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### Research Article

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# Hypoxemia in Pulmonary Embolism, a Clinical Study

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**ABSTRACT** The cause of hypoxemia was studied in 21 patients with no previous heart or lung disease shortly after an episode of acute pulmonary embolism. The diagnosis was based on pulmonary angiography demonstrating distinct vascular filling defects or "cutoffs." It was found that virtually all of the hypoxemia in patients with previously normal heart and lungs could be accounted for on the basis of shunt-like effect. The magnitude of the shunting did not correlate with the percent of the pulmonary vascular bed occluded nor with the mean pulmonary artery pressure. The shunts tended to gradually recede over about a month after embolism. Patients without pulmonary infarction were able to inspire 80–111% of their predicted inspiratory capacities, and this maneuver temporarily diminished the observed shunt. Patients with pulmonary infarcts were able to inhale only to 60–69% of predicted inspiratory capacity, and this did not reverse shunting. These data suggest that the cause of right-to-left shunting in patients with pulmonary emboli is predominantly atelectasis.

When the elevation of mean pulmonary artery pressure was compared to cardiac index per unit of unoccluded lung, it fell within the range of pulmonary hypertension predicted from published data obtained in patients with exercise in all except one case. This observation suggests that pulmonary vasoconstriction following embolism is not important in humans, although these data are applicable only during the time interval in which our patients were studied and in patients receiving heparin.

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## INTRODUCTION

Hypoxemia usually accompanies pulmonary embolism in man (1), but its causes are ill understood, and its natural course is poorly documented. Attempts to determine the cause of the hypoxemia have been made in laboratory animals, but results are contradictory. Moreover, animal studies may not be satisfactory for describing the physiologic events after pulmonary embolism in man for the following reasons. (a) Since animals must be anesthetized, they are studied either under conditions of blunted respiratory response or artificial ventilation. (b) Animals usually are studied immediately after embolization without extended observations. (c) The response to foreign body or autologous blood clot emboli may differ from the response to emboli that have existed as thrombi in peripheral veins. (d) There are considerable species differences in the responses to emboli (2–5).

Interpretation of previous studies in man concerning the cause of hypoxemia after pulmonary embolism is impaired by the following factors. (a) The interval from the first symptom of embolization to the study is frequently over a month (6–8). (b) Patients may have congestive heart failure (9–11) or unrelated pulmonary disease (12) as a cause for hypoxemia. (c) Patients with recurrent emboli are not separated from those with a single episode of embolization (7). (d) Postoperative patients, who may have other causes for hypoxemia, are included (13). (e) The diagnosis frequently is made only on clinical grounds, and the extent of embolic occlusion is seldom assessed. (f) Serial studies on the same patients are not available.

The purposes of the present study were to determine in patients without other heart or lung disease the mechanisms and course of the hypoxemia associated with proven pulmonary emboli and the relationship of hypoxemia to the extent of embolic occlusion.

## METHODS

*Study plan.* Patients had a right heart catheterization in the supine position as soon as possible after pulmonary embolism was suspected. Cardio-green dye was injected from the superior vena cava and pulmonary artery in order to estimate cardiac output and to detect intracardiac right-to-left shunts. Pressures were recorded in the right atrium, ventricle, and pulmonary artery; wedge pressures were obtained when possible. Expired gas was collected for measurements of oxygen consumption and carbon dioxide production while the patient breathed room air; simultaneously, samples of arterial and mixed venous blood were collected for measurement of pH and blood gases. Blood collection was repeated after breathing 100% oxygen for 15 min in order to estimate venous admixture due to true right-to-left shunting. Next, pulmonary angiograms were obtained through a No. 8 catheter with the tip in the main pulmonary artery, injecting 1 mg per kg of Renografin 76<sup>1</sup> up to a maximum of 70 ml.

On one to three occasions during the next 4 wk, expired gas was collected and arterial blood gases were measured while the patient breathed room air and then 100% oxygen in the supine position for 15 min. During 100% oxygen breathing, completeness of nitrogen (N<sub>2</sub>) wash out was determined by continuously monitoring the exhalate with a nitrogen analyzer. The effect of deep breathing (voluntary or induced by intermittent positive pressure at 20-40 cm H<sub>2</sub>O) on the arterial oxygen tension (P<sub>aO<sub>2</sub></sub>) was noted; the maximum tidal volume during deep breathing was recorded. Spirometry was performed serially after each patient was free of pleuritic chest pain. Eight patients had repeat right heart catheterizations and pulmonary angiograms 13-35 (average 22) days after the first study. An additional patient had repeat angiograms at 3 and 13 months.

To further elucidate the cause of hypoxemia, the following studies were performed in selected patients: (a) slow space determination by Briscoe's two balloon-collecting system measuring expired nitrogen concentration at 1-min intervals while breathing 100% oxygen (14-16); (b) airway resistance by the method of DuBois, Botelho, and Comroe

(17); and (c) dynamic compliance by the method of von Neergaard, and Wirz (18).

