Cardiac output and arterial CO₂ response during intermittent positive pressure breathing with oxygen

A comparison of patients with chronic airflow obstruction and controls

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Cardiac output and arterial blood gases were studied before, during, and after intermittent positive pressure breathing, using 40% oxygen (IPPB/O₂). The subjects of this study were eight patients with lung disease, seven of them with chronic airflow obstruction and eight control subjects without respiratory symptoms. During IPPB/O₂, cardiac output was definitely lowered without a significant decrease in arterial PCO₂ in the patients with airflow obstruction. Conversely, the control subjects during IPPB/O₂ had a large decrease in arterial PCO₂ with a moderate reduction in cardiac output. Considering this response of the lung with airflow obstruction, the more frequent use of cardiac output and arterial gas measurements in patients receiving IPPB/O₂ treatments appears desirable. Individual cases are presented.

In the treatment of chronic airflow obstruction in ambulatory patients who are not in acute respiratory failure, the use of intermittent positive pressure breathing (IPPB) is often advocated. Improvement of arterial blood gases during and between treatments has been reported (Hickam, 1963; Daly and Duff, 1963). Some authors have reported a lack of decrease of arterial CO₂ (Kamat, Dulfano, and Segal, 1962; Sukumalchantra, Park, and Williams, 1965). The effect of IPPB on cardiac output has been studied (Courmand, Motley, Werko, and Richards, 1948; Cathcart, Fraimow, Nealon, and Price, 1960; Andersen and Kuchiba, 1967) and the cardiac output has been found to be decreased in many instances, particularly with high mask pressures, with an excessively long inspiratory phase, and when cardiac output is already lower than normal.

The purpose of this study was to compare patients with chronic expiratory airflow obstruction and controls before, during, and after IPPB with 40% oxygen (IPPB/O₂), observing in particular the changes in cardiac output and the changes in arterial carbon dioxide (Paco₂).

METHODS

CLINICAL AND FUNCTIONAL CHARACTERISTICS OF SUBJECTS Sixteen men were studied. There were eight patients with lung disease. Seven of them were diagnosed as having chronic expiratory airflow obstruction on the basis of symptoms and clinical data. In Table I are reported the diagnoses of asthma, chronic bronchitis, and emphysema as applicable to each patient (patients 1 to 7).

Patient 9 had no symptoms of airflow obstruction. A chest radiograph done before abdominal surgery revealed a pneumatocoele but no evidence of generalized lung disease.

The spirometric tests (Table I) show that the vital capacity in the eight patients with lung disease ranged between 72 and 37% of predicted; the maximum voluntary ventilation (MVV) ranged between 42 and 14% of predicted; the forced expiratory volume in one second (FEV_{1.0}) ranged between 54 and 23% of the forced expiratory vital capacity (FEVC). Therefore, by spirometry, they mostly had obstructive, rather than restrictive, reduction in the FEV.

The residual volume to total lung capacity ratio (R/T) ranged from 51 to 72%. Distribution of ventilation was slightly to greatly abnormal, as shown by the Δ CO₂ test (Tulou, 1966). The initial measurement of arterial oxygen showed moderate hypoxaemia (PaO₂ range 70 to 54); arterial PCO₂ varied greatly

TABLE I
CLINICAL CHARACTERISTICS AND PULMONARY FUNCTION DATA

No.	Age	Diagnosis	VC (l.)	% of Pred.	MVV (l.)	% of Pred.	FEV _{1.0} (l.)	% of FEVC	TLC (l.)	RV (l.)	R/T	ΔCO ₂
Patients												
1	69	A, E	1-551	46	27	25	0-354	28	5-119	3-307	64-6	7-3
2	56	E	2-420	53	49	33	1-320	54	6-688	3-997	64-6	12-9
3	67	B, E	2-210	64	33	29	0-677	31	5-464	3-940	72-2	13-1
4	50	A, B, E	2-569	64	59	42	1-285	50	6-565	4-201	64-0	9-2
5	46	B, E	2-849	72	37	34	0-668	23	6-608	4-298	64-9	12-2
6	64	B, E	2-559	59	45	32	1-257	50	—	—	—	12-3
7	56	A, B, E	1-565	37	20	14	0-402	29	9-672	6-598	71-9	15-5
9	50	Pneumatocele	2-751	71	47	34	1-218	47	6-511	2-812	50-9	8-7
Controls												
8	50	No A, B, E	3-377	89	104	78	2-278	68	—	—	—	6-4
10	50	No A, B, E	3-682	91	107	76	2-649	74	6-363	2-714	42-6	5-5
11	49	No A, B, E	4-694	103	106	68	3-084	68	7-207	3-079	42-7	8-5
12	34	No A, B, E	5-232	104	108	61	3-653	74	7-353	2-112	28-7	2-8
13	28	Normal subject	4-759	94	176	97	4-400	92	6-731	2-035	30-2	4-2
14	41	No A, B, E	4-962	110	101	64	3-353	73	6-742	2-260	33-6	4-6
15	38	No A, B, E	4-628	96	181	107	3-560	77	—	—	—	4-2
16	72	No A, B, E	4-139	109	61	51	2-982	72	6-187	2-695	43-5	3-8

