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PHYSIOLOGICAL AND CLINICAL ASPECTS OF PAIRED STIMULATION*

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PHYSIOLOGICAL ASPECTS

ANALYSIS *of the augmenting effect of paired stimulation.* Paired stimulation has an augmenting effect on a number of circulatory characteristics in man and animal.[1-3] This is demonstrated in Figure 1 showing aortic pressure (AP), left intraventricular pressure (LIVP), and aortic flow (AF), during single and paired stimulation in an anesthetized open-chest dog after i.v. injection of 5 mg. propranolol.[4] The mechanical frequency was the same during single and paired stimulation. The increase in cardiac performance is caused by interval dependent changes in contractile force.

For the analysis of these interval dependent contractility-changes we used the isolated rat heart perfused according to the method of Langendorff.[5, 6] Vertical movement of the apex of the heart was recorded isotonically. All experiments were performed at 37° C. Changes in rhythm and frequency were induced via ring-shaped platinum electrodes (0.5 mm.) stitched on the area trabecularis of the right

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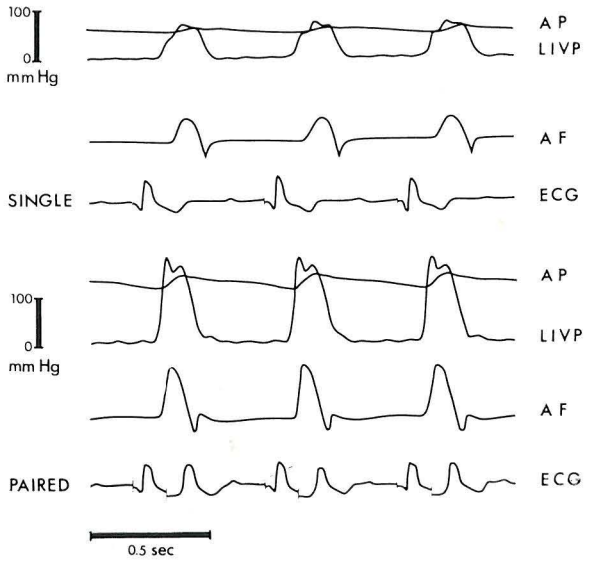

Fig. 1. Aortic pressure (AP), left intraventricular pressure (LIVP) and aortic flow (AF) during paired and single stimulation in the open-chest dog.

ventricle[7] by a stimulator specially designed for these types of experiments.[8] Contractility is defined as contraction amplitude in millimeters and/or contraction area obtained planimetrically in arbitrary units. Contraction area was used since paired stimulation not only increases the height but also the duration of the contraction. Figure 2 illustrates the augmenting effect of paired and tripled stimulation on the isotonically recorded contractions of the isolated perfused rat heart. The mechanical frequency in the upper, middle, and lower row is the same.

The analysis of the augmenting effect of paired stimulation as presented at the Conference on Paired Pulse Stimulation and Postextrasystolic Potentiation in the Heart held in New York on January 13, has been submitted for publication in the American Journal of Physiology.[9] In this paper we therefore limit ourselves to the relevant conclusions of these experiments.

The augmenting effect of paired stimulation is caused by both "*potentiation*" of contractility and by fusion of two contractions. The potentiation during paired stimulation is caused by the fact that the restitution curve[10] of the myocardial tissue is much steeper than that associated with the effective mechanical frequency. This increase in

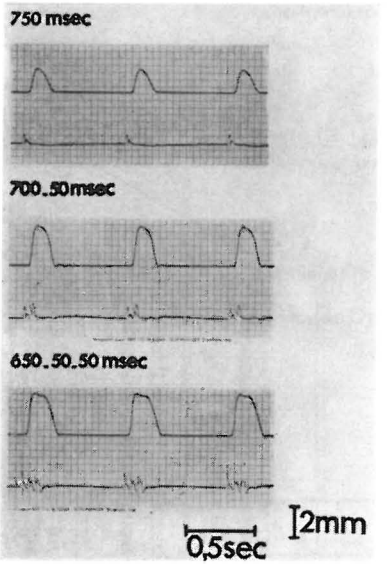

Fig. 2. Effect of paired *(second row)* and tripled *(third row)* stimulation on the isotonic contractions of an isolated perfused rat heart. Tripled stimulation hardly increases contraction height in comparison with paired stimulation. Only the duration of the contraction increased.

speed of the restitution is due to: 1) the electrical frequency—the trigger of the restitution—being twice the mechanical frequency; and 2) close spacing of two electrical impulses followed by a long pause.