*Analytical methods.* Blood oxygen saturation was measured with a reflection oximeter, and blood pH, carbon dioxide tension (P<sub>aCO<sub>2</sub></sub>), and P<sub>aO<sub>2</sub></sub> were measured, respectively, by a glass pH electrode, Severinghaus P<sub>CO<sub>2</sub></sub> electrode, and modified Clark P<sub>O<sub>2</sub></sub> electrode. Each instrument was calibrated just prior to each analysis with standard gases of known composition. Expired gas analysis was performed by infrared and paramagnetic gas analyzers or Scholander microanalysis. These methods have equal accuracy in our laboratory (19). Volumes were determined with a Tissot spirometer.

Blood obtained while the patient breathed 100% oxygen was injected into the cuvette of the P<sub>O<sub>2</sub></sub> electrode within 2 min after withdrawal from the patient. When the P<sub>aO<sub>2</sub></sub> was 300-600 mm Hg the P<sub>O<sub>2</sub></sub> measured in shed blood maintained at 37°C decreased on average 2.5 mm Hg per min; this correction factor agrees with that suggested by Kelman and Nunn (20), and it was added to the determined P<sub>aO<sub>2</sub></sub>. Oxygen is consumed by the Clark P<sub>O<sub>2</sub></sub> electrode as well as by leukocytes during analysis (20). Therefore, a strip recording of oxygen tension with respect to time was obtained, and the slope was back extrapolated to the time of injection of blood into the cuvette for a more accurate estimate of oxygen tension.

*Calculations.* Arteriovenous oxygen difference (A-V O<sub>2</sub>) in ml/100 ml of blood was determined from the product of the arteriovenous oxygen saturation difference in per cent, the blood hemoglobin concentration in g/100 ml, and the normal oxygen capacity of hemoglobin (1.34 ml/g); the additional contribution of dissolved oxygen was determined by multiplying the Bunsen solubility coefficient (0.003 ml per mm Hg/100 ml) times the difference between arterial and mixed venous P<sub>O<sub>2</sub></sub>. Alveolar-arterial oxygen tension differences (A-a D<sub>O<sub>2</sub></sub>) were calculated from the determined P<sub>aO<sub>2</sub></sub> and the mean alveolar oxygen tension (P<sub>AO<sub>2</sub></sub>) determined from the alveolar air equation (21).

The fraction of true shunting was calculated from a modification of the Berggren formula (22, 23):

$$\dot{Q}_s/\dot{Q}_c = \frac{[(A-a D_{O_2})(0.003) + O_2 \text{ cap} (1 - Sa_{O_2})] 100\% O_2}{A-V O_2 + [(A-a D_{O_2})(0.003) + O_2 \text{ cap} (1 - Sa_{O_2})] 100\% O_2} \quad (1)$$

where  $\dot{Q}_s/\dot{Q}_c$  = the fraction of the cardiac output shunted, O<sub>2</sub> cap = the oxygen capacity of hemoglobin/100 ml blood, and Sa<sub>O<sub>2</sub></sub> = the fraction of hemoglobin saturated with oxygen when the patient breathes 100% oxygen. When P<sub>aO<sub>2</sub></sub> is greater than 150 mm Hg, the term O<sub>2</sub> cap (1-Sa<sub>O<sub>2</sub></sub>) is neglected. It is apparent that maneuvers which reduce the A-a D<sub>O<sub>2</sub></sub> breathing 100% oxygen might do so either by reducing A-V O<sub>2</sub> difference (*i.e.*, by increasing cardiac output) or by reducing the shunt (24). However, in three of the patients A-V O<sub>2</sub> differences were measured both during spontaneous and assisted respiration, and the A-V O<sub>2</sub> difference increased slightly during assisted ventilation indicating that any decrease in A-a D<sub>O<sub>2</sub></sub> was caused by change in the shunt flow rather than change in cardiac output.

A calculation was made of the A-a D<sub>O<sub>2</sub></sub> breathing room air which could be explained by the shunt measured while the subject breathed 100% oxygen. These calculations were made assuming that the shunt caused the same oxygen deficit in

arterial blood while breathing room air as while breathing 100% oxygen. Thus,

$$(PAO_2 - PaO_2)_{\text{air}} = \frac{(\text{numerator of eq 1}) - O_2 \text{ cap} (Sc'_{O_2} - Sa_{O_2})}{0.003} \quad (2)$$

where (PAO<sub>2</sub> - PaO<sub>2</sub>)<sub>air</sub> = A-a D<sub>O<sub>2</sub></sub> breathing air. Knowing the alveolar oxygen tension breathing air (P<sub>AO<sub>2</sub></sub>) and assuming that the end-capillary O<sub>2</sub> saturation (Sc'<sub>O<sub>2</sub></sub>) is in equilibrium with the P<sub>AO<sub>2</sub></sub> at arterial pH, the unique values of arterial O<sub>2</sub> tension (P<sub>aO<sub>2</sub></sub>) and O<sub>2</sub> saturation (Sa<sub>O<sub>2</sub></sub>) are located on the oxyhemoglobin dissociation curve (25) which will satisfy equation 2.