Diagnosis: A=asthma, B=chronic bronchitis, E=pulmonary emphysema; R/T=residual volume/total lung capacity ratio; ΔCO₂=end-tidal maximum expiration CO₂ difference, in mmHg.

from subject to subject (Paco₂ range 37 to 57) (Table II).

Eight controls were selected on the basis of having no symptoms or evidence of expiratory airflow obstruction. Most of them were patients admitted to hospital for complaints unrelated to the respiratory system. One (No. 13) was a normal subject.

The spirometric tests (Table I) showed the vital capacity to be 110 to 89% of predicted; the MVV 107 to 51% of predicted; FEV_{1.0} 92 to 68% of FEVC. Although a few of these control subjects did not have perfectly normal spirometric tests, the groups of patients and controls were quite different and there was no overlap for any test.

The controls were also quite different for their R/T ratio (29 to 43%, no overlap) and ΔCO₂ test (only subject 11 had a slightly abnormal test).

TECHNIQUE OF MEASUREMENT OF CARDIAC OUTPUT Fifty microcuries of radioactive serum albumin ¹³¹I (RISA) were injected rapidly into an antecubital vein. Radioactivity was monitored with a scintillation detector¹ aiming at the arch of the aorta through the medial end of the second left intercostal space.

For each measurement of cardiac output a record of radioactivity and the blood volume known from the dilution of RISA gave the necessary data for measurement of cardiac output (Hamilton, 1962; Guyton, 1963). This was done, in the supine patient, under three conditions:

- (1) pre-IPPB control, after a 20-minute period of rest, breathing room air at ambient pressure ('rest');
- (2) during the final minutes of a 20-minute period of IPPB/O₂ with the Pressure Breathing Therapy Unit² at an O₂ concentration of 40% and a peak mask pressure of 12 cm H₂O;

- (3) post-IPPB measurement, 30 minutes after termination of IPPB/O₂ again breathing room air at ambient pressure.

It was necessary to have the patient's aorta and the detector cell in the same relative position at each of the three consecutive measurements. Extreme care is necessary to achieve this, and we had to discard five cases from an original total of 21 because it was felt that a change of position had occurred.

We have accepted the serum albumin method as valid for measuring cardiac output, and have not ourselves assessed the limits of error. Grünert, Oeff, and Schmidt (1963) compared praecordial isotope dilution curves and arterial dilution curves in rabbits, while Zekert, Herbig, and Cooper (1966) compared praecordial isotope dilution curves and indocyanine green dilution curves in man.

MEASUREMENTS OF OTHER VARIABLES With each of the three cardiac output determinations, arterial blood was collected through an indwelling arterial needle in the brachial artery; the pulse rate, breathing rate, blood pressure (by sphygmomanometer), and electrocardiogram were recorded. Arterial blood analysis was done by the Astrup method (Andersen, Engel, Jørgensen, and Astrup, 1960; Andersen and Engel, 1960). Stroke volume was calculated from cardiac output and heart rate.

RESULTS

The initial ('rest') values of cardiac output, cardiac index, stroke volume, Paco₂, and Pao₂, and the same values observed during and after IPPB O₂, are reported in Table II. 'Rest' cardiac output values in the patients covered a wide range (3.8 to 7.0 l./min), and so did Paco₂ (37 to 57 mmHg).

