THE POTENTIATED CONTRACTION AND VENTRICULAR "CONTRACTILITY"*

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THE contractile process in the heart's musculature is subject to a variety of continuing influences arising from heart size, rate, rhythm, and sympathetic outflow, which may vary in intensity from moment to moment. What the ventricle is capable of doing in terms of one or another index of contractility may therefore be of more significance than what it is, in fact, doing. There is evidence[1-4] that a number of inotropic interventions (excluding the length-tension relationship) share a common mediating mechanism that governs the availability of calcium ion at some site critical for contraction. It would thus be of interest to elicit a maximal contribution from this mechanism as a yardstick of the ventricle's capacity for force or pressure development. The experimental results reviewed below suggest that the technique of paired pulse stimulation might be useful in bringing about such a contractile maximum in the *in situ* ventricle.

The contractile process in skeletal muscle, in contrast to that in ventricle, is relatively unalterable in its magnitude and in its time course. With the exception of the length-tension relationship, contraction of skeletal muscle is hardly, if at all, modifiable by any of the many interventions that profoundly change the contraction of ventricular muscle. The staircase effect, for example, is minimal in skeletal muscle,[5] and epinephrine appears to decrease slightly the force plateau of the active state.[6] Although the duration of the skeletal muscle's active state can be prolonged through the replacement of extracellular chloride (in the isolated tissue) by nitrate ion,[7] this is more easily accomplished in ventricular muscle through a slowing of the rate.[8] Thus the contractile

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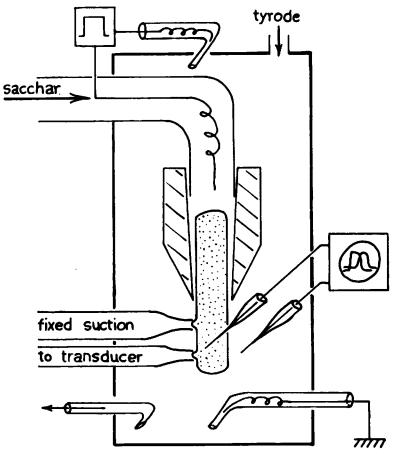

Fig. 1

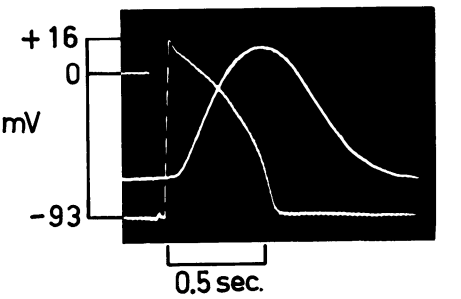

Fig. 2

Fig. 1. Design of the experiment. The diagram shows the ventricular fiber bundle (*stippled area*) in position in the plastic block (*hatched area*). The arrangement of stimulating electrodes is shown in the upper left-hand portion of the diagram; mechanical ("fixed suction" and "to transducer") and electrical (microelectrodes) recording systems are shown in the lower part. Tyrode outflow: lower left-hand corner. For detailed description see Kavaler.[10]

Fig. 2. Simultaneously recorded action potential and tension development in ventricular muscle during a single twitch. The upstroke of the action potential has been drawn in as a dashed line.

"package" delivered by skeletal muscle (the effect of sarcomere length aside) appears to be relatively fixed, or quantal, in character.

The contents of the ventricular contractile "package" are not only more variable, but are capable of being altered during the course of a single heartbeat. In the cooled (8° C.) turtle heart, where systole lasts for several seconds, intracoronary injection of a calcium chloride solution following the upstroke of an action potential resulted in an increase to ventricular force development during the *same beat.*[9] Ventricular contraction is thus continuously responsive to the extracellular calcium level during systole.

It is also continuously responsive to membrane depolarization.[10] Figure 1 shows an experimental arrangement for recording contractile tension from a short (0.3 mm.) length of a ventricular trabecula, under conditions where the time course of the transmembrane action potential can be modified, by current flow, in a manner that is roughly uniform along this length of muscle. The well-known[11] temporal connection between membrane repolarization and relaxation is shown for an unmodified twitch in Figure 2. When membrane repolarization is

