Effects of Intravenous Lanatoside C on the Pulmonary Circulation in Patients with Pulmonary Hypertension

By

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(Received for publication, August 8, 1963)

It has been generally accepted that digitalis preparations may provide beneficial effects on the pulmonary circulation; cardiac output tends to increase, and pressures in the lesser circulation may be reduced.¹⁻⁴⁾ Changes in such parameters of cardiopulmonary dynamics, however, vary according to the type of the pulmonary hypertension existing when the drug is administered.⁵⁻⁷⁾ For the purpose of elucidating the effects of digitalis, therefore, it would be necessary to study the hemodynamic changes in the lung including the left side of the heart, under various conditions causing the pulmonary hypertension. In the present report, by means of right and left heart catheterizations, studies were made on the acute effects of digitalis in patients with obstruction to the passage of blood from the pulmonary artery, as in chronic pulmonary diseases, and also in patients with obstruction to the passage of blood from the left atrium, as in mitral valve disease. A special attention was paid to the relationship between changes in left atrial and pulmonary artery pressures, as well as to the attitude of pulmonary blood volume, with reference to the pulmonary arteriolar resistance existing in these patients.

MATERIALS AND METHODS

Of 14 patients studied, 8 had isolated mitral stenosis, 3 had predominant mitral insufficiency, 2 had undergone left pneumonectomy because of pulmonary tuberculosis, and 1 had chronic pulmonary emphysema. Two patients with mitral stenosis and one with mitral insufficiency had atrial fibrillation, but none of all patients was in congestive heart failure.

A right heart catheter was introduced from an antecubital vein according

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to the standard technique. Pressures were recorded by a Sanborn Twin-Viso Cardiette using a Statham strain gage transducer, type P-23Db. After measuring pressures in the pulmonary artery, the right ventricle, and the right atrium, tip of the catheter was laid in the main pulmonary artery. A Brockenbrough catheter was then introduced from the right femoral vein until its tip lay in the left atrium through the transseptal route. Bloods were sampled from the pulmonary artery and the left atrium at or closest to 3 minutes after beginning of expired gas collection of 5 minute duration. The blood and gas samples were used for calculating cardiac output according to the Fick principle. Succedingly Coomassie blue, 40 to 60 mg, was injected into the left atrium and then into the pulmonary artery through respective catheter. Dilution curves were recorded from an earpiece of the densitometer described previously.⁸⁾ Quantitation of these curves was made by the "one point" calibration.¹⁰⁾ An endtail blood sample was drawn from the left atrium approximately 3 minutes after the first dye injection. Each curve was replotted semilogarithmically and cardiac output and mean transit time were determined as described by Hamilton *et al.*¹⁰⁾ and simplified by Lilienfield *et al.*¹¹⁾ Each cardiac output value was multiplied by 0.72, a correcting factor for earpiece curve described by Beard and Wood,¹²⁾ and the average of the two was listed. The mean "pulmonary" transit time was obtained by subtraction of the mean "left atrium-to-ear" transit time from the mean "pulmonary artery-to-ear" transit time. In every calculation of pulmonary blood volume according to the Stewart-Hamilton method, the cardiac output values obtained by the dye method were used, instead of those by the Fick principle, which were regarded only as comparative parameters. Total pulmonary artery resistance and pulmonary arteriolar resistance were calculated from the equation of Aperia.

Following performance of the control hemodynamic studies, Cedilanid, 0.4 to 0.8 mg, was injected into the pulmonary artery through the right heart catheter over a period of 2 to 3 minutes. Pulse rate and pressures in the pulmonary artery and the left atrium were measured at frequent intervals during the next 60 minutes. At 45 to 50 minutes after administration of the drug, cardiac outputs were estimated in the same way as in the control study. After completion of the cardiac output measurements, pressures in the left atrium, the pulmonary artery, the right ventricle, and the right atrium were measured.

Changes in cardiac output, in pressure, and in pulmonary blood volume, caused by the injection of the drug in the present study were evaluated to be significant, when they surpassed 15 per cent, 2 mm Hg., and 70 ml. per square meter body surface, respectively, in view of the possible scattering range subject to errors in the measurements.