## RESULTS

37 patients suspected of having acute pulmonary embolism had right heart catheterizations and pulmonary

<sup>1</sup> Made by E. R. Squibb & Sons, New York.

angiograms 0–19 (average 6) days after the first symptoms of the present episode of embolism. 21 of the 37 patients had positive angiograms and no other heart or lung disease, and form the basis of this report. Cardiac catheterization data of the patients are listed in Table I and arterial blood gas results in Table II.

**Shunt-like effect.** Each patient had one to four arterial blood gas determinations obtained 0–33 days after the first symptom of embolism. The measurements of A-a  $D_{O_2}$  breathing 21%  $O_2$  have been plotted against the A-a  $D_{O_2}$  which could be accounted for entirely by the shunt measured while breathing 100%  $O_2$  (Fig. 1); the points fall randomly around a line near the line of identity ( $r = 0.80$ );  $P < 0.005$ ). The mean A-a  $D_{O_2}$  measured with the patient breathing air exceeded the mean predicted A-a  $D_{O_2}$  by only 5.5 mm Hg. Thus, true shunting accounted for most of the hypoxemia associated with acute pulmonary embolism in these patients with previously normal heart and lungs.

Shunting usually receded gradually over about a month following embolism (Fig. 2). However, hypoxemia that was severe persisted for only 2 hr in one patient who, 2 days after the acute episode, showed 21% pulmonary vascular occlusion by angiography. The mean A-a  $D_{O_2}$  breathing 100%  $O_2$  the 1st wk after diagnosis was not significantly different from the mean A-a  $D_{O_2}$  the 2nd wk but was significantly different from the mean A-a  $D_{O_2}$  3 wk–6 months after the diagnosis ( $P < 0.05$ ). 12 patients had at least one repeat measurement, and paired  $t$  test analysis of the first with the last A-a  $D_{O_2}$  breathing 100%  $O_2$  showed a statistically significant reduction ( $P < 0.005$ ).

13 patients had serial observations of A-a  $D_{O_2}$  breathing room air and no recent surgical procedures. In seven of these, the A-a  $D_{O_2}$  breathing room air increased at a later time when A-a  $D_{O_2}$  breathing 100%  $O_2$  had decreased. In one of the seven, the cause of the increasing A-a  $D_{O_2}$  breathing room air was undoubtedly due to ventilation-perfusion mismatching. However, in the other six, the increased A-a  $D_{O_2}$  breathing room air was associated with some combination of increased pH, increased RQ, or decreased  $P_{aCO_2}$ —all of which exaggerate an A-a  $D_{O_2}$  breathing room air that is due to a shunt—and the shunt could still explain the A-a  $D_{O_2}$  observed breathing room air.

The magnitude of the shunt did not correlate significantly with the per cent of vascular bed occluded ( $r = 0.07$ ;  $P > 0.30$ ) nor with mean pulmonary artery pressure ( $r = 0.12$ ;  $P > 0.30$ ).

When 100% oxygen was administered to these patients by intermittent positive pressure (IPPB)<sup>2</sup> at pres-

<sup>2</sup> Abbreviations used in this paper: IPPB, intermittent positive pressure; FEV, forced expiratory volume; FVC, forced vital capacity.

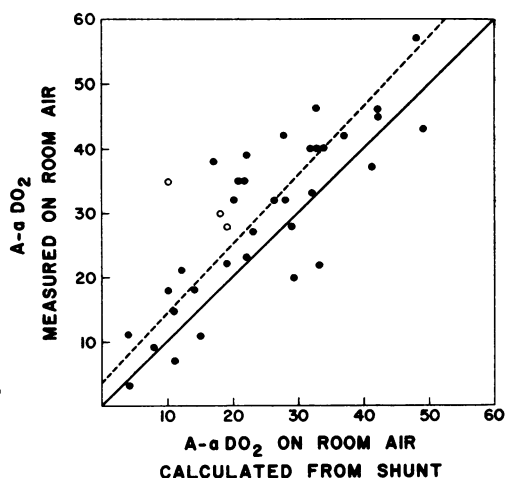


FIGURE 1 Alveolar-arterial oxygen tension differences during room air breathing are compared with the A-a  $D_{O_2}$  that can be accounted for solely by the right-to-left shunt measured during 100% oxygen breathing. These data are from 18 of the patients before any surgical procedures and include one-four (average two) studies on each patient. The solid line is a line of identity, and the dashed line is the orthogonal regression line of best fit for the data. The open circles refer to measurements in three patients obtained before heparin administration.

ures of 20–40 cm  $H_2O$  causing tidal volumes of 1500–4000 ml, two types of response were observed (Fig. 3). Patients with pulmonary infarction had a relatively small A-a  $D_{O_2}$  breathing 100%  $O_2$  at normal tidal volumes, indicating a small shunt, and deep breathing caused little change. However, the maximum tidal volumes of these patients were only 60–69% (average 65%) of their predicted inspiratory capacities. Patients with emboli but no infarction had larger levels of A-a  $D_{O_2}$  breathing 100%  $O_2$  at normal tidal volumes, and the A-a  $D_{O_2}$  was decreased significantly by IPPB; in these patients tidal volumes achieved on IPPB were 80–111% (average 88%) of the predicted inspiratory capacity. Five patients whose A-a  $D_{O_2}$  breathing 100%  $O_2$  decreased during deep breathing continued to breathe 100% oxygen for 15 additional min after deep breathing, and the A-a  $D_{O_2}$  returned to the level observed before deep breathing. One patient performed voluntary inspiratory capacities while breathing room air. The A-a  $D_{O_2}$  breathing 21%  $O_2$  was reduced from 29–20 mm Hg and returned to 26 mm Hg within 15 min. Paired  $t$  test analysis showed that deep breathing caused no significant change in A-a  $D_{O_2}$  breathing 100%  $O_2$  in patients with infarction ( $P > 0.3$ ) but caused a significant reduction in patients without infarction ( $P < 0.02$ ).

