SOME METABOLIC ASPECTS OF PAIRED PACING OF THE HEART*

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IN VIEW of recent evidence that paired pacing is associated with an increase in contractility, an increase in oxygen consumption, and a net potassium loss from the heart,[1-7] it was of interest to compare these changes quantitatively with similar changes known to occur with increasing heart rates. To achieve this, oxygen consumption, potassium fluxes, and strain-arch tension were determined during various stimulation patterns in an isolated, perfused cat-heart preparation designed to minimize the energy requirements due to external work performed by the preparation.

METHODS

Cats weighing from 1.5 to 4 kg. were anesthetized with sodium pentobarbital (30 mg./kg.) and the heart and great vessels surgically prepared for transfer to the perfusion system shown in Figure 1. A modified Krebs-Ringer solution (Na^+ 152 mEq./l.; K^+ 4.0 mEq/l.; Ca^{++} 5.0 mEq./l.; Mg^{++} 1.2 mEq./l.; Cl^- 135 mEq./l.;HCO_3^- 25 mEq./l.; HPO_4^- 1.26 mM.; SO_4^- 1.2 mEq./l.; glucose 5.6 mM./1.; total solution was saturated with CO_2) is pumped from a fluid storage bottle to an oxygenating bottle and then passes through a bubble trap before being transferred by gravity to a heat exchanger unit. From the heat exchanger the fluid is pumped by a Harvard constant flow pump into the aorta through a glass tube from which the entire heart is suspended. A metering valve can be opened to bypass the pump for experiments not designed for constant coronary flow. Coronary outflow is collected from the right ventricle (RV) through a catheter inserted via the pulmonary artery. This cannula is adjusted to have a siphon effect that keeps the right ventricle essentially empty and at a pressure of ± 1 cm. H_2O. The left ventricle is drained at the apex through a short, light-

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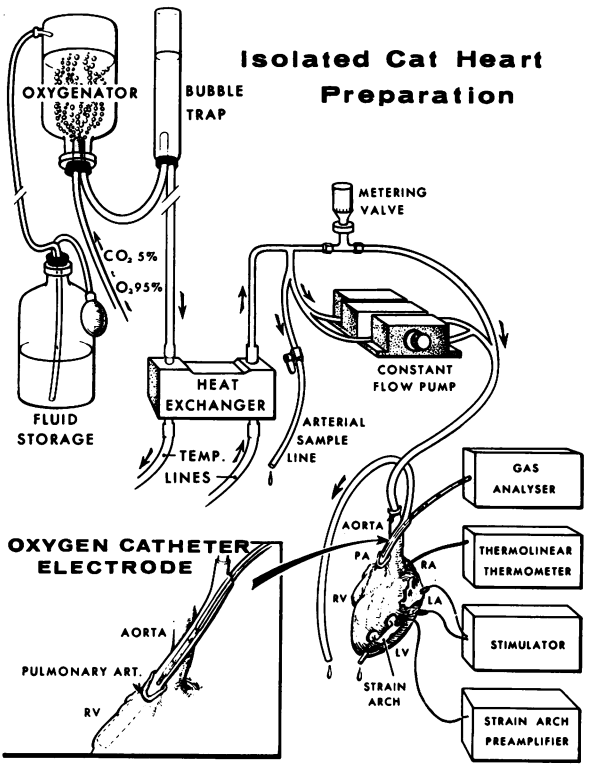

Fig. 1. Diagrammatic sketch of the isolated cat-heart preparation. See text under methods for details.

weight cannula that keeps the ventricle empty and insures aortic valve closure.

Coronary venous PO_2 is measured by an oxygen electrode catheter* that is placed entirely within the coronary outflow catheter in the RV. During a series of 10 initial experiments the arterial PO_2 (PaO_2) was monitored throughout the experiment, but since after a 30-min. equilibration period PaO_2 varied only with equilibration temperature (Te) and barometric pressure, and was identical to the value calculated directly by the formula:

$$PaO_2 = \frac{(\text{baro press}-\text{vapor press } H_2O \text{ at Te})\ (\%\ O_2 \text{ in oxygenating gas})}{(\text{baro press}-\text{vapor press } H_2O \text{ at Te})}$$

further monitoring has not been considered essential. All oxygen consumption (MVO_2) values are based on the dry weight of the total myocardium, which in this preparation has been found to be 25 per cent

*Developed by Beckman Instrument Company, Spinco Division, Palo Alto, Calif., for cardiac catheterization.

of the wet weight.

