INFLUENCE OF PERICARDIAL PRESSURE ON THE RATE OF DENERVATED UNPERFUSED FROG HEARTS

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Summary: Pericardial disension in graded steps in 24 unperfused denervated frog hearts showed significant chronotropic changes. In 13 hearts (54%) the mean control rate rose from 26 ± 9 to 40 ± 11/min at mean pericardial pressure of 4 ± 2 *mm* Hg, the mean acceleration being 53 ± 23%. In these hearts higher pericardial pressures produced deceleration while in the remaining 11 hearts (46%) progressive bradycardia was observed at all pressures. The mean control rate decreased from 28 ± 9 min to 17 ± 9 min. (40 ± 9%) at mean pericardial pressure of 9.9 ± 4 *mm* Hg in all the 24 hearts. The distension acceleration response ($P<0.01$) at low pericardial pressures (0 to 6 *mm* Hg) and the bradycardia ($P<0.001$) were both statistically significant. The disension acceleration increased with sudden large distension and with velocity of injection. At high pericardial pressures (6 to 20 *mm* Hg) bradycardia, conduction blocks, arrhythmias and reduction in voltage of ventricular complex, were observed. The effects of pericardial distension were fully reversible. Frequently marked rebound acceleration even greater than peak distension rate occurred on releasing the distension. The chronotropic changes could only be due to mechanical forces acting on the pacemaker and are related to pericardial distensibility characteristics.

Key words: distension-acceleration, distension-bradycardia, extramural pressure, mechanical stretch, conduction blocks, pacemaker response

INTRODUCTION

Chronotropic changes in isolated hearts due to intramural mechanical stretch have been reported (6,7) and it has been established that mechanical stretch acts as a fundamental stimulus for pacemaker activity (8). Since pacemaker cell size and configuration could also possibly alter due to mechanical force acting from outside, it was considered interesting to investigate the influence of extramural pressure through pericardial distension on the activity of the pacemaker. Although cardiovascular effects of pericardial tamponade have been investigated in dogs (2,3,4,5) and man (10), the chronotropic changes have received no attention. The previous workers either did not record rate changes or ignored them as insignificant. This paper reports significant chronotropic changes due to increase in the pericardial pressure.

MATERIALS AND METHODS

Hearts pithed or decapitated frogs were exposed with intact pericardium. The vagosympathetic trunks were identified and cut as an additional precautionary measure. A needle or polythene catheter was placed in the pericardial cavity. Pericardial distension was conducted

by injecting air or frog Ringer (Nacl 102 *m*M; Kcl 1 *m*M; $Cacl_2$ 1 *m*M; $NaHCO_3$ 1 *m*M; pH 7.6) at room temperature in graded small volume increments or in sudden large volume increment. The distention was reversed by withdrawing the fluid back into the syringe. The pericardial pressure was monitored on a Hg-manometer as well as on an electronic pressure meter through a Statham pressure transducer. The heart rate was monitored on a rate meter triggered by the ventricular complex of the electrocardiogram (ECG). The ECG and pericardial pressure were displayed on a duotrace oscilloscope and recorded on a heat sensitive chart paper on an electronic recorder. The entire system was thoroughly checked for any possible leak several times during each experiment. Changes in heart rate, beat strength and evidence of arrhythmia were also confirmed visually. The sinus venosus was the common reference zero level for the pressure recording system.

RESULTS

The relation of fluid volume in the pericardium to pericardial pressure is shown in Fig. 1. Stepwise increase in the fluid volume produced a slow rise in the pericardial pressure till 3 *ml* had been accommodated. Further increase in the fluid volume resulted in a rather steep rise

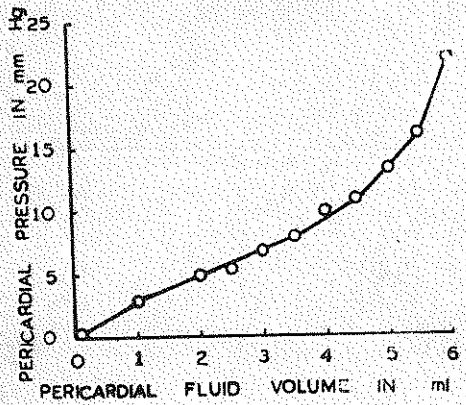

Fig. 1: Pericardial distensibility curve based on volume pressure relationship. The curve has been derived from mean values of 9 trials in 5hearts.