10 of the 21 patients with positive pulmonary angiograms showed discoid atelectasis on roentgenograms of the chest. Only 1 of 10 patients with negative angiograms demonstrated discoid atelectasis, but no association be-

TABLE I  
Right Heart

Patient	Age	Sex	Angiogram occlusion	Mean pulmonary artery pressure	Wedge pressure	Right ventricular end-diastolic pressure	Cardiac index
			%	mm Hg	mm Hg	mm Hg	liters/min/m <sup>2</sup>
D. C.	35	F	70	11	5	7	2.7*
S. M.	31	F	3	11	6	5	4.0
M. S.	59	F	6‡	18	9	6	3.0
H. Mc.	27	F	35‡	25			
L. M.	59	M	52	25			1.3 <sup>  </sup> (2.4)
			39	20	11		2.5
			3	13	5		2.4
N. S.	20	F	8‡	11	6	6	4.3
			0	9			3.7*
B. T.	29	F	61‡	27	12	9	4.3
			0	15			
J. V.	65	M	35	22	5	5	2.8
			3	16	8	8	2.6
L. T.	56	F	80‡	24	7	15	2.3
			11	15	6	8	3.4*
W. W.	68	M	18‡	20	4	8	2.3
			0	12			
J. P.	44	F	14				
D. M.	25	F	22‡	15	9	3	2.5*
			18	15	8	8	2.3
				23		12	
I. R.	59	F	5‡	10	3	4	2.6*
C. L.	42	F	29‡	23	5	2	3.7
M. B.	48	F	6	14	6	5	3.2
			0	14	5	3	3.3
B. L.	43	M	81‡	28	10	11	1.6
			9	16	10	8	3.5
K. M.	34	F	26‡	14	5	5	3.3
L. H.	43	F	8	15		7	
F. B.	31	F	17	12	4	3	6.0
A. R.	53	F	54	16	4	6	5.8
E. T.	60	M	21	14	6	5	3.4

\* Fick cardiac output.

‡ Interval of time since the first symptom of the first episode of embolism studied.

§ Pulmonary infarcts present on chest roentgenogram.

<sup>||</sup> This Fick cardiac output is probably falsely low because of a technical error giving a  $\dot{V}_{O_2}$  of 147 ml/min. On six subsequent occasions  $\dot{V}_{O_2}$  was  $275 \pm 23$  ml/min. Using a  $\dot{V}_{O_2}$  of 275 ml/min gives the cardiac index indicated in parentheses.

tween a positive pulmonary angiogram and the presence of discoid atelectasis could be demonstrated by chi square analysis ( $P > 0.1$ ). Although there was a high incidence of pleuritic chest pain (81%), there was not good correspondence between the severity of pain and the extent of shunting; some patients with severe pain had small shunts. In addition, the A-a  $D_{O_2}$  breathing 100%  $O_2$  was not significantly different in patients requiring no more than one dose of narcotics for pain compared with those requiring two or more doses of nar-

cotics for the pain. The patients received on average 2.4 doses of narcotics (range 0-10 doses) before the first set of blood gases. After the first set of blood gases they received an average of 2.7 doses of narcotics (range 0-25 doses) over the next 2-3 wk.

*Lung compliance.* Specific dynamic compliance was performed on three patients with A-a  $D_{O_2}$  breathing 100%  $O_2$  of 200-122 mm Hg. In two patients the A-a  $D_{O_2}$  breathing 100%  $O_2$  was reduced (61 and 79%) and specific dynamic compliance increased (17 and 30%) by

Catheterization Data

Pulmonary vascular resistance	Arteriovenous oxygen difference		Time since first symptom‡	Time since most recent exacerbation of symptoms	Recurrent emboli at first study	Recurrent emboli since last study
	Air/100% O <sub>2</sub>					
<i>dyne-cm/sec<sup>2</sup></i>	<i>cc/100 cc</i>		<i>days</i>	<i>hr</i>		
100	3.3	3.4	2	24		
91	3.7	3.7	19	96		
160		4.7	14	168		
			14	24		
	5.1		1	24	X	
126	4.5	3.6	95			
114			436			X
61	3.9	3.5	14	72		
	3.4	4.1	33			
148	3.7	3.6	15	24		
			39			
278	5.0		0	6	X	
139	4.4	4.3	32			
252	6.4	6.0	5	120		
99	3.8	4.0	29			
305	6.0	6.3	11	72		
			31	192		
117	3.8	3.8	7	96	X	
151	4.0	3.3	43			X
	3.6		163			X
84	3.4	3.6	5	120		
169	3.9	3.4	19	48		
105	3.8	4.2	5	24		
174	3.6	3.7	18			
480	5.1	3.8	1	6		
75	4.0	4.2	19	120		
106	5.8		5			
			2	24		
65	3.1	4.1	5	72	X	
96	3.3	3.6	8	96		
89	5.5	5.3	3	24		

deep breathing. In the third patient the A-a D<sub>O<sub>2</sub></sub> breathing 100% O<sub>2</sub> decreased less (27%) during deep breathing than in the other two patients, and her specific dynamic compliance was not changed by deep breathing. The right-to-left shunt in this latter patient was at the atrial level as was demonstrated by a superior vena cava dye dilution curve.