RESULTS

Parameters of cardiopulmonary dynamics measured in the present series of 14 patients are shown in Table I. For the sake of brevity, only those values which were obtained before and at or closest to 45 minutes after administration of the drug are tabulated.

Of the 14 patients there were 11 with pulmonary hypertension of mild to severe degrees, and the other 3 showed normal hemodynamics. In the presence of pulmonary hypertension, cases with low pulmonary arteriolar resistance (Cases

TABLE I. Parameters of Cardiopulmonary Dynamics

Case No.	Patient	Diag.	Pulse rate	Stroke volume (ml)	Pressure (mmHg)	
					PA	LA
1	Y.F.	MS	85	61	36/17 24	10
			77	75	38/17 22	9
2	I. S.	MS	59	96	26/11 15	9
			54	98	26/ 9 15	9
3	M.U.	MS	95	56	32/15 22	18
			94	42	33/17 24	17
	Ke.S.	MS	80	42	33/16 25	21
			68	55	29/17 22	15
	Ka.S.	MS	93	40	39/16 25	16
			81	40	40/10 22	13
	K.Y.	MS	102	54	37/14 26	16
			96	48	33/12 23	13
	K.M.	MS	72	48	36/15 24	12
			66	62	37/12 23	8
8	M.K.	MS	74	28	112/30 62	18
			67	45	*	15
	M.O.	MI	68	38	39/14 23	17
			56	44	42/14 24	18
10	S.K.	MI	93	59	65/25 38	22
			86	59	63/25 39	23
11	C.H.	MI	86	60	28/ 9 18	8
			72	83	24/ 6 13	3
12	M.S.	TBC	81	50	34/ 8 22	1
			75	56	35/ 8 22	0
13	M.T.	TBC	78	63	25/ 7 14	4
			70	77	28/ 6 13	1
14	H.S.	CPE	86	72	21/ 8 12	2
			81	75	22/ 9 13	1

Values on the upper and lower lines show those measured before and after right heart catheter was found to lie in the right ventricle shortly after the control PAR: Pulmonary arteriolar resistance; PBV: Pulmonary blood volume; MS: Isolated after pneumonectomy; CPE: Chronic pulmonary emphysema.

3 and 4) had greater pulmonary blood volume, while cases with high pulmonary arteriolar resistance (Cases 10 and 12) had smaller pulmonary blood volume. Cases with mitral regurgitation (Cases 9, 10, and 11) showed a prolongation of mean transit time in the system distal to the left atrium, but not within the lung, unless the cardiac output was reduced as in case 9.

After administration of Cedilanid, pulse rate fell in all cases. No other electrocardiographic change was caused. Mean left atrial pressure decreased in 6 cases, and mean pulmonary artery pressure decreased in 5 cases. A definite

Measured Before and After Administration of Cedilanid

Cardiac output (lit/min)	TPR (dyne/sec/cm ⁻⁵)	PAR	Mean transit time (sec.)			PBV (ml/M ²)
			PA to ear	LA to ear	PA to LA	
5.16	372	217	13.2	7.4	5.8	319
5.77	305	180	13.6	7.5	6.1	376
5.67	212	85	15.1	8.9	6.2	334
5.27	243	106	16.3	9.6	7.2	361
5.30	332	60	20.5	14.1	6.4	409
3.97	383	121	16.2	8.3	7.9	380
3.37	593	95	28.0	15.5	12.5	491
3.75	469	145	25.8	13.3	12.5	546
3.76	532	191	16.8	8.2	8.6	328
3.25	543	197	17.2	8.7	8.5	280
5.54	375	144	10.6	6.5	4.1	265
4.57	368	140	11.7	7.1	4.6	234
3.46	554	277	18.5	9.4	9.1	374
4.12	446	291	14.9	7.5	7.4	398
2.10	2360	1670		12.6		
3.04						
2.61	705	184	31.3	18.2	10.1	326
2.46	781	195	33.2	22.0	11.2	329
5.46	557	234	18.1	13.2	4.9	289
5.03	636	270	23.6	19.8	4.7	256
5.12	281	156	15.4	9.8	5.6	323
5.95	175	134	12.8	8.8	4.0	268
4.07	433	413	12.0	7.3	4.7	259
4.21	418	418	13.8	8.4	5.4	308
5.06	221	158	12.9	7.7	5.2	299
5.38	205	190	14.2	9.0	5.2	317
6.23	154	128	12.8	7.5	5.3	356
6.03	172	159	11.6	7.1	4.3	291

