Systolic time intervals in constrictive pericarditis

A study before and after digitalis

M. L. Bhatia and R. J. Manjuran

From the Department of Cardiology, All India Institute of Medical Sciences, New Delhi, India

Systolic time intervals were studied in 9 patients with documented constrictive pericarditis before and 15 to 20 minutes after intravenous administration of peruvoside (a quick acting digitalis-like glycoside) to determine underlying myocardial dysfunction. Data were compared with those of similarly studied normal subjects and patients with known myocardial dysfunction.

Left ventricular ejection time index (LVETI) decreased in normal subjects ($P < 0.01$) and in most patients with constrictive pericarditis, and increased marginally in those with myocardial dysfunction (NS) after peruvoside administration. Pre-ejection period index (PEPI) shortened significantly ($P < 0.01$) after peruvoside in normal subjects and in patients with myocardial failure, but not in constrictive pericarditis. Likewise the predicted ejection fraction was insignificantly altered in constrictive pericarditis but significantly so ($P < 0.01$) in myocardial failure and normal subjects. The response of one patient with constrictive pericarditis to parenteral peruvoside administration was similar to that seen in patients with myocardial failure. This patient had a delayed recovery after pericardiectomy. PEPI/LVETI ratio and ejection fraction were also abnormal in other patients with constrictive pericarditis when compared to normal subjects. Such abnormalities and the unusual response of some patients to administration of peruvoside may reflect underlying myocardial dysfunction in patients with constrictive pericarditis. However, it is possible that the rigid pericardium also contributes to these abnormalities to a varying extent.

Systolic time indices and their response to digitalis appear to be a useful, atraumatic method for detecting underlying myocardial dysfunction in patients with constrictive pericarditis.

Measurement of systolic time intervals is a well-established, useful, and reliable technique for determination of left ventricular myocardial function (Weissler, Harris, and Schoenfeld, 1969; Weissler and Garrard, 1971b; Weissler, Lewis, and Leighton, 1972). The close correlation of systolic time intervals with the clinical status of patients and haemodynamic parameters like cardiac output, stroke volume, and ejection fraction in congestive heart failure caused by primary myocardial disease, coronary artery disease, and hypertensive heart disease, as well as in normal subjects, has been reported (Weissler, Harris, and Schoenfeld, 1968, 1969; Garrard, Weissler, and Lodge, 1970; Armstrong, Lewis, and Gotsman, 1973). Armstrong *et al.* (1973) have also reported their data on systolic time intervals in patients with constrictive pericarditis and found them to be nearly normal and to be distinct

from those of patients with circulatory congestion caused by primary myocardial disease.

The effect of cardiac glycosides on systolic time intervals in normal subjects (Weissler *et al.*, 1964; Wilson, Tolbert, and DiGuilio, 1970) and patients with congestive heart failure (Weissler and Schoenfeld, 1970) is known. In a previous study (Grover, Bhatia, and Roy, 1972) we reported a significant improvement in the circulatory dynamics of some patients with constrictive pericarditis after acute digitalization suggesting an abnormal left ventricular function. The effect of digitalis on systolic time intervals in patients with constrictive pericarditis has, however, not been reported. In the present study, we report our observations on the effect of 'peruvoside', a quick acting digitalis-like glycoside (De, Vohra, and Kohli, 1963; Arora, Sharma, and Bhatia, 1967; Bhatia, Manchanda, and Roy, 1970; Grover *et al.*, 1972) on systolic time intervals in patients with constrictive pericarditis, in an attempt

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to detect underlying left ventricular dysfunction. These values are compared with systolic time interval data obtained in normal subjects, patients with known myocardial dysfunction, and in some patients with constrictive pericarditis after surgery.

Patients and methods

Nine patients with constrictive pericarditis (with haemodynamic studies in all and pericardiectomy in 5) and 5 patients with congestive heart failure, caused by coronary artery disease in 2 patients and primary myocardial disease in 3, were studied. Ten normal subjects (6 technicians and 4 relatives of patients) with no clinical, electrocardiographic, or x-ray evidence of any

disease were studied as controls. The details of the proposed study were explained and informed consent was obtained in each case. Three patients with constrictive pericarditis were studied again 3 to 6 weeks after a satisfactory pericardiectomy. All patients or subjects were in sinus rhythm. The age and sex of the patients and of normal subjects are given in Tables 1, 2, and 3. None of the patients had received a digitalis preparation for at least two weeks before the study.

