When, on 12 February 1969, it became clear that these tablets contained too much active cardiac glycoside 38,000 tablets had already been delivered. Of these, 6,000 could be recovered, so that 32,000 faulty tablets were used. So far as we know, outside Veenendaal, patients with symptoms of digitalis intoxication due to the use of these tablets were discovered only here and there. This could be explained by the fact that the chemist in Veenendaal was the first in the country to be fully supplied with these tablets and also by the fact that this one chemist was responsible for providing drugs to the whole town (about 30,000 inhabitants) and to the hospital. It is possible that many cases went undiscovered. In our material we observed a pattern of complaints different from what is normally described. In particular, the high percentage of extreme fatigue and of visual symptoms (both 95%) is striking. This can probably be explained by the fact that a similar intoxication with an excessive maintenance dose of digitoxin had never before been observed.

We wish to thank Dr. J. Pool, of the department of cardiology, University Hospital, Leiden, for his help in this investigation.

A preliminary report on this large-scale digitoxin intoxication has been published elsewhere (Lely *et al.*, 1969).

REFERENCES

Chung, E. K. (1969). *Digitalis Intoxication.* Amsterdam, Excerpta Medica.
Church, G., and Marriott, H. J. L. (1959). *Circulation,* **20,** 549.
Church, G., Schamroth, L., Schwartz, N. L., and Marriott, H. J. L. (1962). *Annals of Internal Medicine,* **57,** 946.
Cohen, B. M. (1952). *New England Journal of Medicine,* **246,** 225, 254.
Cozijnsen, M., and Pinckers, A. J. L. G. (1969). *Nederlandsch Tijdschrift voor Geneeskunde,* **113,** 1735.
Crouch, R. B., Herrmann, G. R., and Hejtmancik, M. R. (1956). *Texas State Journal of Medicine,* **52,** 714.
Dall, J. L. C. (1965). *American Heart Journal,* **70,** 572.
Dreifus, L. S., McKnight, E. H., Katz, M., and Likoff, W. (1963). *Geriatrics,* **18,** 494.
Dubnow, M. H., and Burchell, H. B. (1965). *Annals of Internal Medicine,* **62,** 956.
Duroziez, P. (1874). *Gazette Hebdomadaire des Sciences Médicales de Bordeaux,* **11,** 780.
Fenn, G. K., and Gilbert, N. C. (1932). *Journal of the American Medical Association,* **98,** 99.
Flaxman, N. (1948). *American Journal of the Medical Sciences,* **216,** 179.
Friedberg, C. K. (1966). *Diseases of the Heart,* 3rd edn., p. 377. Philadelphia, Saunders.
Gaultier, M., *et al.* (1968). *Bulletin et Mémoires de la Société Médicale des Hôpitaux de Paris,* **119,** 247.
Gotsman, M. C., and Schrire, V. (1966). *South African Medical Journal,* **40,** 590.
Hurwitz, N., and Wade, O. L. (1969). *British Medical Journal,* **1,** 531.
King, J. T. (1950). *Annals of Internal Medicine,* **33,** 1360.
Lely, A. H., van Enter, C. H. J., and Pool, J. (1969). *Nederlandsch Tijdschrift voor Geneeskunde,* **113,** 1729.
Lown, B., Marcus, F., and Levine, H. D. (1959). *New England Journal of Medicine,* **260,** 301.
Mackenzie, Sir J. (1908). *Diseases of the Heart.* London, Frowde.
Meyler, L. (editor) (1966). *Side Effects of Drugs.* vol. 5. Amsterdam, Excerpta Medica.
Moe, G. K., and Farah, A. E. (1965). In *The Pharmacological Basis of Therapeutics,* ed. L. S. Goodman and A. Gilman, 3rd edn., p. 691. New York, Macmillan.
Potter, M., Perrot, L., Vendrinne, J., and Restoy, R. (1964). *L'intoxication Digitalique Massive.* Paris, Masson.
Resnick, N. (1964). *Medical Science (Philadelphia),* **4,** 31.
Rodensky, P. L., and Wasserman, F. (1961). *Archives of Internal Medicine,* **108,** 171.
Rodová, A., and Hovola, D. (1959). *Československá Psychiatrie,* **55,** 357.
Rosenberg, M. S., and Graettinger, J. S. (1962). *Disease-a-Month,* November, p. 1.
Rutledge, D. I., and Haddad, R. (1966). *Medical Clinics of North America,* **50,** 501.
Schölmerich, P., Pabst, K., Jahrreiss, O., and Lange, K. P. (1964). *Deutsche Medizinische Wochenschrift,* **89,** 12.
Shapiro, S., Slone, D., Lewis, G. P., and Jick, H. (1969). *Journal of Chronic Diseases,* **22,** 361.
Shrager, M. W. (1957). *Archives of Internal Medicine,* **100,** 881.
Sodeman, W. A. (1965). *New England Journal of Medicine,* **273,** 35, 93.
Surawicz, B., and Mortelmans, S. (1969). In *Digitalis,* ed. Ch. Fisch and B. Surawicz, p. 127. New York, Grune and Stratton.
von Capeller, D., Copeland, G. D., and Stern, T. N. (1959). *Annals of Internal Medicine,* **50,** 869.
Weenink, H. R., Lely, A. H., and van Enter, C. H. J. (1969). *Nederlandsch Tijdschrift voor Geneeskunde,* **113,** 1733.
Withering, W. (1785). *An account of the foxglove and some of its medical uses,* Birmingham, G. G. J. and Robinson, J. (Reprinted in *Medical Classics,* 1937, **2,** 295).