¹Nuclear Chicago D35

²Bennett Model TV-2P

TABLE II

CARDIAC OUTPUT AND ARTERIAL BLOOD BEFORE, DURING, AND AFTER IPPB/ O_2 IN PATIENTS AND CONTROLS

	Cardiac Output (l./min)			Cardiac Index (l./min/m ²)			Stroke Volume (ml)			Arterial FCO_2 (mmHg)			Arterial PO_2 (mmHg)		
	Rest	IPPB	Post	Rest	IPPB	Post	Rest	IPPB	Post	Rest	IPPB	Post	Rest	IPPB	Post
Patients															
1	6.55	4.07	3.37	4.07	2.53	2.09	55	34	31	37	39	46	70	—	70
2	6.93	5.86	6.08	3.56	3.02	3.13	58	53	55	57	57	54	54	—	62
3	3.81	2.72	2.86	2.37	1.69	1.78	29	21	22	—	—	—	—	—	—
4	3.88	3.53	3.92	2.18	1.98	2.20	35	32	44	49	43	50	65	210	60
5	7.01	3.83	6.93	4.17	2.28	4.13	70	48	87	38.5	31	40	62	236	63
6	6.37	6.39	6.92	3.31	3.33	3.60	64	58	69	38.5	37.5	38.4	59	258	56
7	4.34	3.04	3.97	2.64	1.85	2.42	45	33	45	50	53	51	57	234	55
9	3.86	4.21	3.44	2.57	2.81	2.29	38	44	41	37.5	26	26	70	286	72
Controls															
8	5.53	5.03	5.30	3.41	3.11	3.27	58	56	68	33	15.5	29.5	79	269	83
10	5.61	5.50	6.28	3.46	3.40	3.88	72	65	87	33.5	23.2	28	86	243	86
11	6.98	6.85	5.51	3.39	3.33	2.67	73	95	71	38.5	33.5	39	71	284	74
12	6.84	6.24	4.93	3.26	2.97	2.35	104	104	82	43.2	28.5	41.5	99	316	95
13	6.93	5.67	5.51	3.85	3.15	3.06	89	95	92	37	31	32	98	336	92
14	10.8	10.1	8.26	5.51	5.15	4.21	108	97	86	36.5	26	34.5	69	278	74
15	6.65	7.92	6.72	3.39	4.10	3.43	74	73	102	37	38.5	38	85	289	88
16	6.37	4.52	—	3.39	2.40	—	80	66	—	40	27.5	—	73	310	—

The change in cardiac output during IPPB/ O_2 was a decrease, of more than 1 l./min in five patients. Two were practically unchanged, one increased moderately (case 9). $Paco_2$ did not decrease much except in case 9.

In the controls there was also a wide range of resting cardiac output, but at a higher level (5.53 to 10.8 l./min), $Paco_2$ was more uniform (33 to 43 mmHg). During IPPB/ O_2 cardiac output did not change significantly in five cases. In two cases it decreased by more than 1 l./min while in one

case it increased greatly. $Paco_2$ decreased greatly in all subjects except in one in whom it remained basically unchanged.

Changes in cardiac output and $Paco_2$ from rest to IPPB/ O_2 appeared to be the most important variables to study, and a scattergram was obtained by plotting per cent change in cardiac output against per cent change in $Paco_2$ (Figure). Clearly, the controls and patients form two different populations. A big decrease in cardiac output and a $Paco_2$ unchanged or moderately diminished characterize the patients, except for case 9. In controls, $Paco_2$ decreased greatly; cardiac output was lowered much less than in the patients.

As noted under 'Methods', case 9 was considered a patient with lung disease on the basis of radiological evidence of a pneumatocele; but he did not have symptoms of respiratory obstruction. We calculated mean values in the patients after eliminating case 9 and compared those with the mean values in the controls (Table III). The influence of IPPB/ O_2 on cardiac output and $Paco_2$ is strikingly different in the patients with and without symptoms and signs of chronic air-flow obstruction.

Thirty minutes after IPPB/ O_2 was discontinued the hyperventilating effect (decreased $Paco_2$) in the controls had not completely disappeared, while the moderate hyperventilation in the patients was no longer present. Pao_2 was the same as before IPPB/ O_2 , showing that in both controls and patients there was no lasting effect of IPPB/ O_2 on the blood oxygen.

