Some Factors Influencing Potentiation of Cardiac Contractility Following an Extrasystolic Beat.* (22360)

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The increase in contractility of cardiac muscle following an extrasystole was first described by McWilliams(1). Cattell and Gold (2,3) have confirmed and extended this finding and Garb and Penna(4) have determined the effects of the interval between the basal and extrasystolic beats on the potentiated contraction in cat papillary muscle. The present report deals with some of the factors influencing post-extrasystolic potentiation (PEP) of cardiac contractility as determined in the isolated rabbit auricle.

Methods. The isolated quiescent rabbit auricle suspended in Tyrode solution was used. Details of this preparation and the Tyrode solution used are found in a publication by Rosin and Farah(5). The bath temperature was controlled at 37.0-37.5°C. Electrical stimulation of the auricle was accomplished by means of 2 coupled Grass stimulators (Model S4C). The first stimulator was used for driving at basal rates and served to trigger the second stimulator which provided the extrasystolic beats. The interval between basal and extrasystolic beat as well as voltage and pulse duration could be varied at will. Extrasystolic stimuli were interjected through the same electrodes which delivered the basal stimulus or at a point 2 to 4 mm from the latter electrodes. Results in both instances were essentially the same. Contractility was recorded by means of a Grass force transducer and a Grass inkwriting electroencephalograph. Quinidine sulfate, when used, was added to the bath in a dosage of 0.25-1.0 mg% and readings were made 30 minutes after addition of the drug.

Results. Post-extrasystolic potentiation of cardiac contractility could be demonstrated both in the isolated auricle and isolated ventricular strips of the rabbit. The quantitative data to be reported have been obtained on the quiescent isolated rabbit auricle stimulated at basal rates of 0.2 to 5 beats per second.

Fig. 1A illustrates a typical result. It can be seen that a single extrasystolic beat produced a potentiation of contractility which was increased by interjecting a second and a third extrasystolic beat. This cumulative effect of extrasystolic beats has been regularly observed and usually reached a maximum following 5 to 8 such stimulations. Maximum potentiation of cardiac contractility thus attained exceeded 100 and sometimes attained 300 to 400%. The contraction velocity of the post-extrasystolic beat is accelerated as the peak of the contraction occurs only slightly later than that of the pre-extrasystolic beat (Fig. 1B).

It is difficult to state whether the electrical extrasystole which produced potentiation also produced a mechanical extrasystole. In many of our experiments (see Fig. 1A) there were no readily visible mechanical extrasystoles. However, close inspection of some of the tension curves frequently showed a slight irregularity in the descending part of this curve which may indicate a mechanical change. With the recording methods used it is impossible to decide whether an electrical or both electrical and mechanical extrasystole were essential for the production of potentiation. It is hoped to resolve this problem and such studies are now being initiated.

The effect of resting tension on the production of PEP was studied. In general PEP was observed with low or high initial tensions. Usually an increase of the initial tension by 1 to 2 g increased the height of the basal beat as well as PEP. On occasion an excessive increase in tension would reduce both the basal beat and the PEP. This is in conformity with

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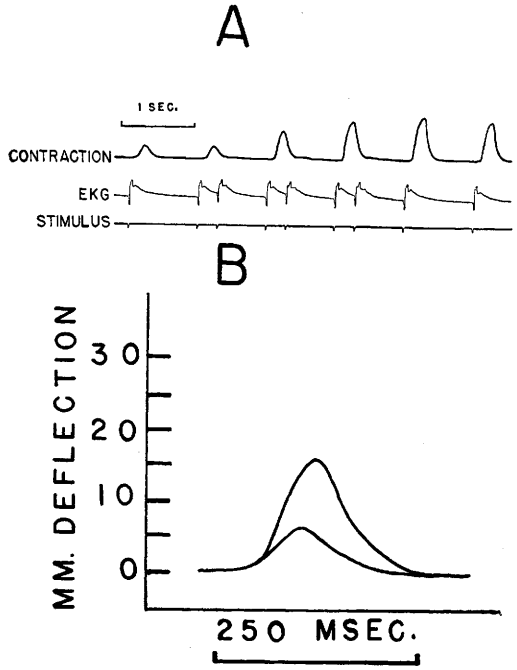

FIG. 1A. Effect of 3 extrasystoles on contractions of isolated left auricle of rabbit. Temp. 37.5°C. Tyrode solution. Note increase in contractile tension following interjection of the extrasystoles.

FIG. 1B. Superimposed records of contractions obtained from isolated left auricular preparation. Lower trace: basal contraction; upper trace: contraction following a single extrasystolic stimulus delivered 80 milliseconds after basal stimulus. Basal rate 2 per sec. Temp. 37°C.