Haemodynamic Studies with Peruvoside in Human Congestive Heart Failure

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Summary: The immediate haemodynamic effects of peruvoside, a cardiac glycoside obtained from the Indian plant *Thevetia neriifolia* Juss, were studied in six patients with congestive heart failure. The drug was found to have an immediate and powerful positive inotropic and negative chronotropic effect, like ouabain, on the failing human heart. Oral peruvoside was also effective in the treatment of congestive heart failure when used on a short-term as well as a long-term basis. It therefore seems that peruvoside is a useful cardiac glycoside in the management of congestive heart failure in man as a quick-acting intravenous preparation. It is equally effective when used orally.

Introduction

Peruvoside, a cardiac glycoside isolated by Rangaswami and Rao (1959) from the kernels of the Indian indigenous plant *Thevetia neriifolia* Juss, is stated to have a positive inotropic effect in the cat papillary muscle (De *et al.*, 1963), guinea-pig heart (Kohli and Vohra, 1960), and the failing heart of mongrel dogs (Arora *et al.*, 1967). Studies in congestive heart failure in man are, however, not available. In this communication we outline the haemodynamic effects of intracardiac peruvoside in six patients with heart failure of varying aetiology. We also report our observations on the clinical response to oral peruvoside in these six and in an additional 22 patients treated for 2 to 54 weeks.

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Patients and Methods

The six patients (two men and four women) with heart failure, physiologically studied, were aged 30 to 60 years. Congestive heart failure was due to coronary heart disease and primary myocardial disease in two patients each and to atrial septal defect and rheumatic mitral incompetence in one patient each. Three patients were in atrial fibrillation at the time of study. Patients were studied within 48 hours of admission. The investigative nature of the treatment was explained to each patient and consent obtained before the study. Any patient who had received a digitalis preparation in the preceding seven days was excluded from the study.

Right heart catheterization was carried out in the post-absorptive resting state in the supine position with standard techniques. The brachial artery was cannulated for continuous monitoring of arterial pressure and as a site for sampling blood-dye mixture for recording indicator dilution curves.

Pressures were recorded through Statham strain gauge pressure transducers of P23 AA series on a multichannel photographic recorder (Electronics for Medicine Inc.). The baseline for all pressure measurements was taken as half the chest thickness at the second costal cartilage with the patient supine (Roy *et al.*, 1957). Indicator dilution curves were obtained through a continuously recording densitometer (Gilford Inc.) following injection of indocyanine green dye into the pulmonary artery. Cardiac output was calculated from these curves by the technique of Hamilton *et al.* (1932). The rate of change of brachial arterial pressure (dp/dt) was recorded with an R.C. differentiator (Electronics for Medicine Inc.).

After obtaining the control data 0·6 to 0·9 mg. of peruvoside was injected slowly into the pulmonary artery. Electrocardiogram and pulmonary arterial and systemic arterial pressures were continuously monitored and were recorded at five-minute intervals for 30 minutes. A second set of cardiac output and pressure measurements was obtained at the end of 30 minutes.