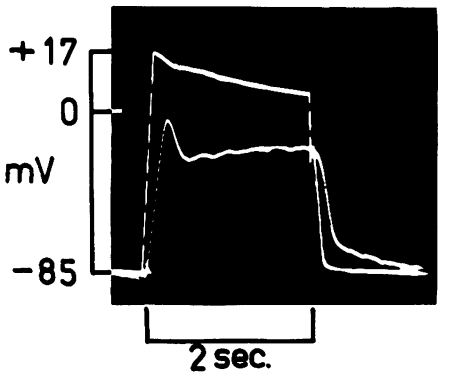

Fig. 3

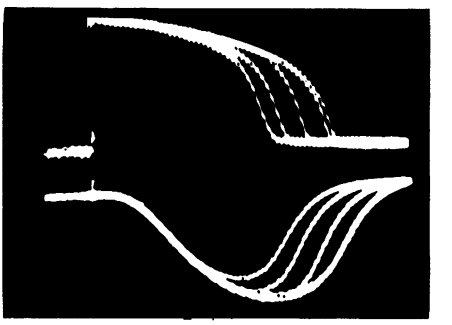

Fig. 4

Fig. 3. Current contracture: electrical (*upper*) and mechanical (*lower*) records. Peak tension value is approximately 10 mg. The electrical upstroke and the early portion of repolarization have been drawn in as dashed lines.

Fig. 4. Superimposed exposure of five consecutive beats of a strip of frog ventricle (rate 12/min.). Upward-going traces display transmembrane potential time courses, downward-going ones isometric tension development. The largest electrical trace is the naturally-occurring action potential (about 120-mV. amplitude, 1 sec. duration at 18° C.). Other electrical traces show increasingly premature repolarization limbs due to 500-msec. hyperpolarizing pulses, applied at progressively earlier intervals during the plateau. Tension develops in all cases with a common time course, but relaxation is correlated with repolarization. Peak tension occurs at a constant level of repolarization, a transmembrane potential of about -20 mV. inside. Tension recorded from a 0.2 mm. length of the muscle strip.

deferred by a 2-second pulse of 2 to 3 times rheobasic strength (Figure 3), contractile tension is maintained at near-peak levels until repolarization is allowed to occur. The opposite maneuver of premature termination of the action potential plateau through "anodal" current flow brings about premature relaxation, roughly coincident—as in all of the other cases—with membrane repolarization. This result, shown in Figure 4 (frog ventricle strip), has also been obtained with cat papillary muscle.

Perhaps the strongest influence on ventricular contraction, at least in the isolated tissue preparation, arises from the preceding systole itself. Each beat exerts both positive (staircase, postextrasystolic potentiation, poststimulation potentiation) and negative (the weak premature beat, rest potentiation) inotropic effects on the succeeding beat. These two opposing residual effects of a contraction have been postulated to decay with different time courses[12] and to account, in this way, for all the inotropisms related to rate and sequence of contraction. Figure 5 illustrates a well-known negative inotropic effect of this sort: the weakness of a premature beat. The two inner traces represent electrical and

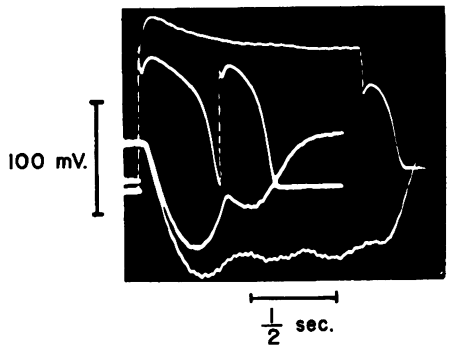

Fig. 5

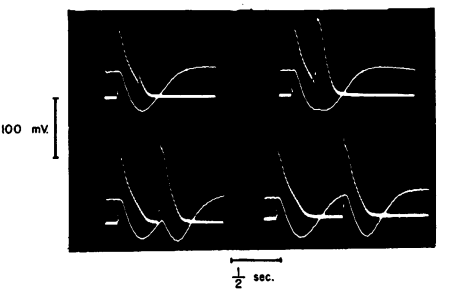

Fig. 6

Fig. 5. Superimposed records of: a premature beat following a driven one (*inner traces*); an electrotonically-induced contracture (*outer traces*). Transmembrane action potentials upward and isometric contractions downward. Action potential upstrokes and initial return from sustained depolarization are drawn as in dashed lines. Tension is of the order of 200 mg. Driven rate 24/min. Normal Tyrode medium.