in the pericardial pressure. Increase in the pericardial pressure produced significant chronotropic changes in all the 24 hearts which were investigated (Table I) leading to one of the following three patterns:—

1. initial acceleration at low pericardial pressures (from 0 to 6 *mm* Hg) followed by deceleration at high pressures (6 to 20 *mm* Hg). The peak rate was reached between 1.5 and 6 *mm* Hg in the majority of hearts (Fig. 2 A,B,C).
2. initial deceleration at low pericardial pressures followed by small acceleration at higher pressures (Fig. 2 D).
3. progressive deceleration with increase in the pericardial pressure (Fig. 2 E,F,G,H).

Analysis of the results demonstrated that 13 hearts (54%) showed distension acceleration while 11 hearts (46%) did not. Distension bradycardia, however, occurred in all hearts. Complete data of deceleration and acceleration effects at different pericardial pressures in all the 24 hearts are given in Table I. It can be seen that the mean heart rate decreased from

TABLE I : Chronotropic changes with pericardia distension

Hearts	*Distension acceleration*				*Distension acceleration*			
	Control rate	*Minimum rate*	*Pericardia pressure mm Hg*	*% decrease in rate*	*Control rate*	*Peak rate*	*Pericardial pressure mm Hg*	*% increase in rate*
1	22	12	21	45	—	—	—	—
2	16	10	12	37	16	26	1.5	62
3	28	10	10.5	64	28	52	1.5	85
4	18	8	14	55	18	28	4.0	55
5	20	12	12	40	—	—	—	—
6	28	10	14	64	28	42	3.5	50
7	26	14	10	46	26	48	5.0	84
8	34	30	12	11	34	58	4.0	70
9	30	18	12	40	30	42	4.0	40
10	22	12	8	45	—	—	—	—
11	16	10	8.5	37	—	—	—	—
12	22	10	9.5	54	—	—	—	—
13	18	12	6.5	33	18	30	3.5	66
14	20	14	8.0	30	—	—	—	—
15	18	12	7.5	33	18	28	4.0	55
16	24	12	14	50	—	—	—	—
17	14	8	8	42	14	26	3.0	85
18	31	19	13	39	31**	66**	pericardium cut	—
19	38	28	7.5	26	—	—	—	—
20	40	32	12	20	40	46	2.0	15
21	52	42	5.0	19	52**	58**	4.0	11
22	40	30	2.0	40	40	48	10.0	20
23	54	30	5.5	44	—	—	—	—
24	54	26	6.5	52	—	—	—	—
Mean*	28	17	9.9	40	26	40	4	53
S.D.	9.6	9 4	4.0	9.0	9 11	11.35	2.1	23.3
S.E.	1.9	1.9	0 8	1 8	2.3	3 2	0.5	6.4
t	—	4.1	—	—	—	3.6	—	—
p	—	.001	—	—	—	.01	—	—

* Mean values are in nearest whole numbers.

** Not included in statistical analysis.

28±9/min to 17±9/min at an average mean pericardial pressure of 9.9±4 *mm* Hg, mean deceleration being 40±9%. In the case of distension acceleration, the mean heart rate of 12 hearts rose from 26±9 per min to 40±11/min at the average mean pericardial pressure of 4±2 *mm* Hg, registering an acceleration of 53±23. Both acceleration response ($P<0.01$) at low pericardial pressure and deceleration response ($P<0.001$) at high pericardial pressures were statistically significant. The chronotropic changes were completely reversed by withdrawal of fluid from the pericardial cavity by suction (Fig. 2 G,H). The acceleration response was increased by increasing the velocity of inflow of fluid into the pericardium. Thus sudden injection of large volume of fluid in one step produced greater acceleration than the same volume injected in slow graded steps. The pericardium became leaky when it was subjected to distension with very high pressures (20 to 25 *mm* Hg). At this stage if the fluid was injected continuously with a greater velocity to maintain a low constant pericardial pressure the acceleration response increased markedly (Fig. 2 A, arrow). The heart of pithed and decapitated frogs behaved identically and injection and suction of air produced similar results.