Calculated data were obtained using the following formulae:

$$\text{Stroke index (ml./beat/m}^2\text{.)} = \frac{\text{Cardiac index (l./min./m.}^2\text{)}}{\text{Heart rate (beats/min.)}}$$

$$\text{Vascular resistance (units)} = \frac{\text{Arterial mean pressure (mm. Hg)} - \text{atrial mean pressure (mm. Hg)}}{\text{Cardiac index (l./min./m.}^2\text{)}}$$

$$\text{Systolic ejection period (sec./min.)} = \text{Systolic ejection period (sec./beat)} \times \text{heart rate (beats/min.)}$$

$$\text{Systolic ejection rate (ml./sec./m.}^2\text{)} = \frac{\text{Cardiac index (ml./min./m.}^2\text{)}}{\text{Systolic ejection period (sec./min.)}}$$

$$\text{Left ventricular work index (kg. m./min./m.}^2\text{)} = \frac{\text{Left ventricular systolic mean pressure (mm. Hg)} - \text{left ventricular filling pressure (mm. Hg)} \times \text{cardiac index (l./min./m.}^2\text{)} \times 1{\cdot}36}{100}$$

$$\text{Left ventricular stroke work index (kg. m./beat/m.}^2\text{)} = \frac{\text{Left ventricular work index (kg. m./min./m.}^2\text{)}}{\text{Heart rate (beats/min.)}}$$

$$\text{Stroke power (kg. m./sec./m.}^2\text{)} = \frac{\text{Left ventricular work index (kg. m./min./m.}^2\text{)}}{\text{Systolic ejection period (sec./min.)}}$$

The haemodynamic data were statistically analysed by standard Student's *t* test.

Another 22 patients (15 male and 7 female) with congestive heart failure were treated with peruvoside by mouth. The average effective dose was 2·4 mg. (1·8 to 3·2 mg.) followed by a maintenance dose of 0·6 mg. (0·3 to 0·9 mg.). Eighteen patients were in sinus rhythm and four had atrial fibrillation. The average period of trial was 15 weeks (range 2 to 42 weeks). To observe the side-effects, if any, of long-term administration of peruvoside 10 patients were treated for more than 12 weeks.

Results

Haemodynamic Studies

Heart Rate, Cardiac Index, and Stroke Index.—As shown in the Table and Fig. 1 the heart rate slowed in all patients (average 36%, range 15 to 58%). Cardiac index increased in all instances though a pronounced increase (32%, 40%, 132%) was seen in only three patients. A consistent and marked increase of stroke index, however, was invariable (average 96%, range 50 to 282%). The increased values for cardiac and stroke indices did not exceed the upper limit of the normal data for our laboratory (Roy *et al.*, 1963).

Right Atrial Mean Pressures (Table, Fig. 2).—Four of the six patients had raised right atrial mean pressures, this being as high as 23 mm. Hg in one patient. Intracardiac peruvoside effectively decreased the raised pressure in these four patients.

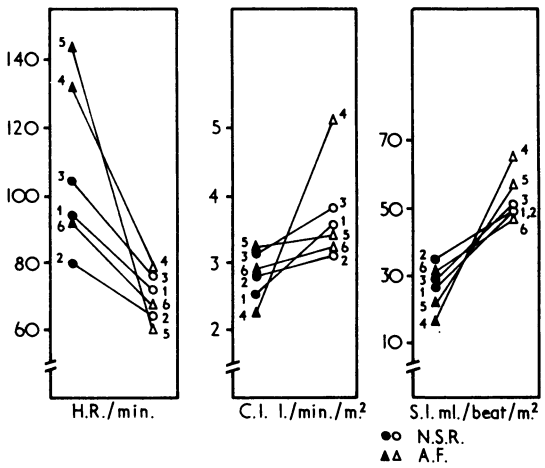

FIG. 1.—Effects of intracardiac peruvoside on heart rate (H.R.), cardiac index (C.I.), and stroke index (S.I.) in six patients with congestive heart failure. Solid and open figures represent values at rest and 30 minutes after administration of peruvoside respectively. Slowing of heart rate and increase of cardiac and stroke indices were recorded in all patients, but changes are more significant in those with atrial fibrillation.

