Hemodynamic Effects of Pneumonia

I. NORMAL AND HYPODYNAMIC RESPONSES

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ABSTRACT Since an excessive mortality from pneumonia persists in spite of antimicrobial therapy, the hemodynamics during and after the acute phase of pneumonia were studied in 17 patients. None of the patients had clinical heart disease and all had normal venous pressures. The arteriovenous oxygen difference was used to assess the adequacy of the circulation to meet peripheral tissue perfusion, and a spectrum of arteriovenous oxygen differences was noted. In 11 patients, tissue perfusion was considered adequate because the arteriovenous oxygen difference did not exceed 5.5 vol %. In six patients, the arteriovenous oxygen difference was greater than 5.5 vol % and these six patients differed hemodynamically from the others. In these six patients during the acute phase of pneumonia, cardiac output was decreased, and total peripheral resistance and hematocrit were increased. When five patients with varying arteriovenous oxygen difference were studied during exercise in the acute phase, cardiac output increased while venous pressure remained unchanged. Arteriovenous oxygen difference in these five exercising patients increased in all, but most markedly in those with an initially widened arteriovenous oxygen difference. The inadequate response to pneumonia is most consistent with depressed myocardial function, but the possibility of decreased intravascular volume as a contributory factor could not be excluded.

INTRODUCTION

A high mortality from pneumonia persists in spite of antimicrobial therapy (1). Pneumonia may pose an excessive load upon the cardiovascular system since cardiovascular collapse has been noted to be the single most frequent cause of death in pneumonia (2). Although much has been written about the cardiovascular system in pneumonia, few hemodynamic observations have been reported. Both hyperdynamic and hypodynamic responses have been observed (3–5), the latter often in patients dying of pneumonia (5). In the present series no patient was in clinical shock and each recovered. Two-thirds of the patients had the expected, "appropriate" response to pneumonia, i.e. an increased cardiac output associated with increased oxygen consumption, and often fever and hypoxia. The remaining one-third of the patients studied had a paradoxical, "inappropriate" hemodynamic response of a relatively low cardiac output resulting in an abnormally wide arteriovenous oxygen difference. The purpose of this communication is to describe and analyze this inappropriate hemodynamic response and to consider possible pathogenetic mechanisms. The accompanying paper clinically tests one of the plausible pathogenetic hypotheses (6).

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METHODS

An attempt was made to investigate all patients with pneumonia on the Second and Fourth Medical Services of the Boston City Hospital between 1962 and 1967. Patients were considered to be in the acute stage of pneumonia if they were febrile and if the studies were performed within 24 hr of admission to the hospital. In some cases, when the pneumonia developed in the hospital, the investigations were performed close to the onset of illness, usually within 24 hr of onset. Antimicrobial therapy, penicillin, was administered in most cases before these studies. Many patients with acute pneumonia were not investigated; lack of notification and refusal of the proposed investigation on the part of the patient or the physician were the primary reasons for exclusion. Informed consent was obtained from all patients studied. An attempt was made to reinvestigate each patient in the convalescent phase of the disease. Patients were considered to be convalescent when they had defervesced. Restudy usually took place on the same admission, but occasionally weeks to months afterwards. Of a total of 37 patients investigated in the acute phase, six patients with heart disease as well as 14 who refused restudy are not included.

Patients were in the fasting state and in the supine position. Systemic arterial blood pressure and blood sam-