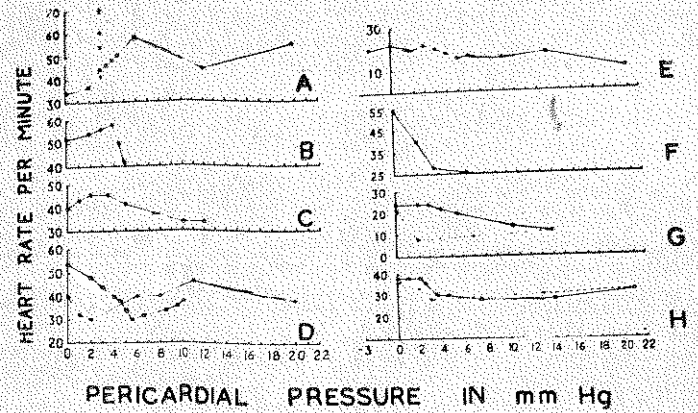

Fig. 2: Chronotropic effect due to increase in pericardial pressure. A, B, C, initial acceleration followed by deceleration in three hearts. D, two hearts showing initial deceleration which was followed by small acceleration. In A, arrow with interrupted line indicates progressive increase in rate when the pericardial pressure was maintained at 3 mm Hg by continuous injection in the presence of a slow leak in the pericardium, which usually developed when distension with pressures above 20 to 25 mm Hg was tested. The effect could be attributed to velocity of fluid inflow. E, F, G, H, four hearts showing progressive bradycardia with increase in pericardial pressure. The interrupted lines in G, and H with reversed arrows from right to left indicate reversal of chronotropic effects when the injected fluid was withdrawn from the pericardium by suction.

Pericardial distension was accompanied by reduction in beat strength and where the heart beat appeared to have ceased at high pericardial pressure, the eletrical activity was still present, although the ventricular complex was attenuated. Electrocardiogram showed increase in sinoatrial conduction at low pericardial pressure. At high pericardial pressure sinoatrial and atrioventricular blocks with associated arrhythmias occured. Conduction block were also

observed when the pacemaker accelerated suddenly to very high rates. Withdrawal of fluid or cutting open the pericardium after distension with high pressure, restored the strength of beat and conduction blocks and arrhythmias usually disappeared. The heart accelerated and the rate returned to pretest initial control value. Frequently there was a rebound acceleration pushing the heart rate to very high values above the control rate (Table I, heart 18). Some of the features of electrocardiographic changes accompanying pericardial distension are illustrated in Fig. 3.

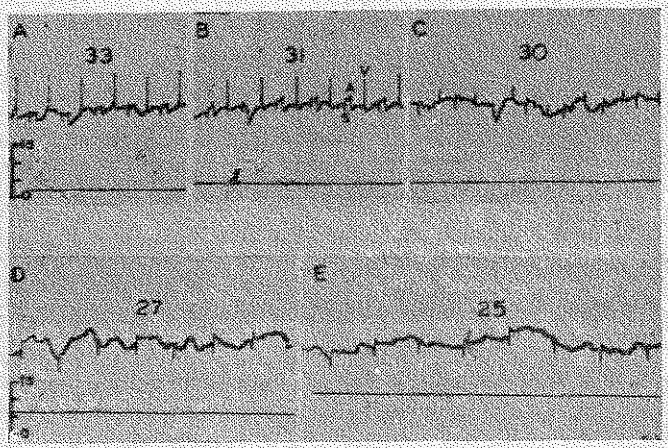

Fig. 3: Extract of record of a heart. In each panel: upper trace, electricardiogram; lower trace, mean pericardial pressure in mm Hg. S, A, V, sinus, atrial and ventricular complexes. A, control record after placement of catheter in the pericardium. B, C, D, and E, records during distension with 1,2,3, and 4 *ml* of Ringer's solution. Numerals at the top middle of each section show sinus (pacemaker) rate/min. Note progressive bradycardia and reduction in ventricular complex voltage with increase in the pericardial pressure. Sinoatrial conduction time increased with 2 *ml* distension (upper panel, C) while complete atrioventricular block with absence of ventricular complexes occurred in D and E in the lower panel.