Haemodynamic Effects of Peruvoside in Congestive Heart Failure

Case No.	Age Sex	Clinical Diagnosis	B.S.A. (m²)	Dose (mg.)	H.R.	Pressures (mm. Hg) R.A.	P.A.W.	R.V. S/ED	P.A. S/D(M)	B.A. S/D(M)	C.I.	S.I.	P.V.R.	S.V.R.	L.V.Wi.	L.V.S.Wi.	S.P.	S.E.P.	S.E.R.	B.A. dp/dt (mm. Hg)
1	55 M.	Coronary heart disease. Sinus rhythm	1·70	0·90 B	93	5	27	45/10	45/27(36)	102/72(84)	2·5	27	3·6	32	2·33	25	89	26·0	96	454
				A	72	2	16	36/5	36/18(23)	125/78(94)	3·5	49	2·0	26	4·47	62	203	22·0	159	823
2	48 F.	Cardiomyopathy. Sinus rhythm	1·38	0·60 B	80	4	16	45/8	45/20(32)	132/80(98)	2·8	35	5·7	34	4·15	52	243	17·1	164	717
				A	63	2	12	38/5	38/14(24)	164/88(115)	3·1	49	3·9	36	5·40	86	344	15·7	197	1195
3	60 M.	Coronary heart disease. Sinus rhythm	1·70	0·90 B	104	10	35	80/18	75/35(48)	142/80(98)	3·1	29	4·2	28	3·58	34	147	24·3	126	920
				A	76	6	20	58/10	58/20(34)	160/65(104)	3·8	50	3·7	26	5·68	75	305	18·6	204	1610
4	30 F.	Rheumatic heart dis. Mitral regurgitation. Atrial fibrillation	1·28	0·60 B	132	11	28	76/15	75/42(60)	125/74(84)	2·2	17	14·5	33	2·21	17	88	25·0	88	1000
				A	73	3	18	54/5	55/32(40)	125/72(84)	5·1	65	4·3	16	5·96	76	380	15·7	325	1540
5	52 F.	Atrial septal defect. Tricuspid regurgitation. Atrial fibrillation	1·22	0·60 B	144	15	19	53/15	50/19(33)	108/75(88)	3·2	22	4·4	23	3·31	23	144	23·0	139	699
				A	60	12	15	45/12	45/15(28)	138/80(100)	3·4	57	3·8	26	4·85	81	270	18·0	189	1198
6	49 F.	Cardiomyopathy. Atrial fibrillation	1·38	0·60 B	92	23	—	45/23	35/22(26)	114/76(88)	2·9	32	—	22	—	—	—	21·0	138	760
				A	66	17	—	35/17	27/18(20)	140/85(108)	3·2	48	—	28	—	—	—	16·0	200	1107
Mean			1·44	0·70 B	107·5	11·3	25·0	S57·3 ED14·8	(39·2)	(90·0)	2·78	27·0	6·5	28·7	3·12	30·2	142·2	22·7	125·2	758·3
S.D.					±25·1	±7·0	±7·6	S ±16·4 ED ±5·4	±12·5	±6·5	±0·38	±6·6	±4·6	±5·2	±0·83	±13·6	±63·2	±3·3	±28·6	±191·0
S.E. of mean					10·3	2·9	3·4	S6·7 ED2·2	5·1	2·9	0·16	2·7	2·0	2·1	0·37	6·1	28·2	1·3	11·7	78·0
Mean				A	69·2	7·0	16·2	S44·3 ED9·0	(28·2)	(100·8)	3·68	53·0	3·5	26·3	5·27	76·0	300·4	17·7	212·3	1245·5
S.D.					±7·3	±6·2	±3·0	S ±9·8 ED ±4·9	±7·6	±10·9	±0·74	±6·7	±0·9	±6·4	±0·61	±9·0	±68·3	±2·5	±57·5	±290·6
S.E. of mean					3·0	2·5	1·4	S4·0 ED2·0	3·1	4·4	0·30	2·7	0·4	2·6	0·27	4·0	30·5	1·0	27·5	118·6
P value					<0·02	<0·01	<0·01	S<0·01 ED<0·01	<0·01	>0·05	<0·05	<0·01	>0·05	>0·05	<0·01	<0·01	<0·01	<0·01	<0·05	<0·01