TABLE I
Clinical Data

Case No.	Age	Sex	Type of pneumonia	No. of lobes involved	Coexistent disease
	yr				
1	45	Male	Pneumococcal	1	Pulmonary emphysema
2	35	Male	Pneumococcal	2	Chronic alcoholism; Laennec's cirrhosis
3	59	Male	Aspiration	1	Chronic alcoholism; Laennec's cirrhosis; chronic bronchitis
4	39	Male	Pneumococcal	1	None
5	45	Female	Pneumococcal	1	None
6	53	Male	Pneumococcal	1	None
7	32	Male	Viral	2	None
8	72	Female	Staphylococcal	1	Acute and chronic pyelonephritis
9	42	Male	Pneumococcal	1	Chronic alcoholism
10	68	Male	Pneumococcal	1	Diabetes mellitus
11	38	Male	Pneumococcal	1	Chronic alcoholism
12	33	Female	Pneumococcal	2	Chronic alcoholism
13	62	Male	Pneumococcal	1	Pulmonary tuberculosis; pulmonary emphysema
14	53	Male	Pneumococcal	1	Chronic alcoholism; pulmonary emphysema; diabetes mellitus; basilar artery insufficiency
15	42	Male	Pneumococcal	1	Chronic alcoholism
16	48	Male	Klebsiella	1	Chronic alcoholism; chronic bronchitis
17	78	Female	Pneumococcal	1	Carcinoma of lung

ples were obtained from a No. 17 gauge Cournand needle in the brachial artery. Central venous pressure was measured by means of a polyethylene catheter (I.D. 1.14 mm) inserted percutaneously or by cutdown into an antecubital vein and advanced to the superior vena cava or right atrium. The position of this polyethylene catheter was noted at the end of the study by fluoroscopy after the injection of a small amount of Hypaque 50%.

Cardiac output was measured by the indicator dilution method using the integrated sample technique for calibration (7). Approximately 3 mg of Indocyanine green dye, stabilized with human albumin, were injected from a calibrated pipette into the superior vena cava or the right atrium and followed by a 10 ml saline flush. Dye dilution curves were recorded oscillographically (Sanborn 150) from the output of a densitometer (8) through which blood was drawn from the brachial artery by a constant withdrawal pump at the rate of 35 ml/min (Harvard Apparatus Co., Inc., Dover, Mass.). The injection pipette was calibrated each study day, human albumin being used to stabilize the standard solution. In two cases (Nos. 6 and 7) cardiac output was measured by the Fick method. Right heart catheterization was performed in these two patients employing Cournand catheters, and mixed venous samples were obtained from the main pulmonary artery. The oxygen content of blood samples was measured by the method of Van Slyke and Neill. For the purpose of analysis, comparisons of cardiac output in the acute and convalescent states were made only between values obtained by the same method.

Oxygen consumption was measured by open circuit. Expired air was collected over a 3 min period in a Douglas bag and measured spirometrically. The concentrations of oxygen and carbon dioxide in the expired air were measured using the micro-Scholander technique.

Systemic arterial and superior vena caval or right atrial pressures were measured with strain gauge transducers (Statham P23D or P23G) and recorded oscillographically (Sanborn 150). The zero reference point was 10 cm above the table. Mean pressures were obtained by electrical damping.

Hematocrits were measured in duplicate using Wintrobe hematocrit tubes. Central blood volume was measured according to the method of Stewart (9) and Hamilton, Walker, Kinsman, and Spurling (10). Total blood volume was determined by injecting approximately 5 mg Evans blue dye intravenously and analyzing spectrophotometrically (Beckman D.U.) a sample of arterial blood obtained 10 min later.

The response to supine exercise was studied in five patients. Exercise was performed upon a bicycle at a work load of 25 w for a period of 10 min. Cardiac output was measured between the 7th and 10th min of exercise.

In each patient at each investigation, at least two and often three measurements of cardiac output, oxygen consumption, as well as near-simultaneous measurements of pressure were made. The average of these determinations and of the derived data from each of these determinations are the values presented.