administration of the drug, respectively. *Values are omitted because the tip of the study. PA: Pulmonary artery; LA: Left atrium; TPR: Total pulmonary resistance; mitral stenosis; MI: Predominant mitral insufficiency; TBC: Pulmonary tuberculosis,

increase in pressure was observed in none. Cardiac output was regarded as unchanged in 9, increased in 3 (Cases 7, 8 and 11), and decreased in 2 (Cases 3 and 6). Stroke volume decreased in only one (Case 3), and either increased or unchanged in others. No distinct tendency of changes in vascular resistance was observed. Mean pulmonary transit time was unchanged in general, only that it was prolonged in 1 case (Case 3) whose cardiac output tended to fall, and shortened in 2 cases (Cases 7 and 11) whose cardiac outputs tended to rise. Changes in pulmonary blood volume were within 70 ml. per square meter body surface in all cases, which was considered to be the error limits.

DISCUSSION

From the viewpoint of pressure change responding to injection of the drug, the data presented above can be considered to indicate three patterns.

The first pattern is illustrated by the results in Cases 1, 2, 3, 9, 10, 12 and 14. These patients revealed no change in pressure, irrespective of its level at the time of the study. Only Case 3 had a decrease in cardiac output, and a prolongation of mean pulmonary transit time. Response to the drug in all 3 patients who had revealed normal hemodynamics belonged to this pattern. Their cardiac outputs were not influenced by the drug, in spite of reduction in pulse rate. A represen-

Fig. 1. Response to administration of Cedilanid indicating the first pattern in a patient with mitral stenosis. No appreciable change other than a fall in pulse rate is seen.

tative case is shown in Fig. 1.

The second pattern is illustrated by the data obtained in Cases 4, 5, 6 and 11. In this group of patients, a reduction in mean left atrial pressure was accompanied by a reduction in mean pulmonary artery pressure. The fall in pressure in the left atrium occurred earlier and more distinctly than in the pulmonary artery. The patients showing this pattern had consistently lower pulmonary arteriolar resistance, i.e. obstruction to the passage of blood from the pulmonary artery to the left atrium was thought to be of lesser degree, and a predominant role in elevating pulmonary artery pressure might be played by a reflection of elevated left atrial pressure. The fall in left atrial pressure tended to be exaggerated when the pulse rate was reduced. A representative case is shown in Fig. 2.

Fig. 2. Response to administration of Cedilanid indicating the second pattern in a patient with mitral insufficiency. Note a fall in left atrial pressure accompanied by a fall in pulmonary artery pressure, which is exaggerated in occurrence of reduction in pulse rate. Pulmonary blood volume is not affected.

The third pattern is represented by the remaining three (Cases 7, 8 and 13). Although significant fall in left atrial pressure occurred, little or no change in pulmonary artery pressure was caused. In Case 8 the pulmonary artery pressure could not be measured after administration of the drug, because the tip of the catheter was found to be dropped in the right ventricle, but its systolic pressure suggested no reduction in pressures in the lesser circulation. Two patients of this

group (Cases 7 and 8) had a larger pressure gradient between the pulmonary artery and the left atrium, so that the calculated pulmonary arteriolar resistance was high. The third patient (Case 13) had undergone left pneumonectomy prior to the present study. Although the pulmonary artery pressure was within normal limits, reserve for the vascular bed in the right lung might have been reduced. As a proof, the pulmonary artery systolic pressure tended to rise, due presumably to an increase in stroke volume into the lung field. All the patients of this group, whatever the cause, were considered to have obstruction to the blood flow from the pulmonary artery to the left atrium. Changes of this pattern have a resemblance to those observed by Ferrer *et al.*¹⁾ in patients with chronic cor pulmonale as acute effects of digoxin. A representative case is shown in Fig. 3.