Substantial evidence that potentiation is an intrinsic cellular mechanism is shown by observations made in our laboratory, where it was found that postextrasystolic potentiation is present in the spontaneously beating myocardial cell tissue culture consisting of six cells. These observations will be published separately.[11]

The O_2-consumption during single, paired, and tripled stimulation in the isolated perfused rat heart. The eventual usefulness of paired stimulation in the treatment of cardiac emergencies depends among other things on the O_2 demand and therefore on the amount of blood that can pass the coronary arteries during a certain time. Using the isolated heart perfused according to the method of Langendorff the total coronary flow per time unit can be measured accurately. Not only is the amount of fluid leaving the coronary sinus measured in this way but so is the fluid passing the myocardial tissue via the Thebesian shunts.

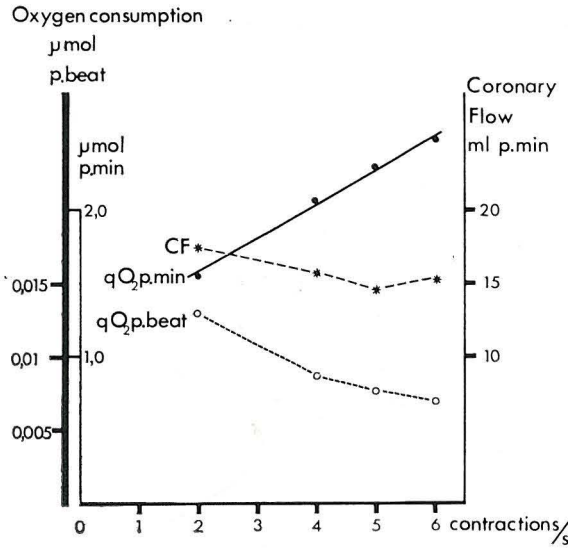

Fig. 3. Oxygen consumption and coronary flow of the isolated perfused rat heart at different stimulation rates.

The heart was placed in a closed chamber completely filled with perfusion fluid to prevent contamination with oxygen from outside. Polarographic oxygen electrodes were fixed in the perfusion setup near to and far from the heart. The coronary flow was measured by weighing the fluid leaving the heart during one minute. In previous experiments it was proved that during this type of perfusion and with the perfusion pressure used the aortic valves remain competent. The coronary perfusion pressure was kept constant. The perfusion fluid used has been described previously.[6] The oxygen consumption (μmole O_2/min.) was calculated by multiplying the oxygen extraction (in μmole O_2/ml. perfusion fluid) with coronary flow (ml./min.).

In Figure 3 the oxygen consumption of an isolated perfused heart performing no measurable external work during single stimulation is demonstrated per beat and per minute. It can be seen that the oxygen consumption per minute is closely related to the steady state frequency with which the heart is beating. At the same time it is indicated that although contractility per beat increases with increase in frequency the oxygen consumption diminishes slightly. If the oxygen consumption per beat at different frequencies is compared with the area per beat at

