The Effect of Epinephrine on Myocardial Synchronization and Diastolic Filling Time[1] (36640)

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Introduction. The rate of myocardial relaxation is an important determinant of ventricular filling (1–3). This parameter assumes added significance when the ventricular filling time is reduced as apparently occurs with increases in heart rate. Early workers have demonstrated that ventricular systole occurs as a result of fractionate contraction of individual myocardial units (4, 5). More recently, systolic synchronization of these units has been demonstrated following injection of catecholamines or stimulation of cardiac sympathetic nerves (6–8). It appears reasonable to assume that the rate of ventricular relaxation might also be increased by synchronizing the activity of these myocardial units. Data are herein presented on the effect of epinephrine on ventricular relaxation rate. New evidence has been obtained on the effect of increasing heart rate on ventricular filling time.

Materials and Methods. Data were obtained from open-chest mongrel dogs (14–18 kg) of both sexes. The animals were anesthetized with intravenous sodium pentobarbital (30 mg/kg) and then heparinized. Positive pressure respiration was maintained at a minute volume of about 4.5 liter/min. Pulsatile aortic pressure was measured via a short rigid catheter with a Statham P 23Db pressure transducer. The heart was suspended in a pericardial cradle and three Brodie–Walton strain gauges were attached to the left ventricle in a manner similar to that of Osadjan and Randall (7). The gauges were balanced at a resting tension by stimulating the left vagus nerve so as to elicit a period of cardiac standstill. At the end of several experiments, sinusoidal alterations in ventricular pressure were produced in the quiescent heart by means of a pump. This showed no phase angle shift between the gauges up to the pump limit of 15 Hz. The myocardial tension changes and the pulsatile aortic pressure were inscribed photographically at a paper speed of 10 in./sec. The response of the recording system was flat to 120 Hz. Changes in myocardial synchronization were elicited by intravenous injection of 1–2 μg/kg synthetic l-epinephrine.

Analysis of Tension Records. Experiments in which epinephrine caused a minimum systolic pressure rise of 30 mm Hg were analyzed. To establish the extent by which the synchronous activity of the myocardium changed, the strain gauge recordings were divided into four phases. Phase I began at the point in time where the tension curve left the baseline and ended at the peak tension inscribed by that gauge; Phase II began at the peak tension and ended at aortic valve closure as indicated by the incisura on the aortic pressure curve; Phase I plus Phase II was the total contraction time for a particular gauge. Phase III began at aortic valve closure and ended as the slope of the isometric relaxation curve deviated from a straight line; Phase IV began at the point just described and ended at the beginning of relative ventricular quiescence. These phases are depicted in Fig. 1 for one of the strain gauge tracings. The alteration of myocardial synchronization during relaxation was determined by measuring the synchronization of the end points of Phase III. The end point of

[1] This work was supported in part by the Bremer Foundation, Youngstown, Ohio and the Eastern Ohio Heart Association.

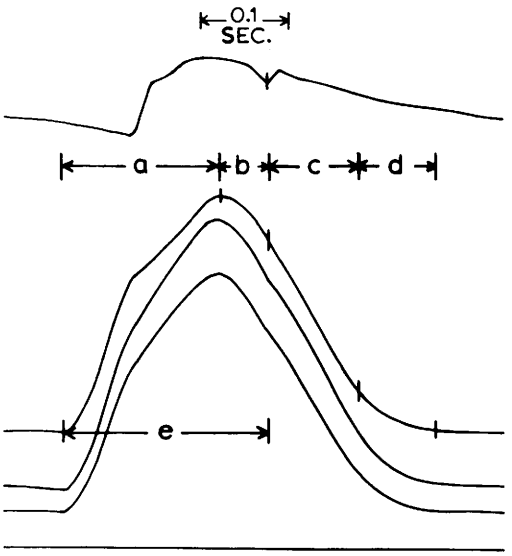

FIG. 1. Control recording of arterial pressure and three strain gauge arches. Phases marked off on one strain gauge recording as follows: a = Phase I; b = Phase II; c = Phase III; d = Phase IV, e = Total Contraction Time.

Phase IV was at times difficult to determine and could not be used as an indicator of altered synchronization. The time differences between these end points of Phase III were subtracted one from the other and an average value established. This average value is hereinafter referred to as $\overline{\Delta T}$. The larger the value for $\overline{\Delta T}$ the less synchronous was myocardial relaxation. A decrease in $\overline{\Delta T}$ as compared to a control value indicated a more synchronous relaxation of myocardial units. Student's t test was used to evaluate significance.

Two control records of 6–8 sec duration were obtained at 5 min intervals. Following injection of the drug, records were taken at the time of the peak pressure response as well as during the declining phase of the drug action as judged by the aortic pressure response. Heart rate, and systolic and diastolic pressure data were obtained from the aortic pressure curves.

