Effect of Frusemide on Pulmonary Blood Volume

M. L. BHATIA,* M.D., D.M. ; INDER SINGH,† F.R.C.P.ED., F.R.C.P.GLASG., F.A.M.S. ; S. C. MANCHANDA,‡ M.D.
P. K. KHANNA,† M.D., D.M. ; SUJOY B. ROY,§ F.R.C.P.ED., F.A.M.S.

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Summary: Intracardiac frusemide given to seven patients recovering from high-altitude pulmonary oedema caused a significant reduction in the pulmonary blood volume before the onset of diuresis. This supports the suggestion that the mobilization of fluid from the pulmonary circuit is responsible for the relief of symptoms in some patients with pulmonary oedema even when a diuresis does not occur.

Introduction

Biagi and Bapat (1967) reported the dramatic effect of frusemide (Lasix) in relieving the symptoms in a 65-year-old patient critically ill with acute pulmonary oedema many hours before the onset of diuresis. They suggested that frusemide first caused fluid to be removed from the pulmonary circulation and then produced a diuresis. To test this hypothesis the effect of intravenous frusemide on the pulmonary blood volume was studied in seven patients recovering from high-altitude pulmonary oedema. These patients were chosen because previous studies (Roy *et al.*, 1965b, 1965c) had shown that their pulmonary blood volume generally remained increased for 3 to 24 weeks after they had been evacuated to the plains and their symptoms relieved.

Subjects and Methods

Studies were made on seven men aged 24 to 29 years, three to eight weeks after recovery from pulmonary oedema. Before cardiac catheterization they were all asymptomatic and had normal physical findings, electrocardiograms, and chest radiographs.

The patients were studied in the fasting state without sedation. Right heart catheterization was performed by positioning a No. 7 cardiac catheter in the pulmonary artery just beyond the valve. The left atrium was entered by the percutaneous transseptal Brockenbrough method (Brockenbrough and Braunwald, 1960) as practised in our laboratory (Roy *et al.*, 1963). The right femoral artery was cannulated to obtain arterial blood pressure and dye curves. Consecutive dye-dilution curves were obtained direct on a Polyviso channel through a continuous recording densitometer (Colson) by injecting 2·5 mg. of indocyanine green dye into the main pulmonary artery and then into the left atrium. The difference in the mean transit times of the two resulting curves was taken as the pulmonary transit time. The cardiac output was measured from the dilution curves by the formula of Hamilton *et al.* (1932). The volume of blood between the pulmonary artery and the left atrium was calculated by multiplying the pulmonary mean transit time by the average cardiac output ; this represented the pulmonary blood volume. Similarly, the volume of blood between the pulmonary and femoral arteries was obtained by multiplying the pulmonary-artery-to-femoral-artery mean transit time by the average cardiac output ; this represented the central blood volume. Details of the technique have already been reported (Roy *et al.*, 1965a). The total blood volume was determined by the Evans blue dye method (Gibson and Evans, 1937).

The intracardiac and femoral artery pressures were recorded through P23AA strain gauge manometers on a four-channel single-gun photographic system. The baseline for all pressure measurements was taken as being half the chest thickness at the second costal cartilage when the patient was lying supine (Roy *et al.*, 1957). After obtaining the control data, 40 mg. of frusemide was injected into the pulmonary artery. Pressures in the pulmonary artery, left atrium, and femoral artery were intermittently recorded for the next 15 minutes, and then a second set of cardiac output, pulmonary blood volume, and pressure measurements was obtained (see Table).

Results

The pulmonary blood volume, compared with our normal values (range 145 to 310, average 210 ml./sq. m.), was found to be significantly increased in two men (Cases 5 and 6) and was high normal in three others (Cases 1, 3, and 7). The central blood volume was within the normal range. Intracardiac frusemide caused an average fall in the pulmonary blood volume by 23% and in the cardiac output by 33%, but a decrease in central blood volume—in only six subjects—by an average of 11%. The total blood volume, which was measured in only two men (Cases 6 and 7), had decreased significantly in both. Furthermore, the heart rate and the femoral and pulmonary artery pressures did not change after giving frusemide ; but, whereas the filling pressures and work index of both ventricles decreased, the pulmonary and systemic vascular resistances increased.

Discussion

The finding that intracardiac frusemide decreased the pulmonary blood volume within 15 minutes of administration and before the onset of diuresis in the seven patients reported above supports the hypothesis of Biagi and Bapat (1967). Similarly it also explains in part the haemodynamic basis for the clinical improvement which also sometimes occurs. Nevertheless, the percentage reduction of the pulmonary blood volume in the present study could not be related to the changes seen either in the central blood volume or in the cardiac output. As similar data on the acute response of the pulmonary blood volume to intravenous frusemide are not available comparisons cannot be made. In a previous study with intravenous morphine, however, the 26% decrease in the pulmonary blood volume value could also not be related to the 19% decrease in the central blood volume or to the 15% decrease in cardiac output (Roy *et al.*, 1965c). In addition, Samet and Bernstein (1968), using intravenous ethacrynic acid in 27 subjects, reported that the pulmonary blood volume decreased by 12% and the cardiac output by 20%.

The events following the circulatory response to intravenous frusemide were probably initiated by a reduction in the total plasma volume, a decrease in the venous return, a fall in the ventricular filling pressures, and a decrease in cardiac output. The role of the total blood volume in the present study, however, cannot be critically appraised, as it was estimated in only two cases (both of which showed considerable decrease), but

* Associate Professor of Cardiology, All India Institute of Medical Sciences, New Delhi-16.
† Directorate General, Armed Forces Medical Services, New Delhi-1.
‡ Research Fellow, All India Institute of Medical Sciences, New Delhi-16.
§ Professor of Cardiology, All India Institute of Medical Sciences, New Delhi-16.