All experiments were done at temperatures between 28° and 31° C. Myocardial temperature was measured by a linear temperature recording system† from a metal-cased, fast-rise time probe, inserted through the right atrium and placed against the interventricular septum in the right ventricle. The heat exchanger and temperature recording system maintained the myocardial temperature ±0.2° C. during the experimental procedures.

A Walton-Brodie cat strain gauge arch,[8] attached to the left ventricle, was used to record the time duration and configuration of contractions, and also to provide an index of the contractile effort expended by the heart. Placement of the arch on the left ventricle involves only a small segment of the myocardium and did not increase MVO_2 more than 5 per cent in any experiment. The arch is measuring the isometric tension developed by only a small fraction of the total number of myocardial fibers, so that the largest fraction of the fibers are contracting only against gravitational influences and the resistances that are intrinsic to the myocardium during undamped shortening. Since both of these fractions are contracting against resistances that are unlikely to change as the stimulation patterns are altered, the effort expended by the two fractions may be expected to have a positive correlation. This correlation may actually be increased if one applies the findings from papillary muscles, that for a given state of contractility the tension developed by isometrically contracting muscles and the tension developed up to the initiation of shortening in isotonically contracting muscles have the some rate of tension development (dp/dt.).[9] Assuming the same relationship obtains in this preparation, the velocity components of contractile element effort are then similar for the two fractions. Therefore the first derivative of the strain arch tension (dSAT/dt) applies to the remaining fibers that are contracting isotonically.

The dSAT/dt was taken from the amplified strain-arch output through an RC differentiator circuit with a 0.0016 sec. time constant. The area under the strain-arch curve (the integral $\int SATdt$) was computed on a beat-to-beat basis from the same strain-arch output by an analog computer. Although it has been demonstrated that the area under the developed tension curve up to the peak tension is probably the best correlate with the observed MVO_2 in isometric preparations,[10, 11] there

†Yellow Springs Instrument Co., Yellow Springs, Ohio.

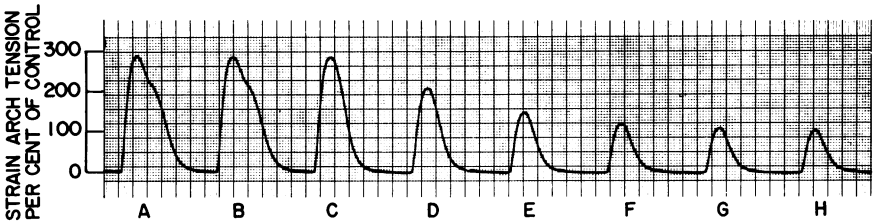

Fig. 2. Strain-arch tension curves recorded as the heart was changed from paired to single pacing. Single pacing begins with contraction *C*. Paper speed 25 mm./sec.

are obvious difficulties in separating out these areas from traces obtained during paired pacing. Therefore Figure 6 contains $\int SATdt$ instantaneously recorded over the entire cycle length. Permanent records were made on a Sanborn direct-writing oscillograph.

To insure complete control of heart rate at slow stimulus rates, the A-V node and a portion of the His bundle were crushed with a hemostat, and pacing electrodes were sewn to the left ventricle and left atrium. Stimuli were delivered at a pulse duration of 2 msec. and at 10 ma. from a paired pacing stimulator developed by one of us (PBM). Stimulus intervals were monitored on a calibrated type 502 Tektronix oscilloscope.

Samples for potassium analysis were taken from the arterial sampling and coronary outflow lines and analyzed on a Technicon Autoanalyzer. Net potassium fluxes were calculated in the following manner: for each 30-sec. sampling interval during the experiment the difference between coronary venous potassium concentration and the control venous potassium concentration was determined, and multiplied by the coronary flow in liters for the same interval. The results taken from all the sampling periods during which a flux occurred were added together to obtain the total net potassium flux.

Results

Altered contractility. Evidence that an increased contractility due to paired pacing (P-P) occurs in this preparation is given in Figure 2. Left ventricular strain-arch tension is shown as the stimulation pattern was changed from paired pacing (A and B) to single pacing (C to H). The persistence of the increased tension developed during paired pacing, that is seen after the change to single pacing, supports the position that paired pacing has increased the contractility of the myocardium.