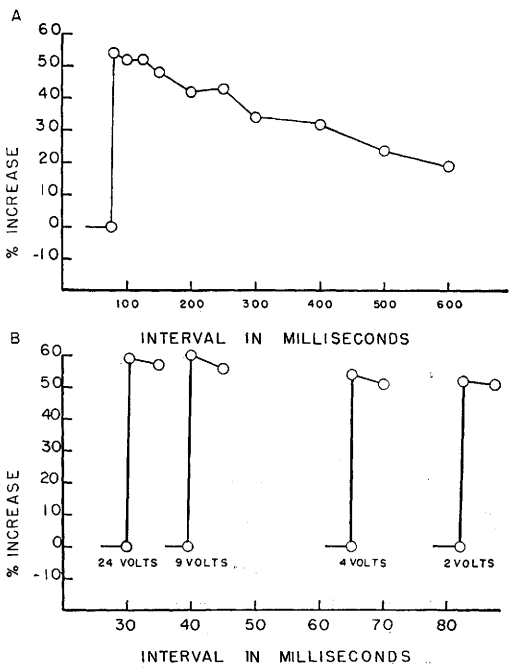

FIG. 2A. Effect of interval between basal and extrasystolic beat on post-extrasystolic potentiation in rabbit auricle. Basal rate = 1 per sec. Temp. 37°C. Height of first post-extrasystolic beat expressed as % of basal beat. Stimulus 15 volts.

FIG. 2B. Effect of stimulus intensity on PEP in rabbit auricle. Conditions as in Fig. 2A except for stimulus intensity.

Starling's law of the heart. The PEP was not accompanied by a measurably different action potential from that of the basal beat (Fig. 1A). In general, the first post-extrasystolic beat showed maximal potentiation, however, the second, third, and even fourth beats following a single extrasystolic beat would show some potentiation. The decay of potentiation followed an exponential curve and in this respect our results confirm those of Cattell and Gold(3), Garb and Penna(4), and Rosin and Farah(5).

The interval between the extrasystolic beat and the post-extrasystolic beat was varied between 1 and 120 seconds. It could be shown that PEP was still apparent after a rest period of 120 seconds. In this respect the results are qualitatively similar to those of Garb and Penna(4) and Rosin and Farah(5) who determined the effect of rest period on post-extrasystolic potentiation, and post-stimulation potentiation of cardiac muscle respectively.

The effects of the interval between basal and extrasystolic beats on PEP were studied in 25 auricles. In general the shorter the interval the greater the PEP until an interval was reached when the auricle would not respond (Fig. 2A). If a threshold stimulus was used the interval necessary to produce maximal potentiation was longer than when supramaximal stimuli were used (Fig. 2B). The shortest possible interval could be obtained by using stimuli equal to 6 to 9 times threshold and this minimal interval corresponded to the effective refractory period, as determined from a strength-interval curve. In most experiments maximal potentiation was seen when the interval between basal and extrasystolic beat was minimal. However, in some experiments maximal potentiation did not

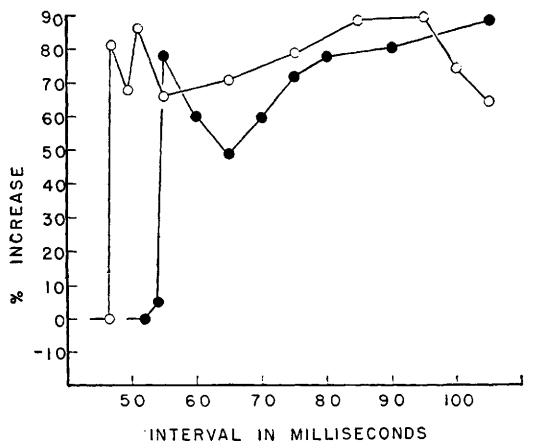

FIG. 3. Effect of interval between basal beat and extrasystole on 1st post-extrasystolic beat showing atypical response curve. Rabbit auricle. Temp. 37°C.

correspond to the effective refractory period but occurred at longer intervals (Fig. 3). We do not have any explanation for this variation, and it was observed only in a few preparations; however, these changes may correspond to the dips in the excitability curve described by Brooks, *et al.*(6).

Since rate of stimulation influences the refractory period of cardiac muscle, we have determined the effects of rate on the PEP in the isolated rabbit auricle. It could be shown that an increase in rate produced a shorter effective refractory period as determined by strength-interval curves and decreased the time interval between the basal and extrasystolic beat necessary to produce a maximal potentiation (Fig. 4A). The observation was made that an increase in rate of stimulation not only decreased the time interval for PEP but also increased the extent of potentiation (Fig. 4B) up to rates of about 3 per second; at higher rates both basal and potentiated beats were reduced. This finding is different from that of Garb and Penna(4) who did not find this relation of rate of stimulation of cat papillary muscle to the magnitude of the PEP.