Effect of Frusemide on Pulmonary Blood Volume and Circulatory Dynamics in Seven Subjects Convalescing from High-altitude Pulmonary Oedema

Case No.	Age	Body Surface Area (sq.m.)	Interval after Oedema (Weeks)	Pressures (mm. Hg)								H.R. per min.	C.I. (l./min./sq.m.)	S.I. (ml./beat/sq.m.)	P.V.R. (mm. Hg)	S.V.R. (l./min./sq.m.)	Ventricular Work (kg.m./min./sq.m.)		Blood Volume (ml./sq.m.)		
				Femoral Artery			Pulmonary Artery			R.A.	L.A.										
										Mean											
				S	D	M	S	D	M								Right	Left	Central	Pulmonary	Total
1	24	1·7	6 B	125	75	88	22	8	12	5	6	64	3·1	48	1·9	27	0·6	4·4	866	296	
			A	122	64	80	18	7	12	2·5	5	60	1·9	32	3·7	41	0·3	2·7	731	242	
2	24	1·9	8 B	120	65	80	24	11	17	3·5	3	72	3·3	46	4·2	23	0·8	4·8	435	250	
			A	106	60	78	23	9	16	2	2	72	2·4	33	5·8	32	0·6	3·1	391	229	
3	25	1·7	8 B	112	65	84	20	11	15	3·5	8	60	3·8	63	1·8	21	0·7	4·8	640	306	
			A	107	78	87	19	7	11	3	5	60	2·6	43	2·3	32	0·5	3·2	703	271	
4	24	1·6	3 B	104	68	81	22	10	16	1·5	4	72	3·9	54	3·1	20	0·9	4·8	600	264	
			A	108	81	90	21	10	14	1	1·5	72	2·7	38	4·6	33	0·6	3·5	528	180	
5	29	1·7	6 B	110	58	78	25	5	13	2	2	67	4·7	70	2·3	16	1·2	6·3	838	478	
			A	115	60	80	25	5	13	1·5	2	66	3·0	45	3·7	26	0·8	4·2	625	275	
6	29	1·6	4 B	130	80	100	24	7	17	5	7	75	5·6	75	1·8	17	1·1	8·3	871	398	3,600
			A	130	80	100	24	10	17	5	6	75	3·4	45	3·2	28	0·7	5·0	688	309	2,200
7	28	1·5	5 B	124	78	95	25	7	15	5	5	75	4·7	63	2·1	19	1·0	6·7	635	298	3,700
			A	126	79	98	18	8	14	2	3	75	3·4	45	3·2	28	0·7	5·1	612	261	2,700
Average	26	1·67	6 B	118	70	87	23	8	15	3·6	5·0	69	4·2	60	2·4	20	0·9	5·7	698	327	
			A	116	72	88	21	8	14	2·4	3·5	69	2·8	40	3·8	31	0·7	3·8	611	252	

B = Before frusemide. A = After frusemide. S = Systolic. D = Diastolic. M = Mean. R.A. = Right atrium. L.A. = Left atrium. H.R. = Heart rate. C.I. = Cardiac index. S.I. = Stroke index. P.V.R. = Pulmonary vascular resistance. S.V.R. = Systemic vascular resistance.

in another similar study in progress at present the average fall in the total blood volume value in eight patients was 20%. Furthermore, the total blood volume of five patients with congestive cardiac failure fell by 21% following the administration of 100 mg. of intravenous frusemide (Davidov, Kakaviatos, and Finnerty, 1967). In the present study it may therefore be surmised that the total blood volume might also have fallen in the other five cases. If reduction in total blood volume initiates circulatory changes the role of the pulmonary blood volume in the chain of events has to be ascertained. The discrepancy between the reduction in the levels in the pulmonary and central blood volumes by frusemide supports our previous observation that the response of the pulmonary blood volume to high-altitude hypoxia was independent of the central blood volume (Roy *et al.*, 1967). This may represent a form of homoeostasis between the pulmonary and the extrapulmonary blood volumes.

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Preliminary Communications

Oral Phenylalanine and Tyrosine Tolerance Tests in Parkinsonian Patients

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Summary: Reduction of dopamine concentrations in the brains of patients with Parkinsonism, together with reported clinical improvement after the administration of dihydroxyphenylalanine, has led to the hypothesis that impaired hydroxylation of tyrosine may be associated with the disease. To test this hypothesis oral loading tests with L-phenylalanine and tyrosine were carried out in patients and controls. After phenylalanine lower blood levels of this were found in Parkinsonian patients than in controls, but tyrosine levels were the same. After tyrosine lower levels of this were also found in patients compared with controls. It is suggested that these findings indicate a decreased rate of tyrosine utilization in Parkinson's disease together with intestinal malabsorption; the latter is supported by the finding of abnormal D-xylose tolerance in these patients.

INTRODUCTION

Increasing evidence supports the belief that abnormal aromatic amino-acids and catechol metabolism may be responsible for the manifestations of Parkinson's disease. Interest has centred chiefly on the role of dihydroxyphenylalanine, which is the precursor of both melanin (decreased in the substantia nigra of patients with Parkinsonism) and dopamine (found in reduced quantities in the substantia nigra and the corpus striatum of