DISCUSSION

Electrocardiogram of frog heart has separate sinus, atrial and ventricular complexes. The observed chronotropic changes are based on the electrocardiographic recording of changes in the frequency of sinus complexes *i.e.* pacemaker response. These chronotropic changes could not be due to any reflex neural mechanism as the hearts were completely denervated. In the present experiments on unperfused frog hearts the venous return decreased with increase in the pericardial pressure, resulting in reduced ventricular contractions. However, relative anoxia due 3 to reduced venous return was not likely to produce such large reversible chronotropic changes. Fuether similar rate changes have been reported previously in perfused frog hearts where the venous pressure (perfusion pressure) was kept constant (9). Thermal effect also cannot be invoked as a causative factor under the present experimental conditions. Thus in

the absence of extrinsic neurohumoral influences, the observed rate changes could only be attributed to direct mechanical effect of pericardial distension on pacemaker frequency. It is interesting to note that the patterns of chronotropic changes observed during pericardial distension are similar to those observed previously by changing the intramural pressure in the sinus venosus (6, 7, 8). It has also been shown that intramural pacemaker stretch *in vivo* (1, 6, 7, 8) and direct stretch of pacemaker cells *in vitro* (1) increase the pacemaker frequency.

Mechanical force whether applied from inside or from outside appears to alter the dimensions and configuration of pacemaking cells leading to changes in impulse generation. At low pericardial pressures stretch of the pacemaker, within limits, produced acceleration. At high pericardial pressures over-stretch or relaxation of pacemaker due to altered anatomy of cardiac chambers, appeared to be responsible for bradycardia, conduction blocks and arrhythmias. The distensibility curve of the pericardium resembles that of the great vessels and other tissues having fibro-elastic component. The distension acceleration response coincided with the slow phase and the distension bradycardia with the steep phase of the distensibility curve. The mechanism of action of stretch induced alteration in pacemaker frequency is not clear. It is likely that release of stored neurotransmitter(s) or changes in membrane metabolism may be involved.

REFERENCES

1. Brooks, C., Mc C., H. H. Lu, G. Lange, R. Mangi, R. B. Shaw and K. Geoly. Effects of localised stretch on the sino-atrial node region of the dog heart. *Am. J. Physiol.*, **211** : 1197, 1966.
2. Kuno, Y. The mechanical effect of fluid in the pericardium on the function of the heart. *J. Physiol.*, **51**: 221-234 1917.
3. Metcalfe, J., J. W. Woodbury, V. Richards and C. S. Barwell. Studies in experimental pericardial tamponade; effect on intravascular pressure and cardiac output. *Circulation.*, **5** : 518-523, 1952.
4. Nerlich, W. E. Determinants of impairment of cardiac filling during progressive pericardial effusion. *Circulation*, **3** : 377-383, 1951.
5. O'Rourke, R. A., D. P. Fischer, E.E. Escobar, V. S. Bishop and E. Rapaport. Effect of acute pericardial tamponade on coronary blood flow. *Am. J. Physiol.*, **212** : 549-552, 1967.
6. Pathak, C. L. The effect of stretch on formation and conduction of electrical impulses in the isolated sinoauricular chamber of frog's heart. *Am. J. Physiol.*, **192** : 111-113, 1958.
7. Pathak, C. L. Stretch sensitive intrinsic autoregulatory mechanism for rhythmicity and contractility of the heart. *Experientia.*, **28** : 650-651, 1972.
8. Pathak, C. L. Mechanical stretch as a fundamental biological stimulus for heart beat and intrinsic autoregulation of pacemaker and myocardium through mechanical stretch. *Indian J. Med., Sci.*, **26** : 18-25, 1972.
9. Pathak, C. L., N. V. Jog and S. Goyal. Chronotropic changes due to pericardial distension in isolated frog hearts perfused *in situ*. *Experientia*, **29** : 980-981, 1973.
10. Sharp, J. T., I. L. Bunnell, J. F. Holland, G. T. Griffith and D. G. Greene. Haemodynamics during induced cardiac tamponade in man. *Am. J. Med.*, **29** : 640-646, 1960.