Fig. 6. Four successive beats, each followed by a premature stimulus (in the order left to right, lower traces after upper traces). Transmembrane potentials and isometric tension as in Figure 5. Peak tension is about 600 mg. Driven rate 24/min. "Twelvefold calcium" Tyrode medium.

mechanical activity of a cat papillary muscle during a driven beat and a closely following extrasystole. The two outer traces show the phenomenon previously referred to: maintained contractile tension during a period of sustained membrane depolarization. It is clear that, during sustained depolarization, the muscle displays little or none of the weakness so evident in the early extrasystole, even at identical time intervals after the onset of contraction. The weakness of the premature beat is thus not a result of the depletion, during activity, of some required factor. It is a discrete negative inotropic event, a consequence of membrane repolarization or of the relaxation process itself.

In a medium sufficiently rich (11 mM.) in calcium ion and of reduced (112 mEq./l.) sodium content (which further promotes tissue calcium uptake during contraction—see Niedergerke[13]) the weakness of the premature beat, along with postextrasystolic potentiation and staircase, is completely abolished. The traces at the upper left in Figure 6 show a driven beat followed by a stimulus so premature as to evoke only a nonpropagated electrical response. When the second stimulus is delivered a bit later (upper right), the premature contraction is not at all reduced and fuses with the driven one. The lower traces show premature responses at progressively greater time intervals after the driven

beat. All contractile responses have magnitudes within 5 per cent of the mean. In addition, the traces at the lower left represent events immediately following those on the upper right (driven rate 24/min.) and there is no postextrasystolic potentiation following a beat of extreme prematurity. The contractile response in this medium also did not vary with rate of stimulation, being fixed at the level shown in Figure 2 at rates of 24/min., 60/min., and 360/min.

The action of the catecholamines appears also to fall into the category of inotropic effects mediated through a mechanism governing calcium availability for the contractile process. Epinephrine augments radiocalcium uptake, with contraction, by cardiac muscle.[3, 4] In addition, in the "calcium-rich" (6 mM. Ca, 75 mEq./l. Na) medium, the drug (1-2 γ/ml.) does not add further to tension development by the cat papillary muscle; the length-tension relationship, in contrast, is not abolished in this medium and, where epinephrine failed to increase contractile tension, an appropriate stretch (prior to stimulation) could be shown to double it.[14]

Thus two of the major influences on ventricular contraction—the rate-sequence and catecholamine actions—which can be supplied by the alternative means of raising the extracellular calcium level, are without effect (or almost so) on skeletal muscle, while sarcomere length, the only major influence on the contraction of skeletal muscle, affects ventricular contraction in a manner apparently independent of the extracellular calcium level. The interpretation of these facts that suggests itself is that calcium availability is not a limiting factor for skeletal muscle but represents an important means by which ventricular contraction is functionally modified. It is, perhaps, the site of action for a great variety of inotropic interventions.

Seen from this point of view, ventricular "contractility," however defined, would be expected to undergo moment-to-moment alterations due to changes in such factors as autonomic discharge (heart rate, rhythm, and mediator effects) and coronary flow (extracellular ion effects), which may be of considerable magnitude, even during the course of a single systole. Any maneuver that could elicit a maximal contribution from the excitation-contraction coupling process (i.e., "calcium availability") might provide a less precariously fluctuating assessment of ventricular muscle function. This has been achieved in the isolated tissue through the use of enormously calcium-rich media.