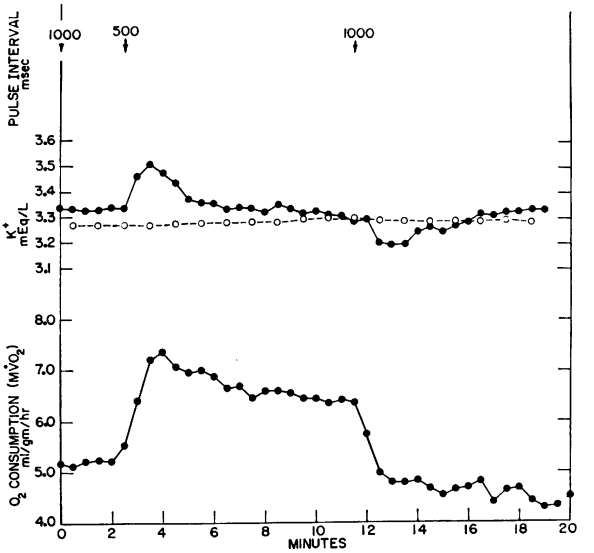

Fig. 3. Graphs of venous *(closed circles)* and arterial *(open circles)* potassium concentrations and MVO_2 as the heart rate was changed from 60 to 120 beats per minute and back to 60. K+ efflux = 5.4 μEq.

Myocardial K+ balance and O_2 consumption. Decreasing the stimulus interval by 50 per cent (doubling the rate) in this preparation increases O_2 consumption and causes a net loss of K^+ from the heart (Figure 3). The reverse occurs when the stimulus interval is returned to its control value. The intitial stimulus interval was 1000 msec. (rate = 60) and was changed to 500 msec. (rate = 120) as marked. Since coronary flow was constant throughout the experiment the coronary venous K^+ concentration reflects a net K^+ loss from the heart. MVO_2 increased almost 2.0 ml./g./hr.* When the stimulus interval was returned to 1000 msec. (rate = 60) there was a net K^+ uptake and the O_2 consumption fell to slightly below control levels.

Figure 4 shows the influence of paired pacing (P-P) in the same heart. A stimulus interval of 1000 msec. was again used, but paired pacing, with a 350-msec. P-P interval, was instituted instead of doubling the rate. During paired pacing the heart again lost K^+ while MVO_2 rose a little more than 2 ml./g./hr. The reverse occurred when the 1000 msec. pulse interval was resumed. The amount of K^+ lost with doubling the rate (Figure 3) was 5.4 μEq. while 5.6 μEq. of K^+ were lost with paired pacing (Figure 4).

*To convert these MVO_2 figures to ml./min./100 g. dry weight, multiply by 1.67.

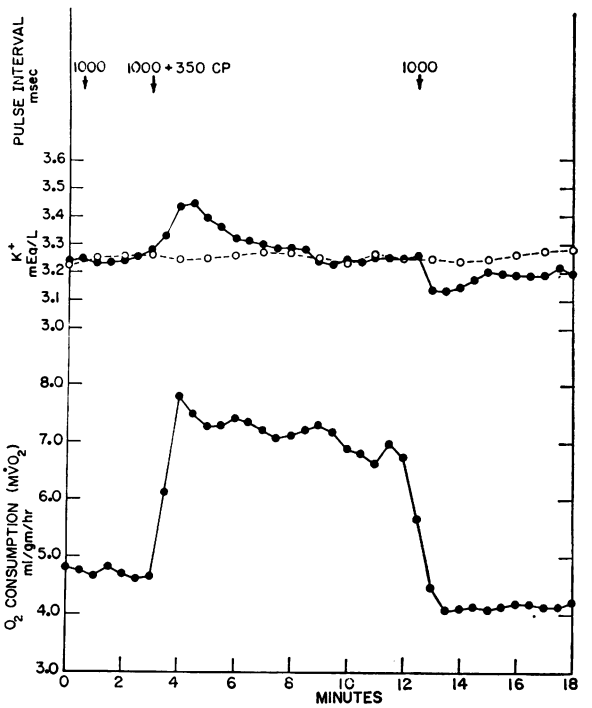

Fig. 4. Same heart as Figure 3. Graphs of venous (*closed circles*) and arterial (*open circles*) potassium concentrations and MVO_2 as heart rate was changed from 60 stimuli/minute to paired pacing at 60 pairs of stimuli/minute, and back again. K+ efflux = 5.6 μEq.