B.S.A. = Surface area. B = Before peruvoside and A = 30 minutes after peruvoside. R.A. = Right atrial. P.A.W. = Pulmonary arterial wedge. R.V. = Right ventricular. P.A. = Pulmonary artery. B.A. = Brachial artery. S/D(M) = Systolic, diastolic (mean). ED = End-diastolic. C.I. = Cardiac index (l./min./m.²). S.I. = Stroke index (ml./beat/m.²). P.V.R. = Pulmonary vascular resistance (units). S.V.R. = Systemic vascular resistance (units). L.V.Wi. = Left ventricular work index (kg. m./min./m.²). L.V.S.Wi. = Left ventricular stroke work index (g. m./beat/m.²). S.P. = Stroke power (g. m./sec./m.²). S.E.P. = Systolic ejection period (sec./min.). S.E.R. = Systolic ejection rate (ml./min./m.²).

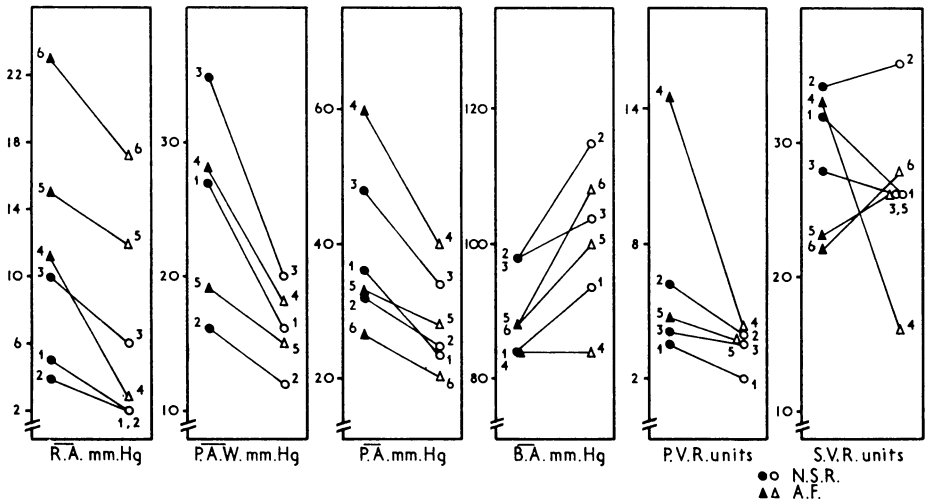

FIG. 2.—At the end of 30 minutes intracardiac peruvoside had significant effect on right atrial (R.A.), pulmonary artery wedge (P.A.W.), and pulmonary arterial (P.A.) mean pressures. The effects on mean brachial artery pressure (B.A.) and systemic vascular resistance (S.V.R.) were variable. Pulmonary vascular resistance (P.V.R.) fell steeply in Case 4 (atrial fibrillation) but the other four patients did not show significant changes.

Pulmonary Artery and Pulmonary Artery Wedge Pressure and Pulmonary Vascular Resistance (Table, Fig. 2).—Pulmonary arterial mean pressure was raised in all patients (average 39 mm. Hg, range 26 to 60 mm. Hg) and peruvoside reduced it when measured 30 minutes after administration. In no instance, however, did the pulmonary arterial mean pressure become normal. High pulmonary artery wedge pressures in five patients (average 25 mm. Hg, range 16 to 35 mm. Hg) were also reduced at the end of 30 minutes by 9 mm. Hg. In only one patient, however, did the pressure become normal, while in others it was still slightly raised. Pulmonary vascular arteriolar resistance was lowered in five patients; in the sixth, where pulmonary arterial wedge pressure could not be obtained, the total pulmonary vascular resistance decreased from 9 to 6·2 units. Except in one instance (Case 1), the calculated resistance was still higher than normal.

Peripheral Arterial Pressure and Vascular Resistance (Table, Fig. 2).—Systolic, diastolic, and mean peripheral arterial pressure increased in five of the six patients at 30 minutes after injection of peruvoside. Calculated peripheral vascular resistance was variably altered. It decreased in three patients, and in two of these (Cases 1 and 4) the change was quite marked. In both patients the cardiac indices had increased considerably following peruvoside therapy. In the other three patients vascular resistance increased, but a significant rise was observed in only one (Case 6).