Cardiac output in the patients was still below the control level, but less so than during IPPB/ O_2 ; while in the controls cardiac output showed a

FIGURE The small number near each symbol ● or ○ is the case number as in the text and tables. The values used in this figure are the per cent changes from pre IPPB control to IPPB/ O_2 for cardiac output and arterial $Paco_2$.

TABLE III

COMPARISON OF PATIENTS WITH SYMPTOMS OF CHRONIC AIRFLOW OBSTRUCTION AND CONTROLS (SEE TEXT): AVERAGES AND PER CENT CHANGES IN CARDIAC OUTPUT, P_{aCO_2} , AND OTHER VARIABLES

	Mean Values	Per cent Changes	
		Pre Control to IPPB/O ₂	Pre Control to Post IPPB Measurement
Patients			
No. of cases	6		
Cardiac output	5.85 l.	- 23	- 10
Stroke volume	55 ml.	- 21	+ 2
Paco ₂	45 mmHg	- 4	+ 5
Pao ₂	61 mmHg	+ 288	- 4
Heart rate	108	- 4	- 10
Controls			
No. of cases	8		
Cardiac output	6.96 l.	- 7	- 13
Stroke volume	81 ml	0	+ 5
Paco ₂	37 mmHg	- 25	- 7
Pao ₂	83 mmHg	+ 257	+ 1
Heart rate	86	- 6	- 15

P_{aCO_2} =arterial PCO_2 ; P_{aO_2} =arterial PO_2 . In the column of mean values are averages of six patients and eight controls at the time of Pre IPPB Control measurement. The two following columns show average per cent changes during IPPB/ O_2 and 30 minutes later.

further decrease to 13% below the pre IPPB control level.

Blood volume was found to be normal in the patients (mean=5.3 l.) and in the controls (mean=5.7 l.).

No material change in blood pressure and electrocardiogram was observed from the first to the last measurement.

CASE REPORTS

CASE 7 This 56-year-old patient had asthma, chronic bronchitis, and emphysema. His vital capacity (Table I) was diminished (37% of predicted); he had severe airway obstruction (MVV 14% of predicted, $FEV_{1.0}$ 29% of FEVC). Residual volume was greatly increased, and the distribution of ventilation was abnormal. Arterial blood at rest (Table II) showed a P_{aCO_2} of 50 and a P_{aO_2} of 57 mmHg. Cardiac output was 4.34 l./min initially. During IPPB/ O_2 , cardiac output decreased to the quite low level of 3.04; this was a 30% decrease from the pre IPPB control level. Since the pulse rate had not changed, there was a decrease of stroke volume. Arterial PCO_2 had slightly increased to 53 (+6%). In Fig. 1 Case 7 showed this lack of decrease of P_{aCO_2} despite the decrease in cardiac output.

CASE 8 Situated apart from the above cases in the Figure was a 50-year-old control subject with no respiratory obstruction. Arterial blood was normal. Cardiac output at pre IPPB control measurement was 5.53 l./min. During IPPB/ O_2 , P_{aCO_2} decreased greatly from 33 to 15 mmHg, demonstrating considerable

alveolar hyperventilation. On the other hand, cardiac output decreased only slightly, by 9%, to 5.03 l./min.

CASE 13 Between the extremes just described was a 28-year-old laboratory technician with normal function tests. Cardiac output was 6.93, pulse rate 78, stroke volume 89. On IPPB/ O_2 , P_{aCO_2} decreased from 37 to 31, cardiac output from 6.93 to 5.67. In the Figure he lay quite close to the cluster of patients, but his stroke volume had increased by 7%. In a scattergram where change in P_{aCO_2} was plotted against change in stroke volume, he was better separated from the patient group.

CASE 16 Of the subjects without respiratory obstruction, this one had the greatest decrease in cardiac output as well as stroke volume during IPPB/ O_2 . He was a 72-year-old man with a normal VC (109% of predicted). The low MVV (51% of predicted) and a residual volume of 2.7 l. would be compatible with chronic airflow obstruction, but the symptoms of this condition were not present, and P_{aCO_2} decreased as in the other controls (-31%).