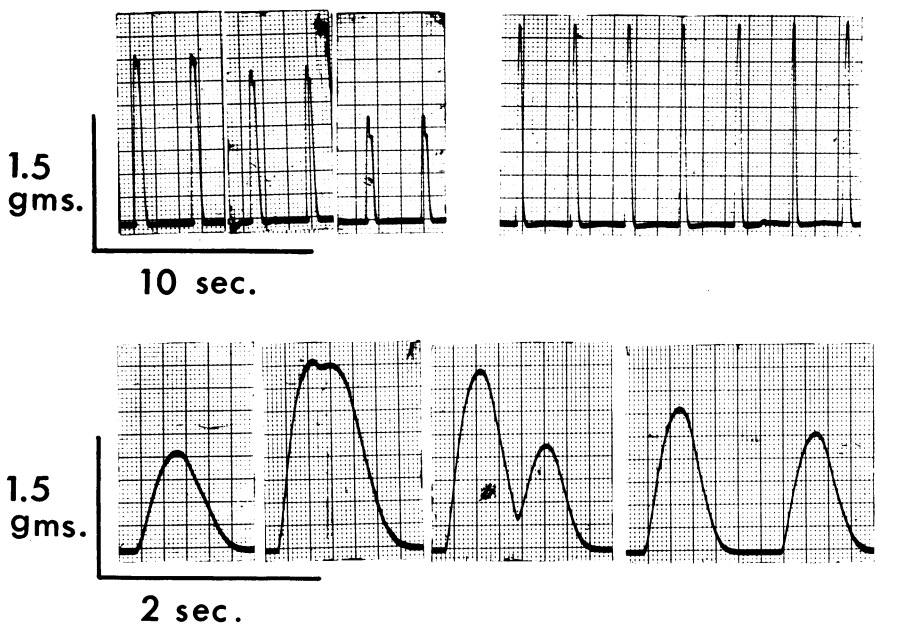

Fig. 7. Isometric tension recording from a cat papillary muscle preparation. Muscle diameter (unstretched) is 1.0 mm. Muscle lengths at which the upper left-hand tracings were obtained are: 1.5 mm. (*left third*); 1.3 mm. (*middle third*); 1.1 mm. (*right third*). Rate of stimulation is 24/min. (for paired pulses, 48/min.), temperature 32° C. See text for further description.

Since extracellular calcium levels of this magnitude can probably not be attained *in vivo*, it was of interest to see how the contraction potentiated by paired pulse stimulation might compare with that in the calcium-rich medium. Figure 7 summarizes results obtained from a cat papillary muscle preparation. The upper row of tracings are the isometric tensions elicited by: paired-pulse stimulation in normal (1.8 mM. Ca) Tyrode (left panel); regular stimulation in calcium-rich (8 mM. Ca, 75 mEq./l. Na) Tyrode (right panel). The upper left panel shows, in addition, the steady-state response at each of three muscle lengths. The greatest response (extreme left—optimal muscle length) amounts to 85 per cent of that achieved in the calcium-rich medium (optimal length), indicating that postextrasystolic potentiation might, indeed, be used to estimate maximal ventricular contractile activity. The lower panels in Figure 7 show, on an expanded time scale, the steady-state records (normal Tyrode) of the control contraction and of the potentiated responses at three drive-extra intervals. Incidentally demonstrated in

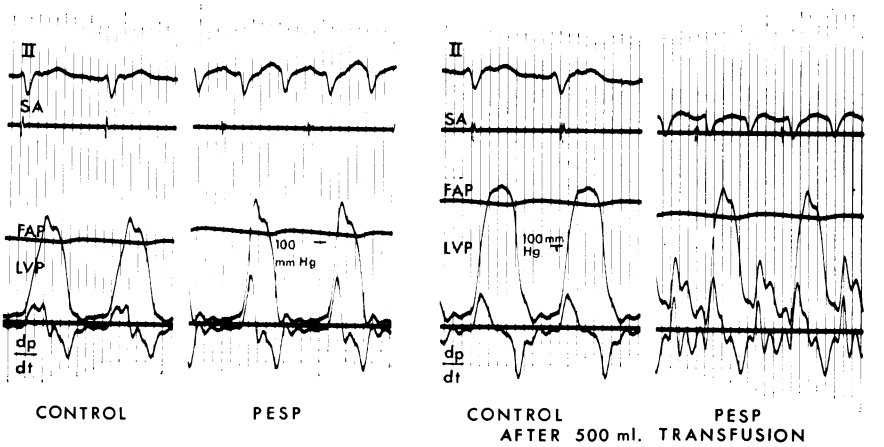

Fig. 8. Effects of paired pulse stimulation on the *in situ*, ejecting left ventricle of a dog. Tracings represent Lead II. electrocardiogram (II), the sinoatrial electrogram (SA), mean femoral artery pressure (FAP), left ventricular pressure (LVP), and the rate of change of left ventricular pressure (dp/dt). Periods of paired pulse stimulation are labeled PESP (postextrasystolic potentiation). All rates are driven from an electrode over the His bundle, although the rhythm is a ventricular one. Time lines indicate 0.04 sec. intervals.

these records is the fact that the degree of postextrasystolic potentiation has no necessary correlation with the weakness of the extrasystole; the greatest potentiation occurs when the peak tension during the extrasystole is almost fully as great as during the driven (identical, in this case, with the postextrasystolic) beat.

