. 1963. Frequency-dependent compliance at different levels of inspiration in normal adults. *J. Appl. Physiol.* **18**: 1061.
25. Briscoe, W. A. 1965. Lung volumes. *Handb. Physiol.* 2 (Sect. 3 Respiration) : 1370.
26. Bedell, G. N., Y. Suzuki, and W. R. Wilson. 1961. Pulmonary abnormalities in congestive heart failure. *J. Lab. Clin. Med.* **58**: 798. (Abstr.)
27. Peters, J. P., Jr., and D. P. Barr. 1920. Studies of the respiratory mechanisms in cardiac dyspnea. II. A note on the effective lung volume in cardiac dyspnea. *Am. J. Physiol.* **54**: 335.
28. Macklem, P. T., and J. Mead. 1967. Resistance of central and peripheral airways measured by a retrograde catheter. *J. Appl. Physiol.* **22**: 395.
29. Macklem, P. T. 1971. Airway obstruction and collateral ventilation. *Physiol. Rev.* **51**: 368.
30. Butler, J., C. G. Caro, R. Alcala, and A. B. DuBois. Physiological factors affecting airway resistance in normal subjects and in patients with obstructive respiratory disease. *J. Clin. Invest.* **39**: 584.
31. Staub, N. C., H. Nagano, and M. L. Pearce. 1967. Pulmonary edema in dogs, especially the sequence of fluid accumulation in the lungs. *J. Appl. Physiol.* **22**: 227.
32. Hughes, J. M. B., J. B. Glazier, D. Y. Rosenzweig, and J. B. West. 1969. Factors determining the distribution of pulmonary blood flow in patients with raised pulmonary venous pressure *Clin. Sci. (Oxf.).* **37**: 847.
33. Mead, J. 1970. The lung's quiet zone. *N. Engl. J. Med.* **282**: 1318.
34. Grimby, G. T., T. Takishima, W. Graham, P. T. Macklem, and J. Mead. 1968. Frequency dependence of flow resistance in patients with obstructive lung disease. *J. Clin. Invest.* **47**: 1455.
35. Bouhuys, A. 1964. Distribution of inspired gas in the lungs. *Handb. Physiol.* 1(Sect. 3 Respiration) : 715.
36. Anthonisen, N. R., J. Danson, P. C. Robertson, and W. R. D. Ross. 1969. Airway closure as a function of age. *Respir. Physiol.* **8**: 58.
37. Woolcock, A. J., N. J. Vincent, and P. T. Macklem. 1969. Frequency dependence of compliance as a test for obstruction in small airways. *J. Clin. Invest.* **48**: 1097.
38. Milic-Emili, J., and F. Ruff. 1971. Effects of pulmonary congestion and edema on the small airways. Bull. *Physio-Pathol. Respir.* **7**: 1181.
39. Ankeney, J. L., C. A. Hubay, and F. W. Tillotson. 1950. The effect of changes in pulmonary circulation on collateral ventilation. *Surg. Forum.* **1**: 25.

40. Hogg, J. C., J. B. Agarawal, A. J. S. Gardiner, W. H. Palmer, and P. T. Macklem. 1972. Distribution of airway resistance with developing pulmonary edema in dogs. *J. Appl. Physiol.* **32**: 20.
41. Menkes, H., D. Lindsay, L. Wood, A. Muir, and P. T. Macklem. 1972. Interdependence of lung units in intact dog lungs. *J. Appl. Physiol.* **32**: 681.
42. Ruff, F., J. M. B. Hughes, N. Stanley, D. McCarthy, R. Greene, A. Aronoff, L. Clayton, and J. Milic-Emili. 1971. Regional lung function in patients with hepatic cirrhosis. *J. Clin. Invest.* **50**: 2403.
43. Pearce, M. L., J. Yamashita, and J. Beazell. 1965. Measurement of pulmonary edema. *Circ. Res.* **16**: 482.
44. Kirk, B. S. 1969. Effect of alteration in pulmonary blood flow on lung-exchangeable water in the dog. *J. Appl. Physiol.* **27**: 607.
45. Fishman, A. P. 1961. Respiratory gases in the regulation of the pulmonary circulation. *Physiol. Rev.* **41**: 214.