CASE 9 This patient behaved quite differently from the others. We considered him to have lung disease because he had a pneumatocele on the chest radiographs and functional signs of airway obstruction (MVV 34%, $FEV_{1.0}$ 47%). But he had no history or symptoms of chronic bronchitis and/or emphysema and no radiographic evidence of diffuse emphysema. His decrease in P_{aCO_2} during IPPB/ O_2 (-31%) with no decrease in cardiac output (+9%) suggested that the factors which prevent alveolar hyperventilation and decrease cardiac output in patients with respiratory obstruction did not exist in this case of pneumatocele.

DISCUSSION

The patients with chronic airflow obstruction did not show abnormally large cardiac output, such as were reported by Harvey, Ferrer, Richards, and Courmand (1951). In this series, the four lowest values were observed in patients with expiratory airflow obstruction. Hypovolaemia was ruled out as a possible cause of low cardiac output by normal blood volume determinations.

The rapid pulse at rest (108 on the average) is a well-known occurrence in patients with advanced chronic bronchitis and emphysema. It has been suggested that a powerful sympathetic drive exists at rest in such patients and is partly reversible by β -adrenergic blockade, as shown by Lockhart, Schrijen, Salmon, Andrada, and Peslin (1967). In our patients the heart rate decreased only 4% during IPPB/ O_2 , and the decrease in cardiac output was related to a decrease in stroke volume (-21%).

The most striking finding of the study was the clearly different response of Paco₂ and cardiac output to IPPB/O₂ in patients with chronic respiratory obstruction and in controls.

If Paco₂ decrease can be considered an index of increase in effective ventilation, this failed remarkably to happen in these patients with airflow obstruction. Anatomical and mechanical alterations of the lung with chronic airflow obstruction, failure to cooperate with the ventilator, and reflex mechanisms (Guyton, 1963) can be thought of as possible reasons. The decrease in cardiac output and stroke volume can be explained by a reduction in venous return, or by interference with alveolar capillary blood flow (Andersen and Kuchiba, 1967) or by a combination of these two mechanisms brought about by increased intrathoracic pressure. It seems noteworthy that the above changes were observed with rather modest positive pressures.

The data in the Figure suggest that if IPPB/O₂ had lowered the Paco₂ in the patients to the same extent as in the controls, the fall in cardiac output would have been extremely large.

IPPB was given with oxygen at a concentration supposed to be 40%. Recent experience has demonstrated to us that the IPPB machine may deliver a higher concentration than it is supposed to deliver. A comparison of IPPB/O₂ and IPPB/air is underway in our laboratory and will be the subject of a later communication. In the present study, Pao₂ values are reported in Table II, and there is no reason to believe that the different responses of patients and controls were due to different concentrations of inspired oxygen. One should keep in mind that O₂ breathing at ambient pressure depresses cardiac output in normals and patients (Cotes, Pisa, and Thomas, 1963).

One factor which may explain the lack of effect of IPPB on Paco₂ is the inequality of distribution of ventilation to different areas of the lungs, a well-known pathophysiological feature of some patients with chronic airflow obstruction caused by bronchitis in particular. While some authors found an improvement of this abnormality during IPPB (Torres, Lyons, and Emerson, 1960), other authors consider that the positive pressure distributes itself preferentially to already well-ventilated areas of the lungs (Jones, Macnamara, and Gaensler, 1960; Sukumalchantra *et al.*, 1965).

POST IPPB MEASUREMENT In some subjects the lack of return of cardiac output to previous values could cause some concern. In case 3, the pre IPPB

value was less than 4.0 l./min and dropped to 2.72 l./min during IPPB/O₂. Thirty minutes post IPPB/O₂ it was still only 2.86 l./minute. These low values could have adverse effects if sustained or repeated. It is interesting to note that this patient experienced no subjective improvement from IPPB treatments.

IPPB machines give the possibility of using higher pressures than were used in this study. In all probability, higher pressures, and longer periods of treatment, could result in more adverse effects than we have observed.

It is evident that a great number of factors influence the effect of IPPB/O₂ on cardiac output and Paco₂. In this study we have attempted to keep constant as many variables as possible. We have learned that, in the same conditions of positive pressure breathing, the lung with chronic expiratory airflow obstruction is not ventilated as well as the normal lung.

Whenever IPPB/O₂ is considered in the treatment of the ambulatory patient with airflow obstruction who is not in acute failure, it should be remembered that an initially low cardiac output may be decreased even more, and an improvement in alveolar ventilation or existing hypercapnia is not to be expected.