Paired pulse stimulation of the *in situ* dog heart (driving electrode over the His bundle) augments the pressure developed by the left ventricle, but rather unimpressively (Figure 8), the increase amounting to only 18 per cent in the control, no increase at all being produced by the paired pulses following a 500-ml. blood transfusion. The rate of rise of left ventricular pressure is about doubled in both cases, however, behaving as does isometric tension in the isolated papillary muscle. The isometric condition can be approximated for the *in situ* left ventricle by maintaining the ventricle at constant volume through an indwelling, fluid-filled balloon during total cardiopulmonary bypass. The pressure developed by this nonejecting left ventricle can now be doubled by the paired pulses, and this marked increase occurs at the three ventricular volumes employed: 15 ml., 25 ml., 35 ml. (Figure 9). The rate of rise of pressure is still more generously affected by the paired pulses, being tripled at all of the volumes.

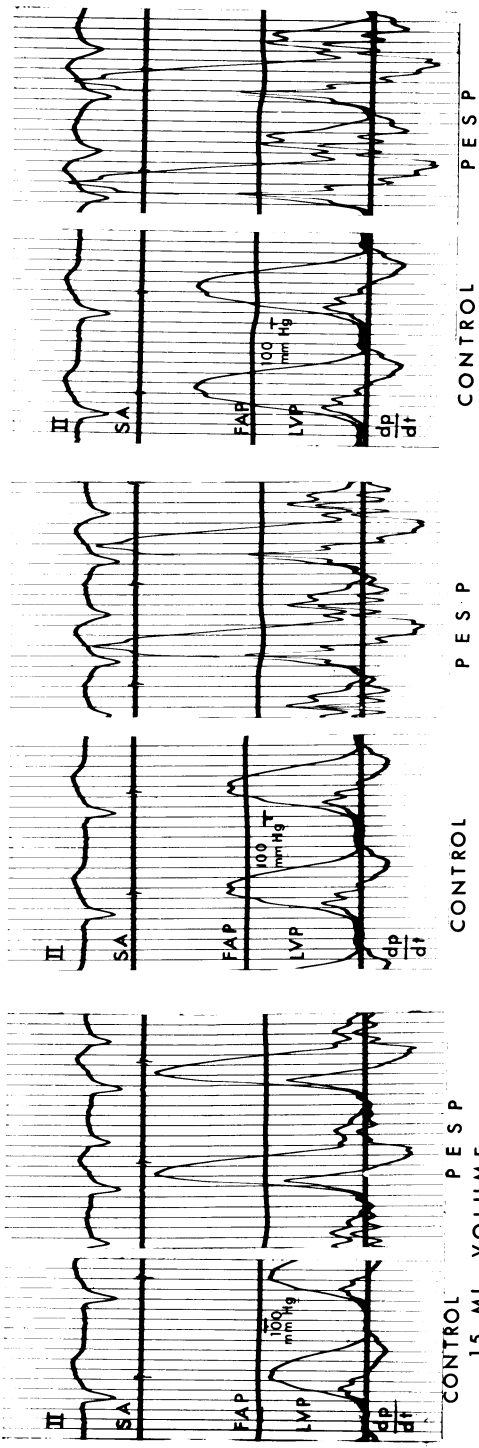

Fig. 9. Effects of paired pulse stimulation on the *in situ*, isovolumetric left ventricle. Symbols, method of driving, time calibration as in Figure 8.

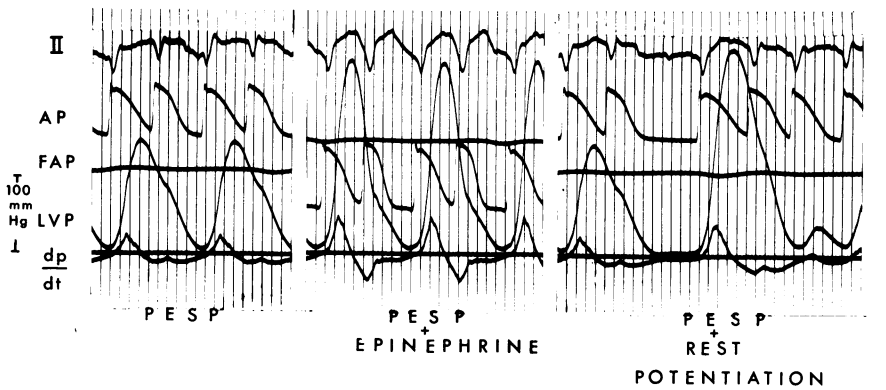

Fig. 10. Interaction of postextrasystolic potentiation, epinephrine inotropism, and rest potentiation in the *in situ*, isovolumetric left ventricle. See description in text. An additional recording in this illustration is that of the monophasic action potential (suction electrode) labeled AP.