Arteriovenous oxygen difference (A-V O_2 difference) was calculated as follows:

$$A - V\,O_2 \text{ difference (ml/1000 ml)} = \frac{O_2 \text{ consumption (ml/min STPD)}}{\text{cardiac output (liters/min)}}$$

Total peripheral resistance (TPR):

$$\text{TPR (dyne-sec-cm}^{-5}\text{)} = \frac{\text{mean arterial pressure (mm Hg)} \times 1.332 \times 60}{\text{cardiac output (liters/min)}}$$

The t tests were calculated from the formulae described by Snedecor (11). Analyses of the hemodynamic data in terms of 10 yr age groups and etiologic type of pneumonia revealed no significant differences between age groups or between types of pneumonia. Therefore, analyses by these subdivisions are not presented.

RESULTS

The clinical data of all the 17 patients studied are listed in Table I. The ages ranged from 32 to 78 with a mean age of 49.6 yr. There were 13 males and four females. The predominant type of pneumonia was pneumococcal (13 patients). There was one case each of aspiration, viral, staphylococcal, and Klebsiella pneumonia. Blood cultures were obtained in all but five cases, and all were negative. Chest X-rays revealed that in 14 cases the pneumonic process involved one lobe; in the other three, two lobes. Sinus tachycardia was noted as the only consistent electrocardiographic change during the acute stage. Other abnormalities in the acute stage were depressed S-T segments and abnormal T waves (Nos. 3, 10, and 11) and right bundle branch block (No. 6). These changes disappeared in convalescence in most instances (Nos. 6, 10, and 11). Chronic alcoholism was the most commonly associated disease (eight cases).

The various measured and calculated hemodynamic parameters of each patient are presented in Table II. The average coefficient of variation for the repeated cardiac output determinations was 0.06 with a range of 0.01–0.12. The patients were listed in order of ascending arteriovenous oxygen difference (A-V O_2 difference) at the time of the acute study. The 17 patients were divided into three groups: group I, A-V O_2 difference of less than 3.71 vol %; group II, A-V O_2 difference from 3.71 to 5.50 vol %; and group III, A-V O_2 difference greater than 5.50 vol %. There were five cases in group I, six in group II, and six in group III.

Hemodynamic changes between the acute and convalescent stages were analyzed for each of the three groups and also for the entire series (Table II). The patients with normal A-V O_2 differences (groups I and II) during acute pneumonia had both qualitative and quantitative hemodynamic differences from those with wide A-V O_2 differences (group III). Patients in groups I and II exhibited the anticipated response to fever during the acute phase of pneumonia (12); oxygen consumption and cardiac output were increased. In convalescence both were proportionately lower and hence there was little change in the A-V O_2 difference between the acute and convalescent phases. In group III patients oxygen consumption was also high in the acute phase. However, in marked contrast to the other two groups, the acute stage was characterized by a low cardiac output associated with a wide A-V O_2 difference. In group III there was a decrease in oxygen consumption and an increase in cardiac output during convalescence. Hence, A-V O_2 difference decreased.

In groups I and II, total peripheral resistance was low during the acute phase, whereas in group III it was elevated. In all three groups during the acute phase, the expected increases were noted with regard to temperature, minute ventilation, and heart rate, although the latter changes were not statistically significant. Arterial pressure tended to be decreased in all three groups during the acute phase. No changes were evident between the acute and convalescent phases in total blood volume. There was no difference in mean right atrial pressure between the acute and convalescent stages in any of the three groups; it was normal throughout. Oxygen saturation was moderately decreased in the acute phase in all three groups.

All group III patients had a higher hematocrit during the acute phase than in the convalescent (Fig. 1). In groups I and II, no consistent statistically significant change in hematocrit was noted (Table II). Furthermore, the central blood volume during the acute phase correlated inversely with increased A-V O_2 difference ($r = 0.651$, $P < 0.05$).

In all five patients (Nos. 2, 3, 8, 11, and 15) studied during exercise in the acute phase, cardiac output increased (Fig. 2). At rest, mean cardiac output was 7.54 liters/min, while during exercise it was 9.85 liters/min. Venous pressure was increased in two and decreased in two; it was not measured in the fifth patient. A-V O_2 difference increased in all five patients, and the increase was most marked in those with an initially wide A-V O_2 difference.