Systolic time intervals were measured from simultaneous recordings of the electrocardiogram, phonocardiogram, and carotid arterial pulse tracing at a paper speed of 100 mm/s on a Sanborn multichannel direct-writing recorder or an Electronics for Medicine multichannel photographic recorder. Lead II, or any other

TABLE 1 Systolic time intervals in patients with constrictive pericarditis (preoperative) before (B) and after (A) peruvoside

Case No.	Age (yr) Sex		HR/min	Q-S ₂ I (ms)	LVETI (ms)	PEPI (ms)	PEPI/LVETI	EF (%)
1	30 M	B	94	522.4	399.3	123.1	0.31	68
		A	88	519.8	396.6	123.2	0.31	68
2	39 F	B	83	526.0	393.8	132.2	0.34	65
		A	71	486.0	376.1	109.9	0.29	74
3	25 M	B	100	523.0	392.2	130.8	0.33	61
		A	88	501.8	371.6	130.2	0.35	59
4	14 M	B	109	510.4	394.9	115.5	0.29	70
		A	105	502.0	387.6	114.3	0.30	69
5	23 M	B	105	531.3	400.5	130.8	0.33	63
6	22 M	B	80	509.0	382.0	127.0	0.33	64
		A	78	511.3	387.1	124.2	0.32	66
7	17 M	B	104	505.4	393.3	112.1	0.29	71
		A	102	500.7	391.9	108.8	0.28	74
8	32 M	B	81	511.1	389.7	121.4	0.31	69
		A	75	496.5	382.5	114.0	0.30	71
9	20 M	B	75	509.5	385.5	124.0	0.32	68
		A	66	499.6	375.2	124.4	0.33	66

HR, heart rate; Q-S₂I, electromechanical systole index. LVETI, left ventricular ejection time index; PEPI, pre-ejection period index; EF, ejection fraction.

TABLE 2 Systolic time intervals in congestive heart failure before (B) and after (A) peruvoside

Case No.	Age and sex	Disease		HR/min	Q-S ₂ I (ms)	LVETI (ms)	PEPI (ms)	PEPI/LVETI	EF (%)
10	60 M	CAD	B	100	531.0	369.0	162.0	0.56	36
			A	88	512.3	374.1	138.2	0.37	55
11	20 M	PMD	B	80	503.0	334.0	169.0	0.51	26
			A	80	494.5	336.0	158.5	0.47	34
12	45 M	PMD	B	96	564.1	370.2	193.9	0.52	19
			A	89	529.9	364.3	165.6	0.45	36
13	60 M	CAD	B	89	499.9	350.3	149.6	0.43	41
			A	86	484.6	354.2	130.4	0.37	55
14	42 M	PMD	B	91	544.1	376.0	168.1	0.45	38
			A	86	535.9	383.5	152.4	0.40	50

CAD, coronary heart disease; PMD, primary myocardial disease; HR, heart rate; Q-S₂I, electromechanical systole index; LVETI, left ventricular ejection time index; PEPI, pre-ejection period index; EF, ejection fraction.

TABLE 3 Systolic time intervals in normal subjects – before (B) and after (A) peruvoside