Since it appeared that paired pacing increased MVO_2 more than did doubling the rate, further experiments were done. In Figure 5 a single pace interval of 1040 msec. was suddenly changed to paired pacing with a 340-msec. P-P interval. Coronary flow was maintained constant ±2 per cent. MVO_2 rose from 4.5 to 6.7 ml./g./hr. The stimulus interval was then changed to 520 msec., a double-rate pattern. MVO_2 decreased and stabilized at 6.4 ml./g./hr. After returning to paired pacing, the MVO_2 increased to the previous value of 6.7 ml./g./hr. When single pacing at 1040 msec. intervals was reinstituted, the MVO_2 fell below and then returned to the control level of 4.5 ml./g./hr. Thus it appears that in an empty contracting heart, although the same number of depolarizations are involved, paired pacing results in a greater O_2 consumption than doubling the rate.

To define further the difference in O_2 consumption between double-rate and paired pacing, 14 experiments of the type shown in Figure 6

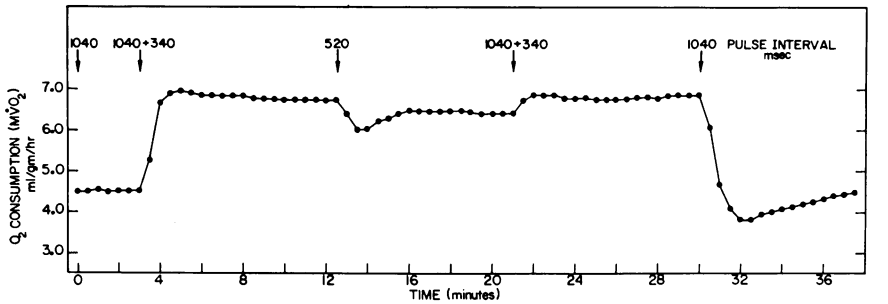

Fig. 5. Graph of MVO_2 as the stimulation patterns were changed in the following sequence: single pacing at 60 stimuli/minute; paired pacing at 60 pairs of stimuli/minute; double-rate pacing at 120 evenly spaced stimuli/minute; paired pacing at 60 pairs of stimuli/minute; single pacing at 60 stimuli/minute. Note the difference in MVO_2 between paired and double-rate pacing.

were performed in six hearts. Using a basic stimulus interval of 1600 msec. the P-P interval was set at 800 msec., producing a double-rate stimulation pattern (panel A). The P-P interval was then shortened by steps of 100 msec. to a narrowest interval of 305 msec. The basic and P-P intervals are shown at the top of each panel, and the O_2 consumption at the bottom. Two of the six hearts showed the amplitude shift phenomenon seen in panels E and F where the strain arch tension of the second contraction has reached a greater amplitude than the first. The other four hearts did not show this shift. The total area under the strain arch trace ($\int SAT/dt$) changed very little as the P-P interval was narrowed. MVO_2 increased progressively to the 400-msec. P-P interval, then reversed. This MVO_2 reversal at P-P intervals below 400 msec. occurred in five of the six hearts studied. No reversal was observed in the other heart.

Maximum positive dSAT/dt for the first contractions increased slightly but progressively without reversal as the P-P interval was narrowed. Maximum positive dSAT/dt for the second contractions are not comparable as only a small portion of the curve is available for analysis. However, it is of interest to note that analysis of the tracings shows that the stimulus-to-peak-tension time (T_{sp}) of the two contractions is very nearly the same until the P-P interval is 400 msec. or less. At these short intervals the stimulus-to-peak-tension time of the second contraction becomes shorter than the T_{sp} of the first contraction by up to 30 per cent.

Maximum negative dSAT/dt for the decay of the second contraction shows only minor variations as the P-P interval is changed.