*Extrapulmonary shunts.* In only 1 of 10 patients in whom superior vena cava (SVC) dye dilution curves were performed was right-to-left shunting demonstrated

at the atrial level. In this patient (F. B.) pulmonary artery pressure was normal; mean right atrial pressure and mean pulmonary wedge pressure were both 4 mm Hg, and the angiogram showed 17% occlusion of the pulmonary vascular bed.

*Ventilation-perfusion-diffusing capacity mismatching.* The average discrepancy between the measured A-a D<sub>O<sub>2</sub></sub> breathing air and that predicted from the shunt calculated with the A-a D<sub>O<sub>2</sub></sub> measured on 100% oxygen was only 5.5 mm Hg, a value easily explained by normal

TABLE II  
Arterial Blood Gas Studies during Hospitalization

Patient	Hemo- globin	Pao <sub>2</sub>			Paco <sub>2</sub>	pH	Respi- ratory rate	Tidal volume	V <sub>D</sub> /V <sub>T</sub>	PAO <sub>2</sub> -PaO <sub>2</sub> breathing 100% O <sub>2</sub>	Oxygen consump- tion	Respi- ratory quotient	Days since embolism
		PAO <sub>2</sub>	Meas	Pred									
	gm%	mm Hg	mm Hg	mm Hg			liters			ml/min			
D. C.	7.6	107	74	75	32	7.53	17	0.282	0.22	120	158	0.74	2
S. M.	10.8	102	67		35	7.47	17	0.398	0.41	200	148	0.86	19*
M. S.	10.6		74		35	7.40				140			14
H. Mc.			80		35	7.40							14
L. M.	14.2	113	70	64	32	7.45	22	0.316	0.45	432	147	0.83	1
	12.6	114	57	66	32	7.47	21	0.531	0.35	318	310	0.76	4
	12.3	108	64	71	33	7.46	18	0.598	0.45	240	277	0.75	10
N. S.	10.3	119	79	87	23	7.52	14	0.618	0.21	112	223	0.75	14
	10.9	95	86	87	41	7.39	12	0.405	0.34	48	188	0.73	33
B. T.	11.6	96	75		36	7.46	25	0.344	0.42		273	0.66	15
	11.2	108	81	85	36	7.44	17	0.478	0.31	140	249	0.85	18
	11.7	101	83	91	40	7.44	14	0.483	0.32	58	237	0.81	22
J. V.	13.4	97	69	78	44	7.40	14	0.496	0.51	144	194	0.82	0
	10.4	112	60		28	7.54	28	0.661	0.52		351	0.76	3*
	9.4	110	72		32	7.50	19	0.707	0.43	196	327	0.82	8*
	10.2	106	76	85	35	7.52	17	0.678	0.40	96	271	0.83	32
L. T.	11.6	99	67	79	32	7.44	17	0.272	0.42	134	139	0.61	5
	9.8	95	62		35	7.45	15	0.562	0.34	84	301	0.69	12*
W. W.	17.0	83	68	72	42	7.39	20	0.230	0.60	140	119	0.60	11
	15.4	91	80	76	37	7.44	19	0.441	0.55	127	235	0.61	15
	15.3	84	77	73	44	7.44	21	0.469	0.53	103	257	0.65	22
J. P.	7.8	97	75		43	7.44	7	0.476	0.38		118	0.80	8
	7.6	94	83	79	35	7.41	9	0.634	0.38	62	218	0.77	15
D. M.	9.2	102	80	83	34	7.46	15	0.316	0.32	91	155	0.72	7
	9.3	101	80	89	37	7.46	12	0.649	0.47	60	218	0.75	12
I. R.	6.6	98	58	66	33	7.49	16	0.260	0.38	153	140	0.58	5
	5.9	118	72	76	27	7.54	16	0.583	0.29	113	215	0.89	11
C. L.	10.7	99	62	58	34	7.48	13	0.613	0.37	311	290	0.64	19
	10.7	93	70	71	39	7.44	12	0.593	0.41	147	255	0.69	23
	10.7	106	88	92	32	7.46	13	0.566	0.22	70	278	0.75	30
M. B.	13.0	103	63	69	39	7.44	20	0.371	0.47	213	181	0.85	5
	13.0	94	66	65	35	7.48	23	0.303	0.43	248	241	0.58	9
	11.4	98	66	70	36	7.44	23	0.289	0.57	196	149	0.68	18
	10.4	127	82	85	24	7.58	22	0.629	0.34	112	214	1.10	32
B. L.	15.2	99	64	89	38	7.43	42	0.214	0.65	94	155	0.72	1
	12.9	112	73	90	30	7.48	23	0.472	0.32	122	283	0.82	4
	13.2	78	75	74	42	7.42	11	0.524	0.40	44	275	0.56	13
	12.8	117	102		34	7.48	21	0.283	0.39		106	1.14	19
K. M.	13.6	98	60	81	38	7.48	23	0.385	0.36	139	305	0.72	5
	13.5	117	71	84	32	7.54	19	0.602	0.36	144	222	1.13	8
	11.4	123	81	95	28	7.55	15	0.863	0.21	79	267	1.15	13
L. H.	14.6	110	78	84	31	7.46	12	0.638	0.29	159	224	0.81	4
F. B.	12.9	107	72	86	36	7.47	17	0.565	0.38	122	268	0.86	5
A. R.	12.6	117	95	84	25	7.60	18	0.831	0.32	93	345	0.81	8
E. T.	11.1	125	95	107	19	7.63	14	1.123	0.25	43	299	0.83	3
	10.0	123	103	94	22	7.63	18	0.990	0.32	49	341	0.86	5