At high rates of stimulation (4.0-5.0/sec.) the potentiation would occasionally be delayed, *i.e.*, no potentiation of the first post-extrasystolic beat but marked potentiation of the second would be observed. Garb and Penna(4) and Rosin and Farah(5) have also observed this delayed potentiation which occurs only at high rates of stimulation.

Quinidine is known to prolong the effective refractory period of cardiac muscle. We have thus determined the effects of quinidine on the interval necessary for the production of PEP as well as the extent of the potentiation produced. Following control readings quinidine was added in increasing cumulative concentrations to the bath and both strength-interval curves and PEP were determined. The data are given in Fig. 5 and it can be seen that quinidine in concentrations of 0.25 to 1.0 mg % prolonged the interval necessary to

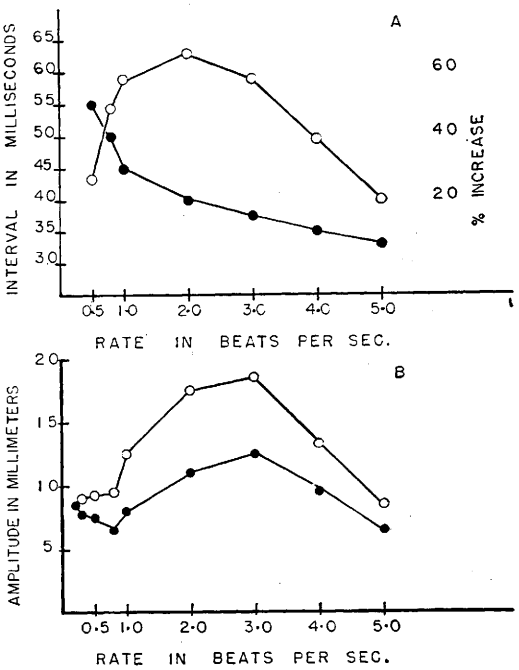

FIG. 4A. Effect of rate of basal stimulation on minimal interval between basal beat and extrasystolic which produced post-extrasystolic potentiation in rabbit auricle. Temp. 37°C. ●—● Minimal interval between basal beat and extrasystole producing potentiation of the first PEP. ○—○ % change in tension of PEP as related to basal beats at each rate.

FIG. 4B. Effect of rate of basal stimulation on post-extrasystolic potentiation. Avg of 4 auricular preparations. Temp. 37°C. Post-extrasystolic potentiation measured at minimal interval between basal and extrasystolic beat producing potentiation. Abscissa: Basal rate. Ordinate: Tension of isometric twitch expressed in millimeters of pen deflection. ●—● Basal beat. ○—○ Potentiated beat.

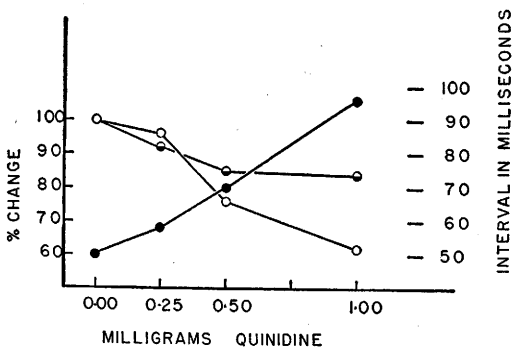

FIG. 5. Effect of quinidine on interval between basal beat and the extrasystole which produced maximal PEP in isolated rabbit auricle. Temp. 37°C. ●—● Minimal interval in milliseconds between basal beat and extrasystole which produces maximal PEP. *Half-solid circles*—Contractility at basal rate (1/sec.) expressed as % of control. ○—○ Change in PEP expressed as % of control.

produce PEP. Quinidine decreased the extent of the potentiation but also decreased the height of the basal contraction. However, the per cent decrease in the potentiated beat exceeded the changes in the basal beat (Fig. 5). It is thus likely that quinidine in some way interfered with the process or processes responsible for the initiation of post-extrasystolic potentiation.