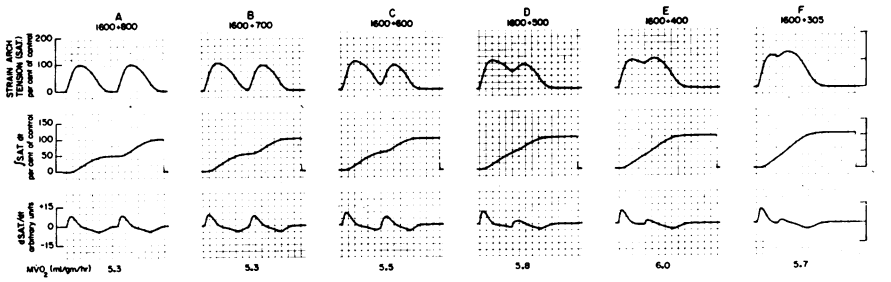

Fig. 6. Instantaneous tracings of strain-arch tension (SAT), ∫SATdt (instantaneous summing of area under SAT curve) and dSAT/dt (the rate of change of SAT with time) as double-rate pacing *(frame A)* is changed to paired pacing *(frame F)* in a series of steps. Basic stimulus interval plus paired pace interval above each frame, the steady-state MVO_2 below each frame. Note the consistency of ∫SATdt, the uniform increase in the maximum dSAT/dt of each first contraction, and the variation of MVO_2 with P-P interval. The MVO_2 for *frame F* is discussed in the text. Paper speed: 50 mm./sec.

Discussion

There are three components of total O_2 consumption in an experimentally controlled heart preparation: the basal or resting MVO_2, the control state MVO_2, and the variable MVO_2 imposed by altered activity during the experiment. The average resting MVO_2 in this preparation is approximately 2.2 ml./g./hr. As may be seen in Figures 3, 4, and 5, at rates of near 60/min. the control state MVO_2 adds 2 to 3 ml./g./hr. to the resting MVO_2. Doubling the control rate adds another 2 to 3 ml./g./hr., as shown in Figure 3. Of significance is the fact that paired pacing (see Figure 4) also adds approximately 2 to 3 ml./g./hr. to the control plus resting MVO_2, demonstrating that in terms of O_2 utilization during similar afterload conditions the two activity states are very similar.

It has been demonstrated in the intact pumping heart that changes in contractility are often accompanied by a net efflux of potassium[12, 13] and this has recently been shown to be true of paired pacing.[14] In this study a net K^+ loss was observed during both double-rate and paired pacing in the same heart. The quantity and time duration of the loss during each intervention were remarkably similar. That Ca^{++} plays a significant role in altered contractility states and myocardial metabolism is well known,[15] but this ion has not as yet been studied in this preparation.

The strain arch curves seen in Figure 6 reflect the contractile effort of the entire heart (see *Methods* section); ∫SATdt is an instantaneous

summing of the area under each curve and represents an index of the total contractile effort during contraction. This study demonstrates that as double-rate pacing is converted to paired pacing ∫SATdt changes very little.

In the six hearts studied the greatest change in ∫SATdt with paired pacing was +30 per cent and the least was −5 per cent as compared to the doubled rate control. Once again the similarity of increased stimulation rate and paired pacing is apparent.

Though double-rate and paired pacing have been shown to be similar they are not the same and, as Figures 5 and 6 demonstrate, there is a small but definite difference in the total MVO_2 between the two interventions in the same heart. The source of this difference is not readily apparent; ∫SATdt does not account for it, as the total area under the tension curves stays essentially constant as the P-P interval is narrowed. The increase in the velocity components of the contractile element effort as shown by an increase in dSAT/dt are directionally similar and may account for the O_2 changes seen in panels A through E but this explanation cannot by itself account for the reversal of MVO_2 seen in panel F, because MVO_2 decreased despite an increase in maximum dSAT/dt of the first contraction and a 20 to 30 per cent shortening of the stimulus-to-peak-tension time (T_{sp}) of the second contraction. This marked shortening of T_{sp} time at narrow P-P intervals was a consistent finding in all experiments.

In heart muscle T_{sp} time is dependent on latency, the stress-strain characteristics of the series elastic component (SE), and the duration and intensity of the active state of the contractile elements.[16] Latency may be decreased by increasing heart rate[17] but no such effect is seen in the first contraction T_{sp} nor in the second contraction up to the 400-msec. P-P interval. Even if the series elastic component (SE) at the short P-P intervals remained stretched by the first contraction until maintained on stretch by the second contraction (thereby diminishing the normal delay time[16] required to stretch the series elastic component after the active state is established), a decrease in the duration of the active state would be necessary to account for the decreased T_{sp} time.