Case No.	Age and sex	HR/min	Q-S ₂ I (ms)	LVETI (ms)	PEPI (ms)	PEPI/LVETI	EF (%)
15	26 M B	80	538.0	411.5	126.5	0.31	70
	A	73	516.3	400.6	115.7	0.29	74
16	25 M B	76	529.6	407.2	122.4	0.30	71
	A	65	516.0	398.0	118.0	0.30	73
17	20 M B	90	497.0	393.0	104.0	0.26	78
	A	85	487.5	389.0	98.5	0.25	80
18	18 M B	88	502.3	399.6	102.7	0.26	79
	A	71	481.1	386.2	94.9	0.25	81
19	20 M B	77	527.7	409.7	115.8	0.28	75
	A	77	519.7	404.2	113.3	0.28	75
20	27 M B	68	524.3	411.1	113.2	0.28	76
	A	68	520.3	410.1	110.2	0.27	78
21	33 M B	73	512.3	404.1	108.2	0.27	78
	A	63	493.3	390.1	103.2	0.27	78
22	29 M B	72	514.7	400.9	113.8	0.28	74
	A	70	507.5	400.0	107.5	0.27	78
23	20 M B	75	501.5	387.5	114.0	0.29	73
	A	62	491.2	384.9	106.3	0.28	76
24	20 M B	81	516.1	409.2	106.9	0.26	78
	A	73	505.8	402.1	103.7	0.26	79

HR, heart rate; Q-S₂I, electromechanical systole index; LVETI, left ventricular ejection time index; PEPI, pre-ejection period index; EF, ejection fraction.

electrocardiograph lead with clearly decipherable 'q' waves, was selected. Phonocardiograms were recorded at frequency settings of 120 to 500 c/s using a PSM-2 (Electronics for Medicine) transducer. The carotid arterial pulse tracing was obtained by using a funnel-shaped pick-up, connected by a short air-filled, semi-rigid tube to a Statham P23 Db pressure transducer. The procedure was carried out after overnight fasting between 8 a.m. and 10 a.m. (Weissler *et al.*, 1969). Tracings were analysed for the following intervals.

- 1) Total electromechanical systolic interval (Q-S₂ interval). This was measured from the onset of 'QRS' of the electrocardiogram to the first high frequency vibration of the aortic component of the second heart sound on the phonocardiogram.
- 2) Left ventricular ejection time (LVET). This was measured from the onset of the upstroke of the external carotid artery tracing to the trough of the incisura of this tracing.
- 3) Pre-ejection period (PEP). This was obtained by subtracting LVET from Q-S₂ interval.
- 4) PEP/LVET ratio was obtained by dividing the measured PEP by LVET.
- 5) Predicted ejection fraction (EF) was calculated by using the equation, $EF = 1.125 - 1.25 \text{ PEP/LVET}$ (Garrard, Weissler, and Dodge, 1970). The results were expressed as a percentage. Systolic time interval indices were calculated from a regression equation (Weissler and Garrard, 1971a). Fifteen consecutive cycles were analysed for the various intervals and average value used for further analysis.

After recording basal systolic time intervals, peruvoside (0.01 mg/kg) was injected intravenously over a

period of 5 minutes into a peripheral vein. Fifteen minutes after the midpoint of the ejection, external tracings were recorded again.

Right heart cardiac catheterization, using standard techniques, was carried out in all patients with constrictive pericarditis before operation and in 3 patients 3 to 6 weeks after pericardiectomy. Haemodynamic studies were not carried out in normal subjects or in patients with congestive heart failure.

Data were statistically analysed by the method of Dunnett (1964) and are given in Table 4.

Results

Mean heart rate (Tables 1 to 4 and Fig. 1 to 6) of patients with constrictive pericarditis (92.3/min) was similar to that of patients with myocardial dysfunction (91.2/min) but significantly higher than in normal subjects (78.0/min, $P < 0.01$). After intravenous peruvoside heart rate was significantly reduced in all the three groups (constrictive pericarditis, $P < 0.01$; congestive heart failure, $P < 0.05$; normal subjects, $P < 0.01$).

Mean QS₂ index (Fig. 1) was similar in the 3 groups. It was statistically significantly reduced in all the groups after intravenous peruvoside (constrictive pericarditis and congestive heart failure, $P < 0.05$; normal, $P < 0.01$). However, the inter-group differences were insignificantly affected by peruvoside.