Results. The effect of epinephrine on myocardial synchronization during relaxation is shown in Fig. 2. Each of the bars in this figure represents the average $\overline{\Delta T}$ (the mean time difference between the end points of Phase III) for ten cardiac cycles recorded during a particular experimental manipulation. The final control was recorded 10–15 min after drug injection. As can be seen from the figure, this was not always a sufficient time interval to allow return to the initial control values. It is apparent that in all these experiments epinephrine produced a more synchronous relaxation.

The $\overline{\Delta T}$ shortening elicited by epinephrine injection is presented in tabular form in Table I. These data were obtained from two animals for two control and two peak epinephrine responses. Also evident in these tables is the typical abbreviation of total contraction time which occurs either with sympathomimetic drugs or sympathetic activation (8–11). In the first animal the contraction time is shortened by about 50 msec while in the second animal contraction time is shortened by about 80 msec. A striking feature of the epinephrine effect on the myocardium becomes evident when one analyzes the strain gauge curves with respect to both the contraction and relaxation times. Total cycle length was measured for control and peak epinephrine response conditions. The results are presented in Table II. It is strikingly apparent that in spite of significant increases in heart rate, the diastolic interval (total cycle length minus total contracion time), is not curtailed in these experiments. It is, in fact, prolonged in some cases. This observation assumes major importance with regard to

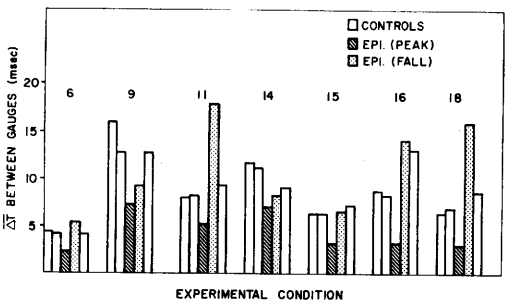

FIG. 2. The effect of epinephrine on synchronization of ventricular relaxation. Each bar represents the mean value of $\overline{\Delta T}$ for ten cardiac cycles for the experimental manipulations indicated.

TABLE I. The Effect of Epinephrine on Duration of Cycle Phases in Experiments 6 and 15. Two Control and Two Epinephrine Cycles per Experiment.

Condition		Phase I (msec)	Phase II (msec)	Phase III (msec)	Phase IV (msec)	$\overline{\Delta T}$ (msec)
Expt. 6						
	Gauge 1	158	49	42	38	
	Gauge 2	164	41	50	45	5.3
	Gauge 3	162	38	47	52	
Control						
	Gauge 1	162	47	41	44	
	Gauge 2	166	39	48	45	4.7
	Gauge 3	163	37	45	53	
	Gauge 1	114	39	34	41	
	Gauge 2	115	35	31	50	2.7
	Gauge 3	112	35	30	54	
Epinephrine						
	Gauge 1	111	38	30	54	
	Gauge 2	112	35	30	54	1.3
	Gauge 3	110	34	28	64	
Expt. 15						
	Gauge 1	163	69	51	45	
	Gauge 2	167	56	50	34	4.7
	Gauge 3	178	46	57	38	
Control						
	Gauge 1	167	67	50	47	
	Gauge 2	169	54	47	38	6.0
	Gauge 3	177	47	56	38	
	Gauge 1	89	53	29	54	
	Gauge 2	83	52	26	26	2.0
	Gauge 3	77	61	29	23	
Epinephrine						
	Gauge 1	91	55	25	65	
	Gauge 2	86	56	23	26	2.0
	Gauge 3	82	62	26	24	

maintenance of an adequate filling time in the face of a markedly curtailed cardiac cycle duration. The only exception in this behavior is experiment number 11.

Discussion. The question arises as to whether the observed effect of epinephrine in these experiments was exerted via its chronotropic activity on pacemaker tissue or by a direct effect on some other component of the myocardium. If the effect had been chronotropic then all phases of the cardiac cycle should have been altered to the same extent and there would have been a proportionate change in the relationship of the gauges one to the other. Consequently, one would expect to find a constant ratio between the value of $\overline{\Delta T}$ and the duration of Phase III for both the control and experimental conditions. That this was not the case is shown in Table III. In only two of these experiments (11 and 15) was there a constant ratio of $\overline{\Delta T}$ to Phase III duration during the peak effect of epinephrine. All other experiments showed a considerable decrease in $\overline{\Delta T}$/Phase III, tending to indicate a specific effect on the contractile mechanism. Experiments 14 and 18 in Table IV provide additional evidence that the decrease in $\overline{\Delta T}$ is not entirely a result of cardiac acceleration. In these two animals, the mean arterial pressure was elevated significantly by epinephrine while the heart rate remained essentially constant. Nevertheless, there occurred a marked decrease in $\overline{\Delta T}$ which tends to support the hypothesis that altered myocardial synchronization is not

TABLE II. Relationship Between Total Cycle Length, Total Contraction Time, and Duration of Diastole.[a]