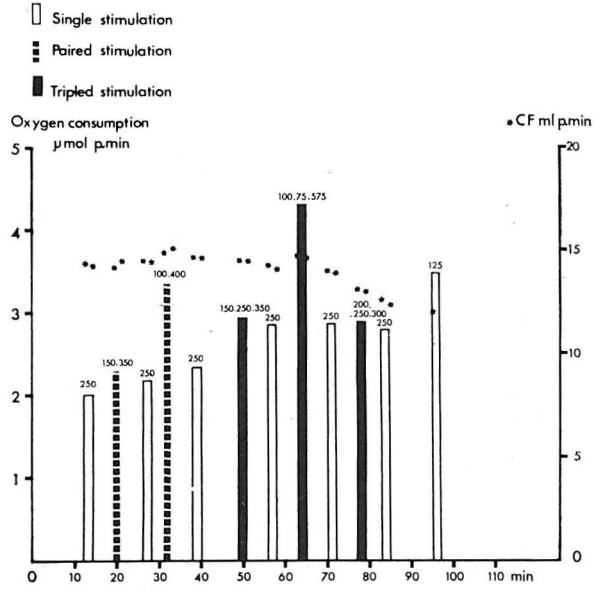

Fig. 4. Oxygen consumption per minute of the isolated rat heart during single, paired and tripled stimulation. The numbers above each bar represent the spacing between the applied stimuli.

different frequencies it can be seen that both parameters show nearly the same regression in their relation with the steady state frequency. This indicates that during single regular stimulation the oxygen consumption per beat is closely related to the area under the contraction in this setup. For this reason we feel justified in using the area under the contraction curve under these experimental conditions as a relevant parameter for the contractile process of the isolated perfused heart. Another interesting phenomenon is the fact that the coronary flow remains approximately constant despite a curtailment of the diastolic pause from 300 msec. at a frequency of 2/sec. to 100 msec. at a frequency of 6/sec. This means an increase of coronary flow per systolic time unit and indicates that the metabolic regulation of coronary perfusion indeed is a dominant factor.[12] The duration of the diastolic pause does not seem to be an important factor in the regulation of coronary flow.

In Figure 2 the effect of single, paired, and tripled stimulation of contractile response of the heart is shown. This demonstrates that

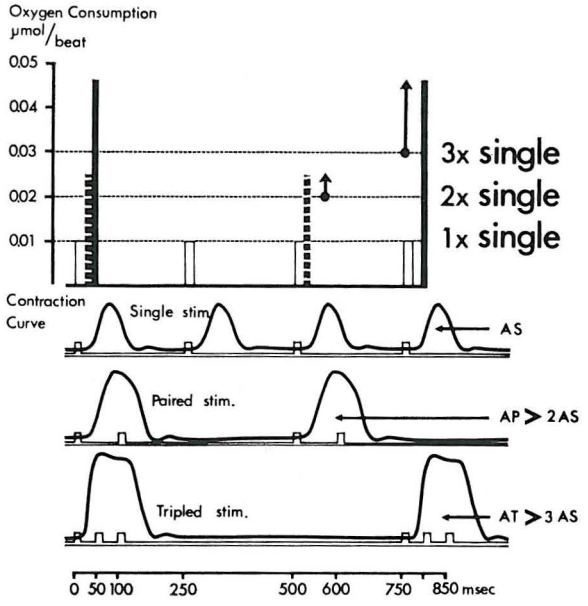

Fig. 5. Oxygen consumption per beat and contraction area during single, paired, and tripled stimulation. For further details see text.

tripled stimulation does not further increase the amplitude but only enlarges the duration of the contraction. The height of each bar in graph 4 represents the oxygen consumption per minute during single, paired, and tripled stimulation. The number of electrical responses of the heart per time unit was of course constant throughout the experiment. It can be seen that the increase in oxygen consumption depends on the spacing of these electrical responses. The closer the spacing, the larger the oxygen consumption. During tripled stimulation the oxygen consumption per unit of time even exceeds the amount of oxygen used during paired stimulation.

Figure 5 illustrates that the oxygen consumption per beat far exceeds the gain in contractility per beat orginated by paired or tripled stimulation. These experiments indicate that, although the gain in contractility by paired stimulation is in the order of magnitude of 100 per cent, the cost in oxygen might limit the applicability of paired stimulation in a number of cardiac emergencies. However more experimental work in animals with occluded coronary arteries is needed to reach a final conclusion in this respect.

In any event, these results should be taken as a warning if one feels that paired stimulation is a last resort for treating cardiac shock caused by myocardial infarction.