\* Blood gases may have been affected by complications of therapy in these studies. S. M. had had an iatrogenic pneumothorax requiring a chest tube on day 18, J. V. a vena caval ligation on day 1, and L. T. an embolectomy on day 7.

degrees of uneven ventilation-perfusion-diffusing capacity relationships.

11 patients had spirometry tracings during the 1st wk after diagnosis at a time when increased A-a D<sub>o2</sub> breathing 100% O<sub>2</sub> was still present. Eight had FEV<sub>1.0</sub> less than 85% of predicted, but seven of these also had restrictive ventilatory defects (FVC less than 85% of predicted). Only three of these eight had FEV<sub>1.0</sub> less than 80% of FVC (57, 78, and 72%). In these three the A-a D<sub>o2</sub> breathing 100% O<sub>2</sub> accounted for all of the

A-a D<sub>o2</sub> breathing air in two of the patients but explained only 75% of the A-a D<sub>o2</sub> breathing air in the patient with the most severe obstructive ventilatory defect.

Two patients with moderate hypoxemia due to pulmonary embolism had determinations of slow space ventilation. One study was 5 days and another 32 days after the first symptom of embolism. Both patients demonstrated normal nitrogen clearance rates and a slowly ventilated compartment could not be clearly defined.

## DISCUSSION

*Extent of embolic occlusion and reliability of its estimate.* The estimated extent of embolic vascular occlusion varied from 3–81% of the pulmonary vascular bed and showed a good correlation with the resting mean pulmonary artery pressure ( $r = 0.66$ ;  $P < 0.01$ ). Thus the study encompasses a wide range of severity. As pulmonary vascular bed becomes progressively occluded by emboli, the remaining fraction of the vascular bed must accept a progressively higher blood flow in order to sustain the normal cardiac output. It is a reasonable approximation to assume that if reflex pulmonary vasoconstriction does not occur after a pulmonary embolus the mean pulmonary artery pressure will rise no higher in response to the increment of blood flow through the remaining vascular bed than would be expected for a

similar increment of pulmonary blood flow in a normal person from rest to exercise. Based upon this assumption the solid lines in Fig. 4 reflect the normal range of mean pulmonary artery pressures expected in our patients from the increments in resting flow through the remaining normal lung after taking into account the extent of occlusion. These ranges were obtained from composite data relating mean pulmonary artery pressure and cardiac output in normal persons at rest and exercise (26–35).

In only one instance was the pulmonary artery pressure higher than could be explained by simple mechanical obstruction; thus the data provide no support to the contention that generalized pulmonary vasoconstriction occurs after an embolus. In those instances where cardiac catheterization was repeated the fall of mean pulmonary