Experiment	Condition	Total cycle length (msec)	Total contraction time (msec)	Duration of diastole (msec)	HR (beats/min)
6	Control	419	204	215	143
	Epinephrine	365	148	217	164
9	Control	468	232	236	128
	Epinephrine	447	206	241	134
11	Control	560	268	292	108
	Epinephrine	354	166	188	169
14	Control	464	194	270	129
	Epinephrine	476	170	306	126
15	Control	373	227	146	160
	Epinephrine	333	144	189	180
16	Control	365	219	146	164
	Epinephrine	314	140	174	191
18	Control	375	210	165	159
	Epinephrine	357	161	196	168

[a] Each value represents an average time for three cardiac cycles.

necessarily a result of the chronotropic effects of epinephrine on pacemaker tissue. Parmley and Sonnenblick noted a significant change in isometric relaxation rate of cardiac muscle under the influence of catecholamine (12). The basis for this observation seems to be a specific stimulatory affect by catecholamines on Ca^{2+} uptake by the sarcoplasmic reticulum. It is herein postulated that the increased rate of Ca^{2+} uptake then leads to an increased synchronization of myocardial units which manifests itself as a more rapid isometric relaxation rate.

Perhaps the most significant observation in this work was the maintenance or even prolongation of the diastolic time interval in spite of increases in heart rate. For example, in experiment number 6 (Table II), the heart rate increased from 143 to 164 beats per min. The durations of diastole in this experiment were 215 and 217 msec, respectively. To the author's knowledge this constancy of the diastolic time interval has not been observed previously. This observation assumes considerable importance in that it is a possible mechanism for permitting adequate ventricular filling in the face of moderate increases in heart rate. Thus, the increased synchronization during relaxation may be in part responsible for maintaining a constant

TABLE III. Ratio of $\overline{\Delta T}$ to Duration of Phase III.

Condition	Experiment						
	6	9	11	14	15	16	18
Controls 1 and 2	0.1021	0.3143	0.0927	0.2011	0.1282	0.1313	0.1480
Epinephrine (peak)	0.0517[a]	0.1866[a]	0.1094[c]	0.1724[b]	0.1240[c]	0.0954[b]	0.0567[a]
Epinephrine (decline)	0.1367	0.2170	0.1660	0.1711	0.1407	0.1921	0.3040
Control 3	0.0901	0.3106	0.1320	0.1522	0.1226	0.1790	0.1762

[a] Significantly different from controls ($p < .001$).
[b] Significantly different from controls ($p < .05$).
[c] Not significantly different from controls.

TABLE IV. Comparison of $\overline{\Delta T}$, Heart Rate, and Mean Arterial Pressure for Control and Peak Epinephrine Conditions.

	Experiment										
	6			9			11			14	
dition	$\overline{\Delta T}$ (msec)	HR (beats/ min)	MAP (mm Hg)	$\overline{\Delta T}$ (msec)	HR (beats/ min)	MAP (mm Hg)	$\overline{\Delta T}$ (msec)	HR (beats/ min)	MAP (mm Hg)	$\overline{\Delta T}$ (msec)	HR (beats/ min)
s 1 and 2	4.3	140	100	14.4	120	87	8.2	104	108	11.5	128
hrine (peak)	2.1[a]	164	128	7.4[a]	134	137	5.2[b]	169	148	7.0[a]	126
3	4.1	141	97	12.8	128	100	9.4	106	98	9.1	122

	Experiment								
	15			16			18		
dition	$\overline{\Delta T}$ (msec)	HR (beats/ min)	MAP (mm Hg)	$\overline{\Delta T}$ (msec)	HR (beats/ min)	MAP (mm Hg)	$\overline{\Delta T}$ (msec)	HR (beats/ min)	MAP (mm Hg)
s 1 and 2	6.4	160	110	8.5	163	85	6.7	168	108
hrine (peak)	3.1[a]	200	124	3.1[a]	191	104	2.9[a]	168	152
3	7.2	158	106	13.0	172	96	8.6	166	112

ificantly different from controls ($p < .001$).
ificantly different from controls ($p < .05$).

stroke volume when there is increased demand on the heart, as in moderate exercise. This constancy of stroke volume during moderate exercise has been observed by Rushmer (13), while Wilson noted slight increases in stroke volume with similar exercise levels (14). It is interesting to note that in the experiments of both these authors the upper heart rate level was about 200 beats/min. An increased stroke volume in spite of a decreased diastolic time interval in conscious animals undergoing strenuous exercise has also been reported (15). However, in these animals the mean heart rate during exercise was 262 beats/min, far exceeding any values obtained in this present study. During the recovery periods in these bouts of exercise when the heart rate was comparable to those in this study, and when left ventricular diameter was at the control level, calculations showed no significant change in stroke volume. It would be interesting to have some information on the diastolic time interval during this recovery period.

Summary. Experiments performed on open-chest dogs indicated that epinephrine affects the synchronization of myocardial units both during the contraction and relaxation phases of cardiac activity. This increased synchronization may contribute significantly to the prolongation of the diastolic filling time which was observed in these experiments at increased heart rates.

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Received Nov. 4, 1971. P.S.E.B.M., 1972, Vol. 140.