The duration of the action potential of an extrasystole becomes shorter as the interval becomes smaller.[18] In addition, a relationship between the duration of the action potential during mass stimulation and the duration of an isometric contraction has been established.[19]

Recent work has suggested a similar relationship between the duration of the action potential and the duration of the active state in skeletal muscle.[20] From these results it would appear that a change in the active state may indeed occur during the second contraction of paired pacing at short intervals. Whether such a change could account for the MVO_2 reversal has not been adequately studied.

Recent work concerning the major determinants of MVO_2 in the heart has stressed the influence of the myocardial tension developed, the period over which it is developed, and how often it is developed per unit time.[10, 11, 21-26] Reports of the oxygen consumption changes during paired pacing in the pumping heart have shown a wide variation,[3, 7] which may be due to variations in the afterload of the second contraction. In a fluid pumping heart during constant cardiac output and heart rate, the principal component of the afterload is aortic pressure. If kept constant, aortic pressure presents the same afterload to all contractions during single or double-rate stimulation patterns. However, in the case of paired pacing this is unlikely to be true, since after the first contraction has ejected the stroke volume and the valve closes, the afterload of the preparation has then become intraventricular pressure. Thus during at least a portion of the second contraction (which does occur in the pumping normothermic isolated heart[14]) the myocardium is working against a reduced afterload, and MVO_2 becomes more difficult to predict and to relate to load. In these experiments in which the heart is beating, though empty, the afterload is the sum of its own weight and the resistances intrinsic to the myocardium during undamped shortening. Therefore one does not expect this afterload to vary regardless of the stimulation pattern applied.

A finding of additional interest during these studies was the influence of lowered temperature on the relative lengths of the myocardial refractory period and mechanical contraction. Working at 28° to 31° C. in this preparation we have never observed a myocardial depolarization without a subsequent mechanical beat. The falling slope of the strain arch tracings always showed a second contraction following a second depolarization. Loss of the response to the second stimulus during paired pacing occurred before the second contraction "disappeared" into the first contraction. This implies that, although the duration of mechanical contraction is more prolonged than the action potential by a decrease in temperature[27] and one expects the second mechanical event

to be obscured by the first, the refractory period is even more prolonged than the mechanical contraction, as has been previously suggested.[28,29]

SUMMARY

The influences of paired pacing and of doubling the heart rate have been studied and compared in an empty, beating, isolated cat-heart preparation. Analysis of the oxygen consumption, potassium flux, and the myocardial contractile effort during these two stimulation patterns has revealed that except for a slightly greater oxygen consumption during paired pacing, the two patterns have very similar influences on the heart. This may indicate a similar mechanism of action for these two inotropic interventions.

It has also been shown that there is a decrease in the stimulus-to-peak tension time (T_{sp}) in the second contraction during paired pacing at short paired pacing stimulus intervals. This shortening of the second contraction T_{sp} is not seen at longer P-P intervals during double-rate pacing or at any time in the first of the paired contractions. There is evidence to suggest this shortening is due to a decreased duration of the active state of the contractile elements.

REFERENCES

1. Chardack, W. M., Gage, H. A. and Dean, D. C. Slowing of the heart by paired pulse pacemaking, *Amer. J. Cardiol. 14*:374-384, 1964.
2. Braunwald, N. S., Gay, W. A. Jr., Morrow, A. G. and Braunwald, E. Sustained, paired electrical stimuli, *Amer. J. Cardiol. 14*:385-393, 1964.
3. Sonnenblick, E. H., Kaiser, G. A., Frommer, P. L. and Braunwald, E. Augmentation of ventricular performance and oxygen consumption by repetitive application of paired electrical stimuli, *Physiologist 7*:239, 1964 (*abst.*).
4. Penna, M. and Garb, S. Relationship of changes in ionic concentrations to the augmentation produced by extra contractions in isolated mammalian ventricular muscle, *Amer. J. Physiol. 184*: 572-574, 1956.
5. Hoffman, B. F., Bindler, E. and Suckling, E. E. Postextrasystolic potentiation of contraction in cardiac muscle, *Amer. J. Physiol. 185*:95-102, 1956.
6. Lopez, J. R., Edelist, A. and Katz, L. N. Slowing of the heart rate by artificial electrical stimulation with pulses of long duration in the dog, *Circulation 28*:759, 1963 (*abst.*).
7. Sarnoff, S. J., Gilmore, J. P., Daggett, W. M., Mansfield, P. B., Weisfeldt, M. L. and McDonald, R. H. Jr. Effect of coupled pacing (continuing postextrasystolic potentiation) on the hemodynamics O_2 consumption and K+ balance of the heart, *Amer. J. Cardiol. 15*:143, 1965 (*abst.*).
8. Boniface, K. J., Brodie, D. J. and Walton, R. P. Resistance strain gauge arches for direct measurement of heart contractile force in animals, *Proc. Soc. Exp. Biol. Med. 84*:263-266, 1953.
9. Siegel, J. H., Sonnenblick, E. H., Judge, R. D. and Wilson, W. S. The

quantification of myocardial contractility in dog and man, *Cardiologia 45:* 189-221, 1964.