Mean left ventricular ejection time index (Fig. 2) was the shortest in patients with congestive heart

TABLE 4 Statistical data

Group	No. of individuals	HR		PEPI/LVETI		EF (%)		Q-S ₂ I (ms)		LVETI (ms)		PEPI (ms)	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
a) Before administration of peruvoside													
Constrictive pericarditis (I)	9	92.33	3.23	0.32	0.01	66.50	1.66	516.4	5.30	392.3	3.33	124.1	3.22
Congestive heart failure (II)	5	91.20	4.33	0.49	0.02	32.00	2.23	528.4	7.11	359.9	4.46	168.5	4.32
Normal (III)	10	78.00	3.06	0.28	0.01	75.20	1.58	516.4	5.03	403.4	3.15	112.8	3.05
Contrast between*													
Groups I and II		NS		P < 0.01		P < 0.01		NS		P < 0.01		P < 0.01	
Groups I and III		P < 0.01		P < 0.01		P < 0.01		NS		P < 0.05		P < 0.05	
b) After administration of peruvoside													
Constrictive pericarditis (I)	8	84.12	3.42	0.31	0.01	68.38	2.02	502.20	7.50	383.60	4.15	118.62	3.33
Congestive heart failure (II)	5	85.80	4.34	0.44	0.03	46.0	2.56	511.4	9.86	362.40	5.25	149.02	4.21
Normal (III)	10	70.70	3.07	0.27	0.01	77.20	1.81	503.87	6.71	396.52	3.72	107.13	2.98
Contrast between													
Groups I and II		NS		P < 0.01		P < 0.01		NS		P < 0.01		P < 0.01	
Groups I and III		P < 0.01		P < 0.01		P < 0.01		NS		P < 0.06		P < 0.05	
c) Change after peruvoside (After peruvoside – Before peruvoside)													
Constrictive pericarditis (I)	8	– 6.62	1.42	– 0.01	0.01	+ 1.38	1.28	– 12.39	4.70	– 7.76	2.99	– 4.63	2.67
Congestive heart failure (II)	5	– 5.40	2.01	– 0.05	0.01	+ 14.00	1.92	– 16.98	4.75	+ 2.52	2.28	– 19.50	3.09
Normal (III)	10	– 7.30	1.79	– 0.01	0.002	+ 2.00	0.45	– 12.48	1.95	– 6.86	1.54	– 5.62	0.82
Constrictive pericarditis (I)		P < 0.01		NS		NS		P < 0.05		P < 0.05		NS	
Congestive heart failure (II)		P = 0.05		P < 0.01		P < 0.01		P < 0.05		NS		P < 0.05	
Normal (III)		P < 0.01		P < 0.01		P < 0.01		P < 0.01		P < 0.01		P < 0.01	

Dunnnett's procedure for multiple comparisons with standard was used. SE, standard error. NS, not significant.

failure (359.9 ms) as compared to patients with constrictive pericarditis (392.3 ms) and normal subjects (403.3 ms). The differences between constrictive pericarditis and congestive heart failure ($P < 0.01$) and between constrictive pericarditis and normal subjects ($P < 0.05$) were of statistical significance. Peruvoside resulted in variable alteration of LVETI. Thus it increased in 4 and decreased in 1 patient with congestive heart failure, decreased in all normal

subjects, and in all but 1 patient with constrictive pericarditis. The mean LVETI after peruvoside in patients with constrictive pericarditis was significantly different from that of patients with congestive heart failure ($P < 0.01$) and normal subjects ($P < 0.05$).

Pre-ejection period index (Fig. 3) in constrictive pericarditis (124.1 ms) was shorter than in congestive heart failure (168.5 ms, $P < 0.01$), but longer

FIG. 1 Electromechanical systole index ($Q-S_2I$) in constrictive pericarditis (CP), congestive heart failure (CCF), and normal subjects, before (○) and after peruvoside (●). Broken lines connect mean values for each group. Note the striking reduction in $Q-S_2I$ after peruvoside in Case 2 with constrictive pericarditis, comparable with that seen in patients with heart failure.

than that of normal subjects (112.8 ms, $P < 0.05$). After peruvoside PEPI was reduced significantly in all patients with congestive heart failure ($P < 0.01$). There was a lesser but significant reduction in normal subjects ($P < 0.01$) but not in constrictive pericarditis. Of interest was the response of one patient with constrictive pericarditis (Case 2, Table 1) in whom the reduction of PEPI after peruvoside administration was of almost similar magnitude to that seen in patients with myocardial dysfunction.