An additional test of the maximal character of the paired-pulse response is shown in Figure 10. Records were again obtained from an isovolumetric left ventricle of a dog during cardiopulmonary bypass. It is apparent that the potentiated ventricular pressure shown in the left panel is not a maximal response, since an epinephrine infusion (middle panel)—that presumably shares the same inotropic mechanism—can bring about a considerable further increase. The reason for this is indicated in the right panel, where the beat following a spontaneously occurring pause (failure of one driving pulse to evoke a propagated response) is shown to be of about the same magnitude (very slightly greater) as that due to the combination of postextrasystolic potentiation and catecholamine infusion (middle panel). The rapid rate involved here interferes with contractility through a mechanism apparently related to that which causes a premature beat to be weak. If sufficient time is allowed for "recovery" of contractility, postextrasystolic potentiation—by itself—can evoke a maximal or near-maximal response from the ventricular musculature. In most of the results shown here, the rate of rise of ventricular pressure roughly correlates with peak pressure in the isovolumetric preparation. For the potentiated beat shown in the right panel of Figure 10, however, the recorded dp/dt is less (five sixths) than that in the middle panel, although the isovolumetric pressure peak is slightly higher. Whether the rate of rise of ventricular pressure will be the best means of measuring the potentiated contractile response of the ejecting ventricle remains to be evaluated.

SUMMARY

Since the ventricle is continuously exposed to a variety of influences that can profoundly alter the contractile event, measurements of "contractility" should be subject to a wide and capricious variability. A large number of these inotropic effects are shown to be mediated by a common mechanism (calcium availability for contraction), and means were sought to evoke a maximal response from this mechanism. Paired pulse stimulation appears to accomplish this and may therefore be useful in the assessment of ventricular muscle function in the intact heart.

REFERENCES

1. Winegrad, S. and Shanes, A. M. Calcium flux and contractility in guinea pig atria, *J. Gen. Physiol. 45*:371-394, 1962.
2. Kavaler, F. Uniformity of the contractile response of ventricular muscle in high-calcium Tyrode's solution, *Nature 196*:1104-1106, 1962.
3. Grossman, A. and Furchgott, R. F. The effects of various drugs on calcium exchange in the isolated guinea pig left auricle, *J. Pharmacol. Exptl. Therap. 145*:162-172, 1964.
4. Reuter, H. Über den Ca-Umsatz des Meerschweinchenvorhofs unter der Einwirkung von Adrenalin, *Naunyn Schmiedeberg Arch. Exp. Path. 247*:330, 1964.
5. Ritchie, J. M. and Wilkie, D. R. The effect of previous stimulation on the active state of muscle, *J. Physiol. 130*: 488-496, 1955.
6. Goffart, M. and Ritchie, J. M. The effect of adrenaline on the contraction of mammalian skeletal muscle, *J. Physiol. 116*:357-371, 1952.
7. Hill, A. V. and Macpherson, L. The effect of nitrate, iodide and bromide on the duration of the active state in skeletal muscle, *Proc. Roy. Soc. B 143*:81-102, 1954.
8. Trautwein, W. and Dudel, J. Aktionspotential und Mechanogramm des Warmblüterherzmuskels als Funktion der Schlagfrequenz, *Pflüger Arch. Ges. Physiol. 260*:24-39, 1954.
9. Weidmann, S. Effect of increasing the calcium concentration during a single heartbeat. *Experientia 15*:128, 1959.
10. Kavaler, F. Membrane depolarization as a cause of tension development in mammalian ventricular muscle, *Amer. J. Physiol. 197*:968-970, 1959.
11. Schütz, E. Elektrophysiologie des Herzens bei einphasischer Ableitung, *Ergebn. Physiol. 38*:493-620, 1936.
12. Braveny, P. and Kruta, V. Dissociation de deux facteurs: Resitution et potentiation dans l'action de l'intervalle sur l'amplitude de la contraction du myocarde, *Arch. Int. Physiol. 66*:633-652, 1958.
13. Niedergerke, R. Movement of Ca in beating ventricles of the frog heart, *J. Physiol. 167*:551-580, 1963.
14. Kavaler, F. and Morad, M. Paradoxical effects of epinephrine on excitation-contraction coupling in cardiac muscle. *Circ. Res.* In press.