Whenever possible, direct measurement of the changes in Paco₂ and cardiac output during IPPB/O₂ should be obtained.

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REFERENCES

- Andersen, M. N., and Kuchiba, K. (1967). Depression of cardiac output with mechanical ventilation. Comparative studies of intermittent positive, positive-negative, and assisted ventilation. *J. thorac. cardiovasc. Surg.*, **54**, 182.
- Andersen, O. Siggaard, and Engel, K. (1960). A new acid-base nomogram. An improved method for the calculation of the relevant blood acid-base data. *Scand. J. clin. Lab. Invest.*, **12**, 177.
- — — Jørgensen, K., and Astrup, P. (1960). A micro method for determination of pH, carbon dioxide tension, base excess and standard bicarbonate in capillary blood. *Scand. J. clin. Lab. Invest.*, **12**, 172.
- Cathart, R. T., Fraimow, W., Nealon, T. F., and Price, J. (1960). Effect of intermittent positive pressure breathing on the cardiac output of patients with chronic pulmonary disease. *Dis. Chest*, **37**, 222.
- Cotes, J. E., Pisa, Z., and Thomas, A. J. (1963). Effect of breathing oxygen upon cardiac output, heart rate, ventilation, systemic and pulmonary blood pressure in patients with chronic lung disease. *Clin. Sci.*, **25**, 305.

- Cournand, A., Motley, H. L., Werko, L., and Richards, D. W., Jr. (1948). Physiological studies of the effects of intermittent positive pressure breathing on cardiac output in man. *Amer. J. Physiol.*, **152**, 162.
- Daly, J. J., and Duff, R. S. (1963). Effect of intermittent positive pressure breathing on pulmonary circulation in emphysema. *Brit. Heart J.*, **25**, 47.
- Grünert, R. D., Oeff, K., and Schmidt, H. (1963). Precordial recording of albumin- I^{131} in estimation of cardiac output in the rabbit. *Amer. J. Physiol.*, **204**, 595.
- Guyton, A. C. (1963). *Circulatory Physiology Cardiac Output and its Regulation*. Saunders Philadelphia.
- Hamilton, W. F. (1962). Measurement of the cardiac output. In *Handbook of Physiology*, Section 2, *Circulation*, Vol. 1. Chapter 17, p. 577. American Physiological Society, Washington, D.C.
- Harvey, R. M., Ferrer, M. I., Richards, D. W., Jr., and Cournand, A. (1951). Influence of chronic pulmonary disease on the heart and circulation. *Amer. J. Med.*, **10**, 719.
- Hickam, J. B. (1963). In *Cecil-Loeb Textbook of Medicine*, 11th ed., edited by P. B. Beeson and W. McDermott, p. 577. Saunders, Philadelphia and London.
- Jones, R. H., Macnamara, J., and Gaensler, E. A. (1960). The effects of intermittent positive pressure breathing in simulated pulmonary obstruction. *Amer. Rev. resp. Dis.*, **82**, 164.
- Kamat, S. R., Dulfano, M. J., and Segal, M. S. (1962). The effects of intermittent positive pressure breathing (IPPB/I) with compressed air in patients with severe chronic nonspecific obstructive pulmonary disease. *Amer. Rev. resp. Dis.*, **86**, 360.
- Lockhart, A., Schrijen, F., Salmon, D., Andrada, L., and Peslin, R. (1967). Haemodynamic effects of propranolol in chronic lung diseases. *Clin. Sci.*, **33**, 101.
- Sukumalchantra, Y., Park, S. S., and Williams, M. H., Jr. (1965). The effect of intermittent positive pressure breathing (IPPB) in acute ventilatory failure. *Amer. Rev. resp. Dis.*, **92**, 885.
- Torres, G., Lyons, H. A., and Emerson, P. (1960). The effects of intermittent positive pressure breathing on the intrapulmonary distribution of inspired air. *Amer. J. Med.*, **29**, 946.
- Tulou, P. P. (1966). Distribution of ventilation; clinical evaluation by rapid CO_2 analysis. *Dis. Chest.*, **49**, 139.
- Zekert, H., Herbig, F., and Cooper, T. (1966). Serial determination of cardiac output from precordial isotope dilution curves. *J. nucl. Med.*, **7**, 424.