PEPI/LVETI ratio (Fig. 4) was dissimilar in the three groups. Values obtained in constrictive pericarditis (0.31) were different from those with congestive heart failure (0.49) but similar to those in normal subjects (0.28). Furthermore peruvoside did not produce any significant change in constrictive pericarditis and normal subjects but reduced the PEPI/LVETI ratio significantly in patients with congestive heart failure. However, in Case 2 in the constrictive pericarditis group, a disproportionate reduction (from 0.34 to 0.29) followed peruvoside administration, a response similar to that seen in patients with congestive heart failure.

FIG. 2 Left ventricular ejection time index (LVETI) in constrictive pericarditis, congestive heart failure, and normal subjects. Note similar fall in LVETI after peruvoside in patients with constrictive pericarditis and in normal subjects, contrasted with slight increase in patients with heart failure.

Calculated ejection fraction (Fig. 5) in constrictive pericarditis (66.5%) was higher than that of patients with congestive heart failure (32.0%; $P < 0.01$) but lower than in normal subjects (75.2%, $P < 0.01$). After peruvoside, ejection fraction increased significantly in normal subjects ($P < 0.01$) and in patients with congestive heart failure ($P < 0.01$) but the increase was insignificant in patients with constrictive pericarditis except for Case 2 where the increase was from 65 to 74 per cent.

Postoperative studies were available in 3 patients (Fig. 6). It was interesting to note that the ejection fraction in Case 2 increased (from 66 to 70%) after operation and was further improved by peruvoside (from 70% to 79%). PEPI/LVETI ratio on the other hand decreased from 0.34 preoperatively to 0.31 postoperatively. Peruvoside reduced the ratio still further, both pre- and postoperatively (0.34 to 0.39 and 0.31 to 0.24, respectively).

Discussion

Myocardial dysfunction in constrictive pericarditis has been reported in some patients on the basis of haemodynamic (Vogel, Horgan, and Strahl, 1971;

FIG. 3 Pre-ejection period index (PEPI) in constrictive pericarditis, congestive heart failure, and normal subjects. Note similar slight fall in PEPI after peruvoside in all except one of the patients with constrictive pericarditis and in normal subjects, but much greater fall in patients with heart failure and in one patient (Case 2) with constrictive pericarditis.

Grover *et al.*, 1972; Bhatia, Sugathan, and Roy, 1972) and histopathological studies (Dines, Edwards, and Burchell, 1958; Levine, 1973). It is desirable that such patients be identified for optimal medical and surgical management.

Determination of systolic time intervals, a well-established technique for assessing left ventricular myocardial function in man, appears suitable for this purpose. Surprisingly only one report (Armstrong *et al.*, 1973) is available regarding systolic time intervals in constrictive pericarditis. These investigators reported no evidence of left ventricular dysfunction in a study of 18 such patients. However, they did not determine the response of systolic time intervals to digitalis as an additional parameter for detecting myocardial dysfunction.

Our results showed significantly abnormal PEPI/LVETI ratio and predicted ejection fraction in patients with constrictive pericarditis when compared to the findings in normal subjects ($P < 0.01$), though the abnormalities were less striking ($P < 0.01$)

FIG. 4 Ratio of pre-ejection index to left ventricular ejection time index in constrictive pericarditis, congestive heart failure, and normal subjects.

Note that there is little change in PEPI/LVETI after peruvoside in patients with constrictive pericarditis and in normal subjects, compared with a striking fall in the ratio after peruvoside in patients with heart failure and in Case 2 with constrictive pericarditis.

FIG. 5 Calculated ejection fraction (EF) in constrictive pericarditis, congestive heart failure, and normal subjects. There is no significant change after peruvoside in the constrictive pericarditis and normal groups, but ejection fraction increases after peruvoside in patients with heart failure and in Case 2 with constrictive pericarditis.