Discussion. The presence of post-extrasystolic potentiation (PEP) of cardiac beats was demonstrated in both isolated auricular and ventricular muscle strips of the rabbit. This phenomenon of PEP has been observed by others in isolated cardiac muscle preparations (1-4). In our own experience PEP occurs in the isolated heart of dogs, rabbits and cats perfused by the Langendorff technic. Furthermore, PEP has been observed in occasional auricular and ventricular strips of the rabbit when spontaneous extrasystoles occurred. In the dog heart-lung preparation we have observed that the appearance of one or more extrasystoles would significantly improve the cardiac function especially if the heart showed signs of decompensation. The effects of such extrasystoles became apparent by a temporary decrease in the right auricular pressure and cardiac size, a temporary increase in cardiac output and stroke volume. All these changes have been frequently observed but have been explained on the basis of changes in cardiac filling and "Starling's law of the heart." The observations in the heart-lung preparation are difficult to analyze since changes in fiber length occur and thus the relation of PEP to changes in fiber length cannot be clearly formulated. Recently Siebens, *et al.*(7) studied this phenomenon in the dog heart and changes in fiber length of the ventricle could be excluded as a cause of post-extrasystolic potentiation. It is thus likely that the PEP studied in the isolated auricular and ventricular strip is not characteristic of the isolated preparation alone but also occurs in blood-perfused, intact hearts.

The relation of post-extrasystolic potentiation to post-stimulation potentiation and to the staircase (Treppe) phenomenon should be considered. In our experience the behavior of these 3 phenomena responds to physical as well as pharmacological changes in the same directions and it is likely that the underlying fundamental mechanisms for all 3 types of potentiation are the same. As regards the mechanism of post-extrasystolic potentiation little can be said at this time. Ellis(8) has suggested that glucose-phosphate is related to the staircase phenomenon. Recently Ritchie and Wilkie(9) have concluded that the staircase phenomenon and post-tetanic potentiation in frog striated muscle were caused by the delay in the fall of the active state of muscle postulated by Hill(10). It is possible that the active state of muscle is related to post-extrasystolic and post-stimulation potentiation. The active state persists for milliseconds while the potentiation of contractility persists for several beats and can be elicited minutes after the extra-systolic beat. These properties of PEP and post-stimulation potentiation make it difficult to explain these phenomena solely on the basis of a prolongation of the active state. A process which is only slowly reversible and which is dissipated by the following contractions may precede the active state and may determine the length of the active state and velocity of contraction.

The PEP of auricular muscle is related to the refractory period since an increase or decrease in the refractory period also produced parallel changes in the PEP.

Summary. Post-extrasystolic potentiation (PEP) of cardiac contractility was studied in rabbit auricular muscle. It is shown that potentiation is related to the interval between basal beat and extrasystolic beat. An increase in driving rate up to about 3 per second increased the extent of potentiation and decreased the interval between basal beat and the extrasystole necessary for the production of maximal potentiation. Quinidine increased the effective refractory period and the interval for producing PEP and decreased the degree of potentiation produced by the extrasystole.

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Metabolic Actions of Acetic Acid Analogs of Thyroxine and Triiodothyronine.* (22361)

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In the field of thyroxine analogs and possible derivatives which may have special metabolic characteristics, the most striking recent observations were those of Gross and Pitt-Rivers(1) and of Roche, Lissitzky and Michel(2) that 3,5,3′-triiodothyronine (Trit) was several times more active than thyroxine. Many workers have since confirmed this on a variety of test animals(3). The time of delay before the metabolic effects of Trit are seen is now recognized as shorter than with thyroxine(4-7), but still present. The duration of Trit action is also more brief, effects which are more striking in the myxedematous human than in experimental animals(8,9).

Thibault and Pitt-Rivers(10,11) reported that 3,5,3′,5′-tetraiodothyroacetic acid (Tetrac) and 3,5,3′-triiodothyroacetic acid (Triac) produced an immediate *in vitro* stimulation of kidney and liver slices appearing at concentrations about 0.01 μg Triac per ml or 0.05 μg Tetrac per ml and reaching a maximum at respectively, 1.0 and 5.0 μg per ml. In addition, Tetrac was stated to cause a considerable rise in metabolic rate of thyroidectomized rats in 2 hours followed by a return to the starting level after 4 hours. Pitt-Rivers had previously reported on the activity of Tetrac and Triac(12), noting no unusual results except for unexpectedly high toxicities. The present report concerns possible qualitatively distinct properties of Tetrac and Triac.†

Methods. All rats used were from the Sprague-Dawley strain, thyroidectomized at least 6 weeks previously. Most tissues were prepared as previously discussed(13). Ehrlich mouse ascites tumor cells, cultured *in vivo* in Carworth white mice,‡ were washed sev-

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† Samples of Tetrac and Triac were obtained through the generosity of Dr. Pitt-Rivers and of Dr. John A. King, Warner-Chilcott Laboratories.

‡ These cells from a Southern Research Institute culture were obtained through the courtesy of Dr. Warner W. Carlson and Mr. J. T. Huggins.