Calculated Values of Cardiac Contractility (Table, Fig. 3).—All measures of cardiac contractility calculated from the recorded data showed significant improvement. Thus the left ventricular systolic work, left ventricular stroke work, left ventricular stroke power, systolic ejection rate, and brachial artery dp/dt increased by 52·5%, 120%, 110%, 69·5%, and 64·5% respectively, while the systolic ejection period decreased by 44%. A plot of mean pulmonary artery wedge pressure and left ventricular external stroke work index (Fig. 4) also showed a significant improvement in myocardial contractility, with a leftward shift of the curve on which the left ventricle functioned.

Statistical Analysis

As shown in the Table, all the haemodynamic values when subjected to statistical analysis, except brachial artery mean pressure and the pulmonary and systemic vascular resistances, showed highly significant P values.

Clinical Response to Peruvoside

Heart rate decreased in 20 of the 28 patients and remained virtually unchanged in six patients (less than 15%) who were in normal sinus rhythm. Heart rate reduction was greater in patients with atrial fibrillation (40·9%) than in those in normal sinus rhythm (20·5%). In two patients with atrial fibrillation of recent onset the cardiac rhythm became normal sinus while the patients were still being treated with peruvoside, and in one patient with intermittent left bundle-branch block the electrocardiogram remained normal during the course of the therapy. Noticeable clinical improvement was recorded in 18 patients with reduction of dyspnoea and other evidence of congestive heart failure. Of the other 10 patients one died

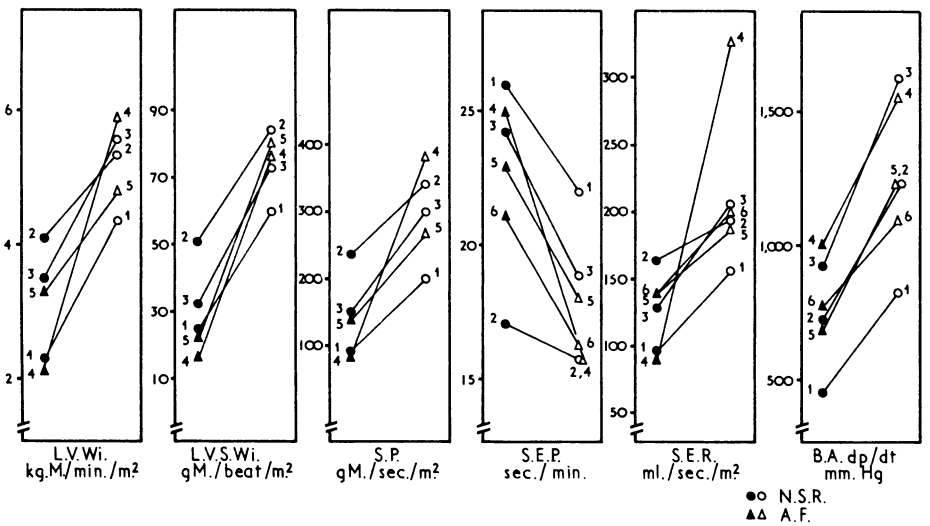

FIG. 3.—Immediate effect of intracardiac peruvoside on calculated values of ventricular contractility. The left ventricular work index (L.V.Wi.), left ventricular stroke work index (L.V.S.Wi.), stroke power (S.P.), systolic ejection rate (S.E.R.), and brachial artery dp/dt showed significant increase in their respective values, while the systolic ejection period (S.E.P.) decreased considerably. The response of these calculated values of ventricular contractility had highly significant P values.