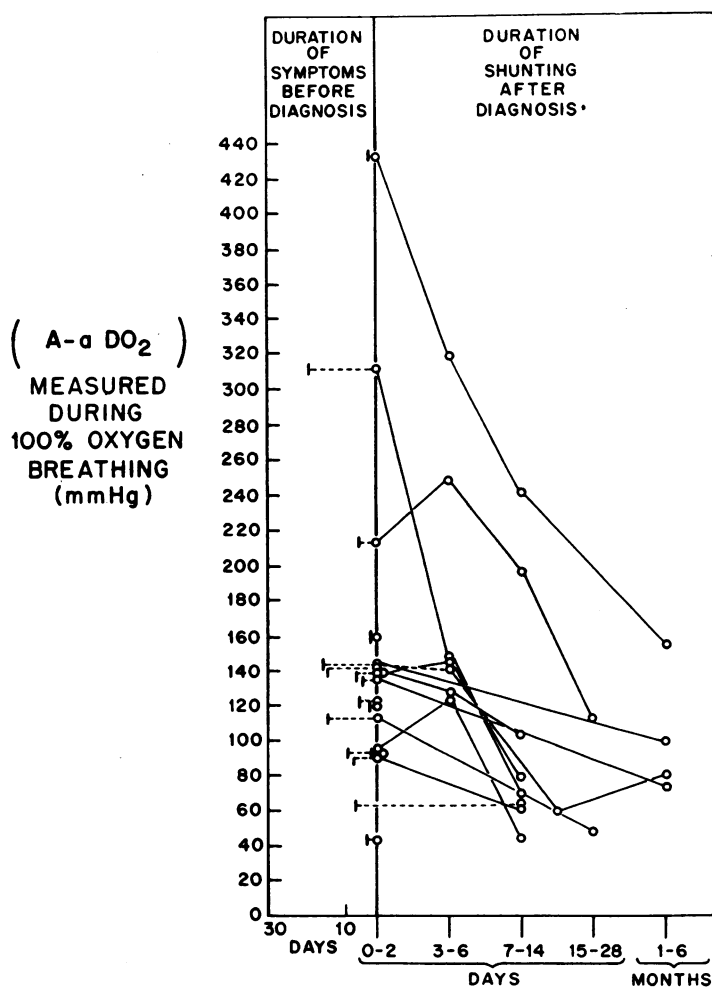


FIGURE 2 Duration of right-to-left shunting. The solid vertical line indicates the time of angiographic diagnosis of pulmonary embolism. The dashed lines to the left indicate the duration of symptoms before angiography, and the solid lines to the right indicate the  $A-a D_{O_2}$  while breathing 100% oxygen as an estimate of shunting.



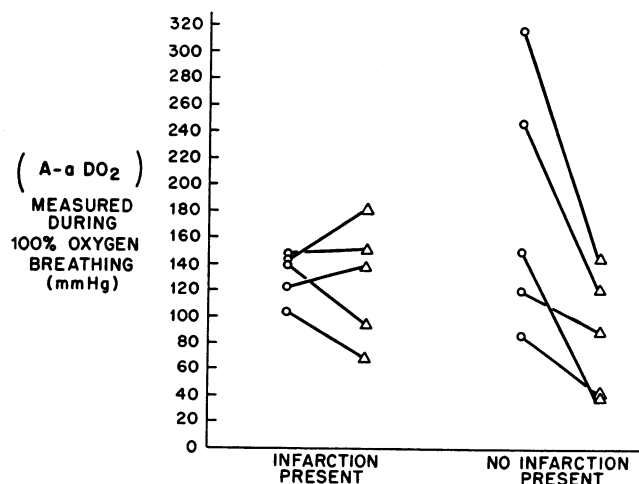


FIGURE 3 Changes in A-a  $D_{O_2}$  during 100% oxygen breathing are shown before and after deep breathing. The open circles indicate measurements during normal tidal volumes, and the triangles indicate those during large tidal volumes. Tidal volumes of 60–69% of predicted inspiratory capacity were achieved in patients with pulmonary infarction, and tidal volumes of 80–111% of predicted inspiratory capacity were possible in patients without lung infarction.

artery pressure seemed to accurately reflect the amount of angiographic clearing. This internal consistency of the results lends credence to the accuracy of the angiographic assessment of the extent of vascular occlusion. In only one instance was there a marked discrepancy between the estimated extent of occlusion and the level of resting mean pulmonary artery pressure (patient D. C.). The angiogram in this instance showed filling defects in both major pulmonary arteries without any sharp cut-offs; peripheral vasculature filled well and the scintillation scan showed no perfusion defect. The hemodynamic importance of the filling defects in this instance was obviously less than our arbitrary assessment of the angiogram indicated.

*Shunts as the cause of hypoxemia.* Among these patients who denied any prior lung disease, some degree of arterial hypoxia was almost always present within the first 3 wk after a pulmonary embolus, although in no instance was the hypoxia profound. The lowest arterial  $P_{O_2}$  breathing air was 57 mm Hg. The average A-a  $D_{O_2}$  was 29.8 mm Hg and 24.3 mm Hg on average could be accounted for by the shunt measured while breathing 100% oxygen. Only 5.5 mm Hg remain to be explained by mechanisms other than shunt. Since the unexplained 5.5 mm Hg are no more than the normal A-a  $D_{O_2}$  attributable to uneven ventilation-perfusion or uneven perfusion-diffusing capacity relationships in the lung, we must conclude that the major mechanism of the hypoxemia among our patients was right-to-left shunting of a fraction of the cardiac output. These results

are in contrast to the findings of Kafer (8) who attributed most of the hypoxemia in pulmonary thromboembolic disease to ventilation-perfusion ( $\dot{V}/\dot{Q}$ ) mismatching. However, most of his cases were studied in the subacute or chronic stage with a mean duration of symptoms of 29 months prior to study while our patients were studied within 19 days of the acute episode.