DISCUSSION

A normal or narrowed A-V O_2 difference in the absence of an anatomic or physiologic shunt is an indication of adequate tissue perfusion and hence of a physiologically adequate circulation. Under pathologic demands such as fever, the physiologic circulatory response is an increase in cardiac output in proportion to or in excess of oxygen consumption. Thus, A-V O_2 difference tends to remain normal or narrow (12). The expected hemodynamic response to fever was found in 11 of 17 patients; the A-V O_2 difference during the acute stage of pneumonia was normal or narrow. However, six patients responded hemodynamically to pneumonia in an inadequate fashion; their A-V O_2 difference widened. The resulting abnormally increased oxygen extraction suggests inadequate tissue perfusion.

The six patients with widened A-V O_2 differences (group III) had significantly lower oxygen consumptions in convalescence and also significantly and disproportionately higher cardiac outputs. Thus, in con-

TABLE II

Acute and Convalescent Hemodynamic Data of 17

Group No.		Case No.	Status	Body surface area	Calculated arterio-venous oxygen difference	Cardiac output	Temper-ature
				m²	*Vol %*	*liters/min*	*°F*
I	Calculated arterio-venous oxygen differ-ence less than 3.71 Vol %	1	Acute	1.85	2.9	10.0	—
			Convalescent	1.84	3.3	6.4	—
		2	Acute	2.09	3.0	13.2	99.8
			Convalescent	2.03	4.5	7.7	99.2
		3	Acute	2.05	3.3	8.8	—
			Convalescent	2.06	2.1	8.7	—
		4	Acute	1.58	3.6	7.8	101.7
			Convalescent	1.82	4.4	5.9	99.2
		5	Acute	1.67	3.6	5.6	100.5
			Convalescent	1.68	6.7	3.5	98.0
	No.				5	5	3
	Mean acute				3.3	9.1	100.7
	Mean convlaescent				4.2	6.4	98.8
	t test				1.32	−2.89	−2.95
	P				NS	<0.05	NS
II	Calculated arterio-venous oxygen differ-ence 3.71–5.50 Vol %	6	Acute	1.69	4.2	5.0	101.6
			Convalescent	1.74	4.8	6.6	99.0
		7	Acute	—	4.6	7.8	—
			Convalescent	—	3.5	7.1	—
		8	Acute	1.67	4.6	5.5	—
			Convalsecent	1.68	4.4	4.2	—
		9	Acute	1.40	4.6	4.8	101.8
			Convalescent	1.40	3.1	4.4	99.6
		10	Acute	1.75	4.9	6.9	100.8
			Convalescent	1.74	4.4	6.6	98.9
		11	Acute	2.01	5.3	6.3	99.8
			Convalescent	2.04	4.4	7.2	99.0
	No.				6	6	4
	Mean acute				4.7	6.0	101.0
	Mean convalescent				4.1	6.0	99.1
	t test				−1.98	−0.06	−4.68
	P				NS	NS	<0.05
III	Calculated arterio-venous oxygen differ-ence greater than 5.50 Vol %	12	Acute	1.61	6.4	4.3	101.1
			Convalescent	1.61	3.0	5.5	100.2
		13	Acute	1.50	6.7	3.6	97.5
			Convalescent	1.50	5.3	4.6	98.5
		14	Acute	1.54	6.7	3.7	98.2
			Convalescent	1.54	5.3	4.7	98.0
		15	Acute	1.75	7.0	3.9	98.5
			Convalescent	1.79	5.6	4.5	97.0
		16	Acute	1.58	7.8	4.1	101.3
			Convalescent	1.57	4.3	5.9	99.7
		17	Acute	1.52	8.3	3.9	101.4
			Convalescent	1.51	2.9	5.0	98.6
	No.				6	6	6
	Mean acute				7.1	3.9	99.7
	Mean convalescent				4.4	5.0	98.7
	t test				−4.21	6.28	−1.90
	P				<0.01	<0.001	NS
	Totals						
	No.				17	17	13
	Mean acute				5.1	6.2	100.3
	Mean convalescent				4.2	5.8	98.8
	t test				−1.88	−0.82	−4.72
	P				NS	NS	<0.001