10. Monroe, R. G. Myocardial oxygen consumption during ventricular contraction and relaxation, *Circ. Res. 14:*294-300, 1964.
11. McDonald, R. H. Jr. Developed tension: a major determinant of myocardial oxygen consumption. Presented at the *14th Annual Meeting, American College of Cardiology,* 1965.
12. Sarnoff, S. J., Gilmore, J. P., Mitchell, J. H. and Remensnyder, J. P. Potassium changes in the heart during homeometric autoregulation and acetyl strophanthidin, *Amer. J. Med. 34:*440-451, 1963.
13. Sarnoff, S. J., Gilmore, J. P. and Wallace, A. G. The influence of autonomic nerve activity on adaptive mechanisms in the heart. In: *Nervous Control of the Heart.* W. C. Randall, ed., Baltimore, Williams and Wilkins, 1965, pp. 54-129.
14. Sarnoff, S. J., Gilmore, J. P., Daggett, W. M., Mansfield, P. B., Weisfeldt, M. L. and McDonald, R. H. Jr. The influence of continuous postextrasystolic potentiation on myocardial contractility, oxygen consumption and potassium balance. In preparation.
15. Mommaerts, F. H. M. Energy utilization by cardiac muscle. *Second Natl. Conf. on Cardiovascular Diseases 1:*37-48, 1964. Preprint Report.
16. Sonnenblick, E. H. Implications of muscle mechanics in the heart, *Fed. Proc. 21:*975-990, 1962.
17. Sonnenblick, E. H. Force-velocity relations in mammalian heart muscle, *Amer. J. Physiol. 202:*931-939, 1962.
18. Hoffman, B. F. and Cranefield, P. F. *Electrophysiology of the Heart.* New York, McGraw-Hill, 1960, p. 53.
19. Kavaler, F. Membrane depolarization as a cause of tension development in mammalian ventricular muscle, *Amer. J. Physiol. 197:*968-970, 1959.
20. Brady, A. J. Reference to paper in press given by author at *Second Natl. Conf. on Cardiovascular Diseases,* 1964.
21. Sarnoff, S. J., Braunwald, E., Welch, G. H. Jr., Case, R. B., Stainsby, W. N. and Macruz, R. Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension time index, *Amer. J. Physiol. 192:* 148-156, 1958.
22. Monroe, R. G. and French, G. N. Left ventricular pressure — volume relationships and myocardial oxygen consumption in the isolated heart, *Circ. Res. 9:* 362-374, 1961.
23. Rodbard, S., Williams, F. and Williams, C. Spherical dynamics of the heart, *Amer. Heart J. 57:*348-360, 1959.
24. Neill, W. A., Levine, H. J., Wagman, R. J. and Gordin, R. Left ventricular oxygen utilization in intact dogs: effects of systemic hemodynamic factors, *Circ. Res. 12:*163-169, 1963.
25. Levine, H. J. and Wagman, R. J. Energetics of the human heart, *Amer. J. Cardiol. 9:*372-383, 1962.
26. Britman, N. A. and Levine, H. J. Contractile element work: a major determinant of myocardial oxygen consumption, *J. Clin. Invest. 43:*1397-1408, 1964.
27. Trautwein, W. und Dudel, J. Aktionspotential und Mechanogramm des Katzenpapillarmuskels als Funktion der Temperatur, *Pflüger Arch. Ges. Physiol. 260:*104-115, 1954.
28. Schütz, E. Elektrophysiologie des Herzens bei einphasischer Ableitung, *Ergebn. Physiol. 38:*493-620, 1936.
29. Brooks, C. McC., Hoffman, B. F., Suckling, E. E. and Orias, O. *Excitability of the Heart.* New York, Grune and Stratton, 1955, p. 182.