Fig. 3. Response to administration of Cedilanid indicating the third pattern in a patient who had undergone left pneumonectomy because of pulmonary tuberculosis. Note a tendency to rise in pulmonary artery systolic pressure, in contrast to a fall in left atrial pressure. Pulmonary blood volume remains unchanged.

In these three patterns observed in this study, changes in cardiac output were variable. It is not clear why the cardiac output was unchanged or increased in some cases while decreased in others, under the similar circulatory condition. Furthermore, any consistent correlation between the changes in cardiac output and in pressures in the lesser circulation was not found. A possible explanation for the difference in effects of the drug is that the functional status of the heart, including

strength of contractile force and mode of conduction, might have been variable depending on the case.

It is worth stating that pulmonary blood volume remained unaltered irrespective of the change in cardiac output and in pressure. In the 4 patients (Cases 3, 6, 7 and 11) studied, the cardiac output and the mean pulmonary transit time tended to have changes in an inverse relationship to each other, where the pulmonary blood volume was neither to increase nor to diminish. Such constancy of the pulmonary blood volume suggests that its reduction is not necessarily a factor in reducing pulmonary hypertension, as mentioned by Greene *et al.*¹³⁾ In fact, a significant reduction in pulmonary artery pressure occurred (Cases 4 and 5) without any hemodynamic changes except for a reduction in left atrial pressure. This might interpret that an effect of lanatoside C to reduce pulmonary artery pressure results, at least partly, from decrease in left atrial pressure, and not from dilatation of the pulmonary vascular system. This concept is also supported by the fact that in some patients with obstruction to the blood flow from the pulmonary artery, and not from the left atrium, the pulmonary artery pressure may be even elevated by administration of lanatoside C, as demonstrated in Case 13.

It would be of interest to note that pulmonary hypertension can be reduced by administration of digitalis preparations even in the absence of cardiac failure, provided the pulmonary hypertension is caused by an elevation in left atrial pressure, and the outflow from the pulmonary artery is unobstructed. Another interest is that if both the pressures in the pulmonary artery and in the left atrium can be reduced without changing the pulmonary blood volume, the pulmonary vascular compliance what Milnor *et al.*¹⁴⁾ state would be increased. This may provide some clinical significance in terms of an improvement of the pulmonary function in patients with pulmonary hypertension. These observations, therefore, may extend an indication for digitalis therapy to include some cases without cardiac failure.

SUMMARY

The acute effects of intravenous lanatoside C on cardiopulmonary dynamics were studied in 11 patients with mitral valve disease and 3 patients with chronic pulmonary diseases. All patients were not in cardiac failure, and control data revealed that pulmonary hypertension of mild to severe degrees was present in 11 patients.

In studying parameters of cardiopulmonary dynamics including the left side of the heart, before and after administration of the drug, the following results were obtained.

1. Mean pulmonary artery pressure decreased in 5 cases, and cardiac output rose in 3 and fell in 2.

2. The cardiodynamic responses were distinguished by 3 patterns. In the first pattern, a complete absence of hemodynamic changes except for diminished pulse rate was noted. The second pattern demonstrated a reduction in left atrial pressure accompanied by a reduction in pulmonary artery pressure. The third pattern was characterized by a reduction in left atrial pressure with little or no change in pulmonary artery pressure.

3. All patients with normal hemodynamics showed the first pattern. The second pattern was observed in patients with unobstructed outflow from the pulmonary artery to the left atrium, while the third pattern was observed only in patients who had obstruction to the passage of blood into the pulmonary vascular system.

4. Pulmonary blood volume was unchanged irrespective of changes in cardiac output or in pressures in the lesser circulation.

5. On the basis of the data obtained, mode of action in reducing pulmonary hypertension and its clinical significance were related.

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