Possible role of calcium in potentiation phenomena. The discussion of the role of calcium played in the contractile process as such is beyond the scope of this paper. At the moment the influence of calcium upon the so-called force-interval relationship and several types of potentiation is under study in our laboratory.[13] Some preliminary results have already revealed that calcium plays an important role in potentiation phenomena.

In 1962 Kavaler[14] reported that in a medium of composition equivalent to that of 12-fold calcium Tyrode, weakness of a premature beat as well as postextrasystolic potentiation are entirely abolished. This amount of extracellular calcium, however, is not compatible with life and its physiological significance must be questioned. We limited ourselves to the study of those extracellular calcium concentrations that did not seriously interfere with spontaneous and/or driven contractions of the isolated perfused heart. The perfusion fluid used normally contains 2.6 mEq. Ca^{++}/l. This is approximately the same concentration as that of nonionized calcium found in the plasma of mammals. The extreme levels of calcium concentration that could be used in these experiments were 0.5 mEq./l and 8.4 mEq./l.

In Figure 6 the same experiment performed during low, normal, and high calcium perfusion is shown. At the normal calcium concentration (2.6 mEq./l.) the well-known reactions of the contractile process on changes in frequency and rhythm are visible. They are given here for comparison. At a low calcium concentration (0.5 mEq./l.) the contraction height is much lower at each frequency under study. At normal calcium the contraction height during regular single stimulation with a frequency of 4/sec. is slightly more than 3 mm., at low calcium with the same frequency 0.6 mm. At the shift of high frequency (4/sec.) to low frequency (2/sec.) the poststimulation potentiation at normal calcium is a fraction of the contraction height. However, at low calcium there is an increase of contraction of more than 100 per cent. At the same time it should be noted that the time it takes to shift from one contractile level to another is the same at each calcium level. Thus the duration of this shift seems to be not influenced by and might therefore not be related to the calcium-ion. Postextrasystolic potentiation (panel