Patients Grouped by Arteriovenous Oxygen Difference

Oxygen consumption	Heart rate	Mean right atrial pressure	Mean brachial arterial pressure	Total peripheral resistance	Central blood volume	Total blood volume	Hematocrit	Arterial oxygen saturation
cc/min STPD	*beats/min*	*mm Hg*	*mm Hg*	*dyne-sec-cm^{-5}*	*liters*	*liters*	*Vol %*	*%*
296	102	4	75	598	—	—	34	92.6
220	132	5	83	997	—	—	41	94.9
396	114	5	85	515	1.88	7.90	37	86.5
352	74	8	83	885	1.80	7.58	35	91.2
288	92	9	82	749	1.65	7.24	46	87.4
183	92	6	77	709	1.58	7.54	38	86.6
261	100	6	80	762	1.29	—	30	—
259	66	5	115	1583	1.63	—	42	—
207	102	7	82	1171	1.35	5.04	42	—
221	62	10	107	2467	1.24	4.52	37	—
5	5	5	5	5	4	3	5	3
290	102	6	81	759	1.54	6.73	38	88.8
247	85	7	93	1328	1.56	6.55	39	90.9
−1.93	−1.19	0.63	1.58	2.51	0.17	−0.73	0.26	5.80
NS	NS	NS	NS	NS	NS	NS	NS	<0.005
209	75	2	95	1526	—	—	—	94.0
317	84	3	90	1082	—	—	49	96.8
357	—	—	—	—	—	—	42	92.1
250	—	—	—	—	—	—	37	93.0
256	93	4	90	1315	1.17	3.95	36	—
182	107	8	107	2021	1.13	3.48	28	—
217	108	—	100	1702	0.90	3.40	33	92.5
147	105	—	100	1717	0.91	3.85	34	94.6
347	102	8	78	886	1.41	4.97	51	93.3
280	78	7	95	1140	1.21	4.83	48	93.7
339	90	1	90	1135	1.26	5.84	45	—
316	78	1	82	910	1.20	5.83	38	—
6	5	4	5	5	4	4	5–6	4
287	94	4	91	1313	1.19	4.54	42	93.0
249	90	5	95	1374	1.11	4.50	39	94.5
−1.24	−0.46	0.93	0.79	0.31	−1.60	−0.22	−2.35	1.17
NS	NS	NS	NS	NS	NS	NS	NS	NS
253	126	1	101	1881	0.71	—	40	91.0
176	115	1	95	1378	0.92	—	32	93.7
240	84	2	90	2004	0.81	4.03	35	94.5
242	89	3	86	1505	0.80	3.87	26	88.0
249	101	8	81	1738	0.68	4.22	39	92.4
249	104	8	110	1862	1.07	4.63	37	84.1
274	90	5	100	2044	1.29	4.45	43	84.8
245	72	3	96	1721	1.25	5.26	41	95.8
318	114	4	76	1500	0.90	4.98	37	98.0
254	93	1	84	1144	1.05	4.40	31	95.8
299	80	5	76	1583	1.19	4.70	36	91.2
160	82	7	82	1280	1.57	4.49	34	96.3
6	6	6	6	6	6	5	6	6
272	99	4	87	1792	0.93	4.48	38	92.0
221	92	4	92	1482	1.11	4.53	33	92.3
−2.33	−1.49	−0.58	0.91	−3.30	2.41	0.23	−3.95	−1.17
NS	NS	NS	NS	<0.05	0.06	NS	<0.01	NS
17	16	15	16	16	14	12	15	13
283	98	5	86	1319	1.18	5.06	38	91.6
238	90	5	93	1400	1.24	5.02	35	92.6
−3.14	−1.76	0.61	2.03	0.61	1.18	−0.28	−1.94	1.77
<0.01	NS	NS	NS	NS	NS	NS	NS	NS