Most of our patients were receiving heparin by the time the first measurements were made. Considering only the measurements in which the A-a  $D_{O_2}$  breathing air was above 20 mm Hg, there were 7 patients out of 16 in whom the shunt explains less than 70% of the measured A-a  $D_{O_2}$  (J. V., L. T., D. M., B. L., K. M., F. B., and E. T.). Three of these patients (J. V., B. L., and E. T. noted as open circles in Fig. 1) were the only patients studied prior to heparin administration. In these three patients an average of 15 mm Hg of the A-a  $D_{O_2}$  remained unexplained by the shunt (approximately 50% of the total A-a  $D_{O_2}$ ). Therefore, we have not ruled out the possibility that early heparin therapy eliminated some ventilation-perfusion mismatching which might have existed before heparin therapy. The tendency of heparin to relieve bronchospasm after pulmonary embolism has been reported by others (36). Furthermore, our data do not clearly exclude the possibility that much of the hypoxemia due to ventilation-perfusion disturbances could have spontaneously receded within hours after embolization before our initial measurements were made.

There was mismatching of ventilation with perfusion in the form of wasted ventilation as indicated by an increased  $V_D/V_T$  in 17 of 19 of our patients with the appropriate measurement. However, part of the explanation for increased  $V_D/V_T$  is related to shallow breathing which increases the relative importance of anatomic dead space. It is difficult to quantitate whether wasted ventilation in one region leads to relative overperfusion in another region, but the rest of our data suggest that such an effect was minor in our patients.

The calculation of the fraction of the alveolar-arterial oxygen tension difference while breathing air that is due to true shunting is based on the assumption that the A-V  $O_2$  difference and the fraction of cardiac output shunted do not change from air to 100% oxygen breathing. These assumptions may not be invariably correct, but they are reasonable approximations which have been made by others (24, 37, 38). We have experimental evidence that the A-V  $O_2$  difference did not change significantly from room air to 100% oxygen breathing during the cardiac catheterization study ( $P > 0.6$ ). We had no independent way of estimating the fraction of cardiac output shunted under the two conditions, but it seems an unlikely source of systematic error since there were no other significant hemodynamic alterations between air and 100% oxygen breathing during cardiac catheterization.

*Cause of right-to-left shunts.* The lack of correlation between the mean pulmonary artery pressure and the per cent of the cardiac output shunted weighs against the opening of potential anatomical pathways for shunting which, though normally present, are usually not patent; this is a mechanism proposed but not proven by animal experimentation (39-42) and human autopsy studies (43, 44). Furthermore, our data indicate that intracardiac shunts occasionally do occur but were relatively infrequent among our subjects.

Both atelectasis (45) and temporary airway closure due to pneumoconstriction (46) or pulmonary edema (47) can cause right-to-left shunting that can be temporarily reversed by deep breathing. Indeed pulmonary edema has been suggested as one source of hypoxemia in animals following starch embolism (3, 48). In the present study the persistence of the shunting for several weeks after the embolus makes pulmonary edema unlikely as a cause. Furthermore, a significant obstructive ventilatory defect was uncommon suggesting that bronchoconstriction was not a major cause. The considerations above, along with the high incidence of discoid atelectasis observed after embolization on routine chest roentgenograms, favor atelectasis as the cause of the shunting. The fact that the shunts reappear so promptly after deep breathing and the fact that IPPB treatment does not seem to alter the natural, prolonged course of

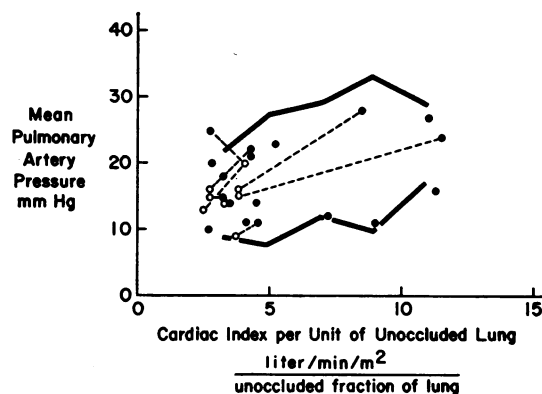


FIGURE 4 Mean pulmonary artery pressure is compared to cardiac index through unoccluded lung. The per cent of pulmonary vascular bed occluded was estimated from pulmonary angiograms. The closed circles represent the initial measurement. The open circles indicate repeat studies and are connected by straight lines to the corresponding data on the same patient obtained during earlier studies. In each instance a significant fall of mean pulmonary artery pressure occurred on the second study as the pulmonary arteries were recanalized. The solid lines represent the limits of mean pulmonary artery pressure expected from the increment in pulmonary blood flow through the remaining normal vascular bed; in only one instance was the pulmonary artery pressure greater than could be explained by the increase in cardiac output through unoccluded lung.

disappearance of these shunts make it apparent that the shunts are not simply a consequence of an altered pattern of breathing. The lungs seem mechanically predisposed to atelectasis. In order for the shunt-like effect to appear perfusion would have to be preserved or restored in the area of atelectasis. Possible explanations are that pulmonary emboli that only partially occlude flow cause alteration in surface-active properties enough to cause atelectasis, or that spontaneous fibrinolysis with clearing of some emboli occurs faster than restoration of surface active properties of the alveoli in that region. A similar process may explain shunting through infarcted areas that cannot be reversed by deep breathing—spontaneous fibrinolysis with recanalization may occur in the infarcted area where the alveoli cannot function either because of destruction or delayed clearance of red cells and debris. The duration of shunts agrees well with the time over which most of the clot lysis and arterial recanalization occurs.

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