FIG. 6 Systolic time intervals before (B) and after (A) peruvoside, in three patients with constrictive pericarditis, before (●—●) and after (○---○) operation. Note the abnormal response of Case 2 to peruvoside before operation, but improved ejection fraction and decreased PEPI/LVETI after operation. This patient showed only partial clinical response to pericardiectomy in the immediate postoperative phase but improved gradually over the next 18 months.

than those present in patients with known myocardial failure. Armstrong *et al.* (1973) reported a clear demarcation of PEP/LVET ratio and ejection fraction between patients with primary myocardial disease and those with constrictive pericarditis, suggesting absence of myocardial dysfunction in the latter. However, a perusal of their data shows that though the mean values were distinctly different, some overlap was present in individual patients of the two groups for both these parameters. Since the investigators did not report their findings in normal subjects, no comments regarding the differences in systolic time intervals in patients with constrictive pericarditis from those of normal subjects are possible.

In a previous study (Grover *et al.*, 1972) we reported the usefulness of determining the haemodynamic effects of acute digitalization in patients with constrictive pericarditis for detecting abnormal myocardial function. A response similar to that recorded in patients with congestive heart failure was noted in several patients. This consisted of slowing of the heart rate, increase of cardiac and stroke index, and reduction of right and left heart filling pressures. The reversion to normal haemodynamics after pericardiectomy in patients with

constrictive pericarditis was absent or delayed in patients with such a response and suggested co-existing myocardial disease. The present study shows that some patients with constrictive pericarditis may have abnormal systolic time indices similar to those seen in patients with known left ventricular dysfunction. The response of systolic time intervals to acute digitalization with 'peruvoside' in such patients is also similar to that of patients with myocardial failure, with a reduction of the raised PEPI/LVET ratio and an increase of the reduced ejection fraction. It was interesting to note that in one patient in the present series with these findings the post-pericardiectomy improvement was inadequate and delayed. In a haemodynamic and angiographic study Vogel *et al.* (1971) also observed myocardial functional abnormalities in patients with constrictive pericarditis with a reduced ejection fraction and circumferential shortening rate. No data on the effects of rapid digitalization on these parameters was reported. However, one of their patients studied 2 months after an adequate pericardiectomy continued to show abnormal pressures, reduced ejection fraction and circumferential shortening rate indicating persistent left ventricular dysfunction.

On the other hand, Gaasch, Peterson, and Shabetai (1974) recently described normal myocardial function in the presence of greatly depressed pump function in 2 patients with constrictive pericarditis, who were studied in detail. They suggested that this apparent discrepancy was related to restriction of the end-diastolic fibre stretch and hence a reduction in the potential to augment the stroke volume by way of the Frank-Starling mechanism. However, their study does not rule out the possibility of existing myocardial dysfunction in some patients with constrictive pericarditis as observed by us and other investigators on the basis of clinical, haemodynamic, and histopathological studies.

To be certain about the non-existence of myocardial dysfunction, a sufficiently large patient population of constrictive pericarditis would need to be studied since, as is known, not all but only some patients with this disease have associated depressed muscle function.

The contribution of the rigid, non-compliant pericardium to the abnormalities in systolic time intervals, seen in most patients with constrictive pericarditis studied by us, is debatable. It is possible that some of the documented differences, as compared to normal subjects, represent the effect of a rigid pericardium rather than myocardial dysfunction. The striking improvement in systolic time intervals recorded within two months of pericardiectomy, in 2 of our 3 patients suggests the same.

It appears likely that the circulatory abnormalities in constrictive pericarditis are an amalgam of restricted diastolic expansion caused by the rigid pericardium and abnormal systolic contraction caused by ventricular myocardial dysfunction, the contribution of each of these two factors varying in individual patients. Resting systolic time intervals, specially PEPI/LVETI ratio and ejection fraction, and their response to rapid digitalization appear to be sensitive indices in detecting the element of ventricular dysfunction. The atraumatic nature of the procedure makes it useful for preoperative evaluation of such patients and their postoperative serial follow-up.

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Requests for reprints to Dr. M. L. Bhatia, Department of Cardiology, All India Institute of Medical Sciences, New Delhi-110016, India.