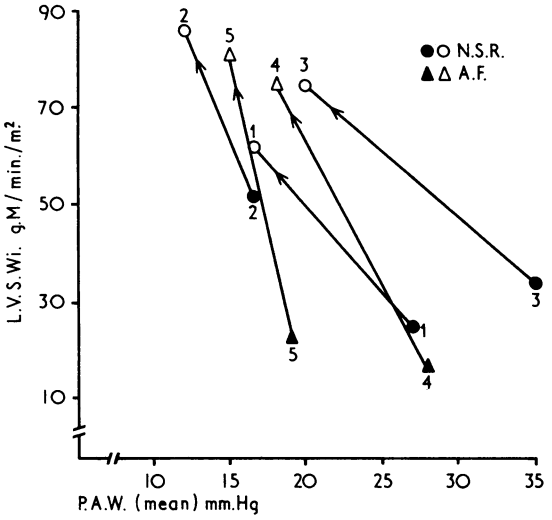

FIG. 4.—Pulmonary artery wedge pressures (P.A.W.) decreased after peruvoside administration with an increase of external left ventricular stroke work index (L.V.S.Wi.) indirectly indicating an improvement of left ventricular functions.

from acute myocardial infarction and another from severe aortic incompetence, four were lost to follow-up, and in four peruvoside gave no benefit.

Side-effects consisted of anorexia, nausea, vomiting, and diarrhoea in 10 patients and cardiac arrhythmias in nine (premature contractions in seven, significant first degree heart block in one, and intermittent short-term complete heart block in one). These were reversible on reducing the dose or stopping the drug.

Discussion

Previous experimental studies in animals by Kohli and Vohra (1960), De *et al.* (1963), and Arora *et al.* (1967) showed that peruvoside exerted a marked positive inotropic effect in the normal and failing heart and that the drug was quick-acting and as potent as ouabain. Similar data in congestive heart failure in man are not available. This may in part be due to non-availability of the pure glycoside. The present haemodynamic studies support the observations made in experimental animals, and show that peruvoside possesses a marked positive inotropic and negative chronotropic activity in congestive heart failure of varying aetiology in man. It reduced heart rate and increased cardiac and stroke indices, left ventricular work index and left ventricular stroke work index, stroke power, brachial artery dp/dt, and systolic ejection rate, while reducing pulmonary arterial, and reflected left and right atrial pressures, and systolic ejection period. Peruvoside treatment thus resulted in improved myocardial function at lowered left atrial mean pressure, a leftward shift of the ventricular function curve at which the heart operated, an action similar to that of other digitalis preparations (Braunwald *et al.*, 1965).

The immediate haemodynamic responses to intravenous peruvoside were observed only in six subjects, but when the data were subjected to statistical analysis it was found that the changes in these values were statistically highly significant. No data on changes in ventricular volume which effect ventricular function were obtained in this study. Nor are such data available even in experimental animals. The role of peruvoside in producing such a change and thereby changing cardiac function is a possibility and remains to be studied.

Clinical trials by us (Arora *et al.*, 1967) in a small number of patients and by others (Dalal *et al.*, 1970) showed the usefulness of peruvoside in effective management of most patients with congestive heart failure. Trials in the present group of 28 patients likewise showed beneficial effects with this therapy, without significant short-term or long-term side-effects, except those reversible effects expected with digitalis therapy. Probably the great advantage of peruvoside is its quick ouabain-like action when given intravenously and its oral effectiveness when used on a short-term or long-term basis.

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REFERENCES

Arora, R. B., Sharma, J. N., and Bhatia, M. L. (1967). *Indian Journal of Experimental Biology*, **5**, 31.
Braunwald, E., Mason, D. T., and Ross, J. (1965). *Medicine*, **44**, 233.
Dalal, N. J., Billimoria, A. R., Vakil, B. J., and Shah, S. L. J. (1970). *Journal of the Association of Physicians of India*, **18**, 237.
De, N. N., Vohra, M. M., and Kohli, J. D. (1963). In *New Aspects of Cardiac Glycosides*, ed. W. Wilbrandt, vol. 3, p.277. Oxford, Pergamon.
Hamilton, W. F., Moore, J. W., Kinsman, J. M., and Spurling, R. G. (1932). *American Journal of Physiology*, **99**, 534.
Kohli, J. D., and Vohra, M. M. (1960). *Archives Internationales de Pharmacodynamie et de Thérapie*, **126**, 412.
Rangaswami, S., and Rao, E. V. (1959). *Journal of Scientific and Industrial Research*, **18B**, 443.
Roy, S. B., Bhatia, M. L., Mathur, V. S., and Virmani, S. (1963). *Circulation*, **28**, 346.
Roy, S. B., Gadboys, H. L., and Dow, J. W. (1957). *American Heart Journal*, **54**, 753.