valescence, there was a normalization of A-V O_2 difference. Total peripheral resistance was quite high in these patients during the acute phase, and it decreased significantly in convalescence. The hematocrit was also significantly higher in the acute phase, and the central blood volume was decreased. In contrast, the hemodynamic changes in groups I and II were largely opposite in direction to those found in group III. Thus, the patients with widened A-V O_2 difference reacted hemodynamically to pneumonia in an aberrant fashion, compared with both themselves and also with the patients in the other groups.

What are the pathophysiologic mechanisms involved in this hypodynamic circulatory response? Such a response is consistent with depressed myocardial function and/or decreased circulatory volume. Patients with clinically apparent heart disease were excluded from the present series. The lack of clinical heart disease was supported by normal venous pressures in the entire series. During exercise, it remained low in three patients, and was slightly elevated in the fourth (9 mm Hg at rest and 12 mm Hg during exercise). However, the A-V O_2 difference remained essentially unchanged in the latter patient during exercise. Furthermore, all group III patients had normal hemodynamics in convalescence. There is thus no evidence that any of the changes noted in the present series were due to underlying heart disease.

Ethanol may diminish myocardial function (13). Furthermore, an excessive mortality has been noted in patients with pneumonia when alcoholism was present (14). In the present series, four of the six patients with widened A-V O_2 difference suffered from chronic alcoholism. Of the remaining 11 patients, four suffered from alcoholism. Alcoholism was thus present in a larger percentage of those with an inadequate response, but a causal relationship has not been established.

Decreased myocardial contractility in pneumonia might result from a concomitant myocarditis. Indeed, in one series of 67 cases of fatal pneumonia, 26 cases

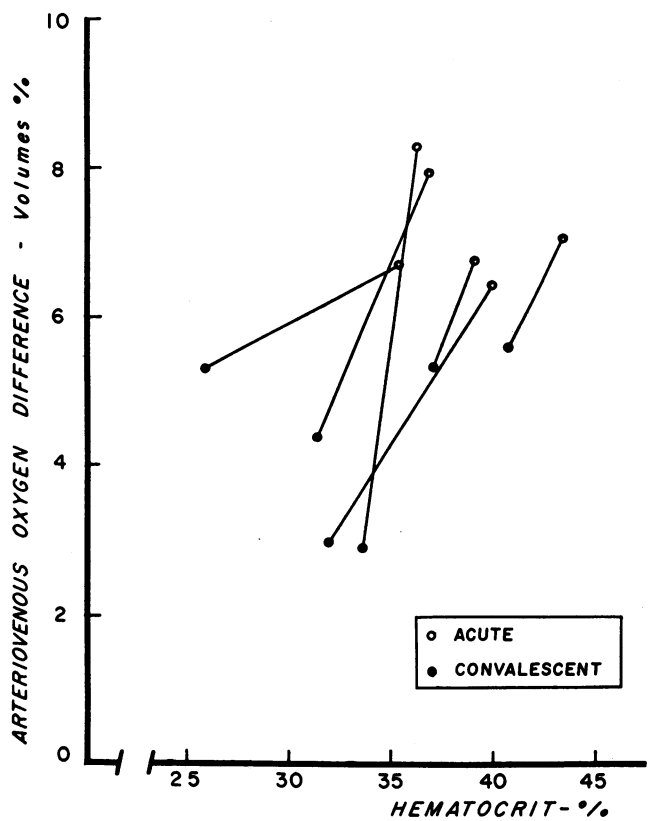

FIGURE 1 The relation of arteriovenous oxygen difference to hematocrit in group III patients (see text). Open circles represent the acute phase of pnuemonia. Solid circles represent the convalescent phase of pneumonia. In all six patients, a decrease in the hematocrit is associated with a decrease in the arteriovenous oxygen difference in convalescence.

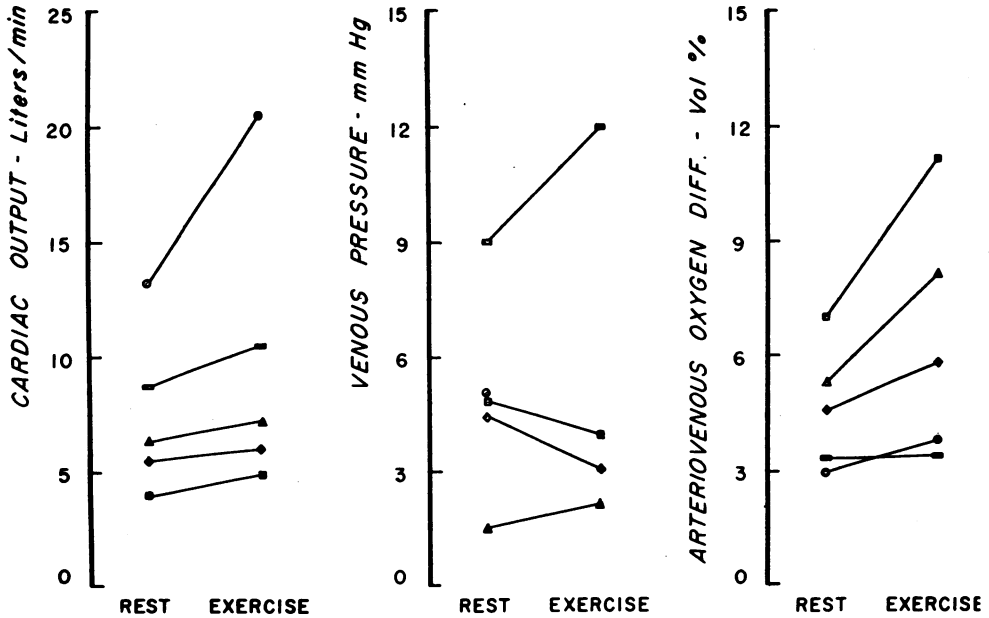

FIGURE 2 The relation of cardiac output, venous pressure, and arteriovenous oxygen difference to rest and exercise in five patients during the acute phase of pneumonia. Open symbols represent the resting state. Closed symbols represent the exercise state. Each patient is represented by a different symbol: squares, case No. 15; diamonds, case No. 8; triangles, case No. 11; rectangles, case No. 3; and circles, case No. 2. In all five patients, cardiac output increased with exercise. Venous pressure was inconsistently changed with exercise.. Arteriovenous oxygen difference increased in all five patients and increased most in those patients with initially increased values.

or 38.8% exhibited inflammatory changes in the myocardium considered to reflect acute myocarditis (15). Others, however, have not found myocarditis in patients dying of pneumonia (5, 16). The present series cannot exclude myocarditis as a factor related to the inadequate response. Decreased myocardial contractility has been reported in animals secondary to the use of some antibiotics (17). Penicillin, which was the only antibiotic used in all but two of the present cases, has no such effect. In cases 5 and 13, erythromycin and tetracycline were administered respectively.

There were however, in this study, results to suggest that decreased circulatory volume might be related to the inadequate response. The hematocrit was significantly higher in patients whose A-V O_2 difference was widened in the acute stage when compared to convalescence. No such changes were noted in the patients with lowered or normal A-V O_2 differences. In order to test the importance of a possibly decreased blood volume in the inadequate response to pneumonia, nine cases with acute pneumonia were rapidly infused with a plasma volume expander. The results of these infusions and their possible therapeutic importance form the basis of the accompanying communication (6).

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