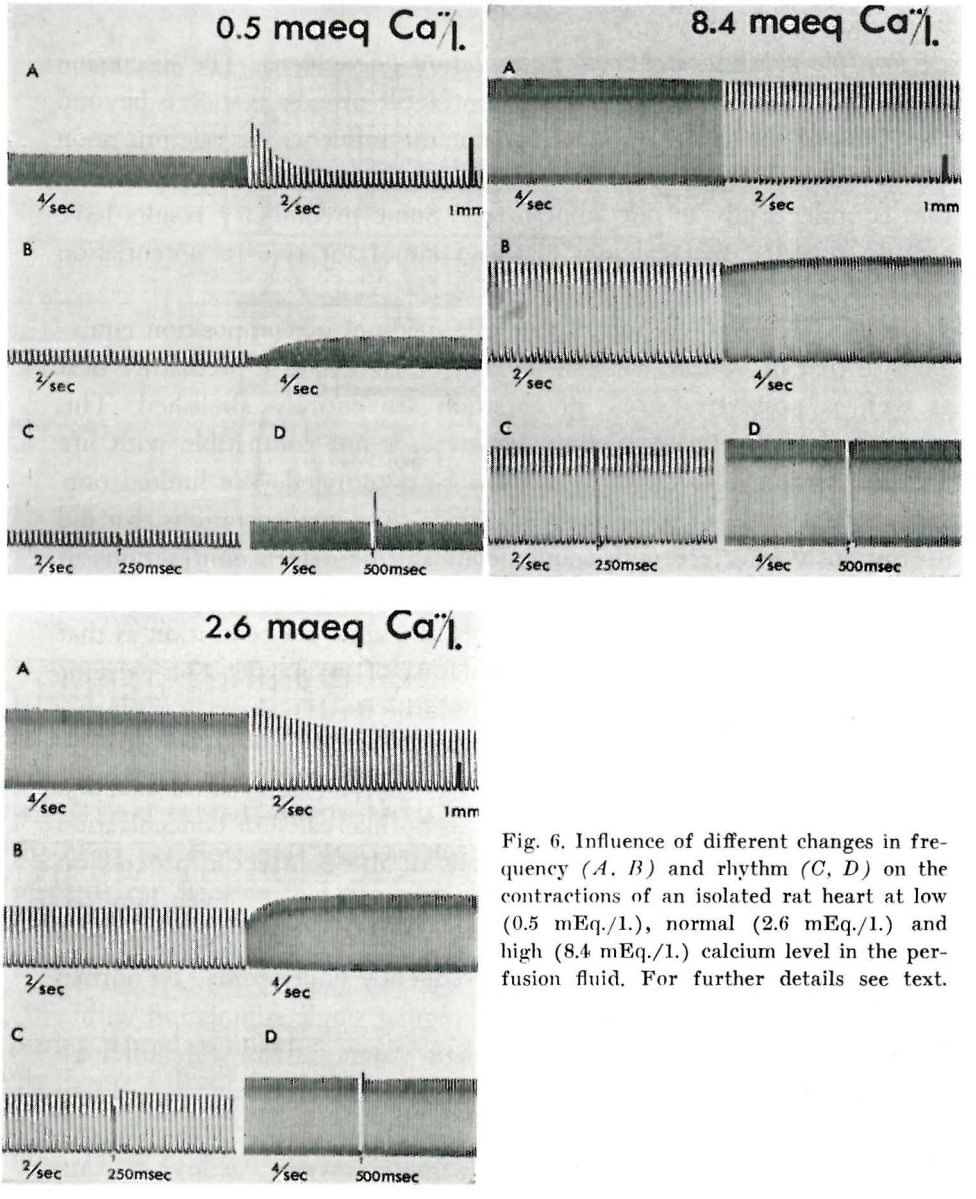

Fig. 6. Influence of different changes in frequency *(A, B)* and rhythm *(C, D)* on the contractions of an isolated rat heart at low (0.5 mEq./1.), normal (2.6 mEq./1.) and high (8.4 mEq./1.) calcium level in the perfusion fluid. For further details see text.

C) is not altered by changes in calcium concentration. In contrast to this is the influence of extracellular calcium concentration on the so-called rest contraction (panel *D*). It was found that at high calcium concentration the frequency contraction height relation flattens, in other words the contractions are more or less the same at different frequencies.

However the contraction height is increased at high calcium concentration, being 4.5 mm., which is approximately 30 per cent of the total diastolic length of the rat heart. A decrease of frequency does not give rise to potentiation although it can be seen that it takes a certain time (panel *B*) to shift from the contraction level belonging to 2/sec. to that of 4/sec. This time seems to be the same as during perfusion with low and normal calcium.

Potentiation phenomena are entirely abolished during the high calcium perfusion possibly due to the fact that the contraction has already reached its so-called ceiling. Our findings at high calcium levels are in agreement with Kavaler's findings. At high calcium levels the restitution is always maximal, which implies that further increase in restitution cannot occur. At low calcium levels restitution has been diminished but reaches a relatively high level if time is available (poststimulation potentiation, rest contractions). At the same time we feel that it is evident that a weakly contracting heart can easily enlarge its contractions but that a maximally strongly contracting heart has reached its limit, beyond which it cannot further strengthen its contraction. Paired stimulation strengthens the heart to its maximum since a further increase in amplitude cannot be reached by tripled stimulation (for as shown in Figure 2 the contraction height is already 4 mm.). This is of the same order of magnitude as during high calcium perfusion. At a certain extracellular calcium level it can be supposed that interval changes are translated into contractility changes by a shift in extraintracellular calcium flux and/or by an alteration in intraextracellular calcium gradient. The time needed to shift from one contractile level to another is more or less the same at different calcium levels. This indicates that if calcium translates interval changes into contractility changes, it can only do so if the metabolic processes have adapted to these new demands. This adaptation takes time which is independent of extracellular calcium and the number of contractions during that time. Beat-to-beat estimation of oxygen consumption could either substantiate or reject this hypothesis.

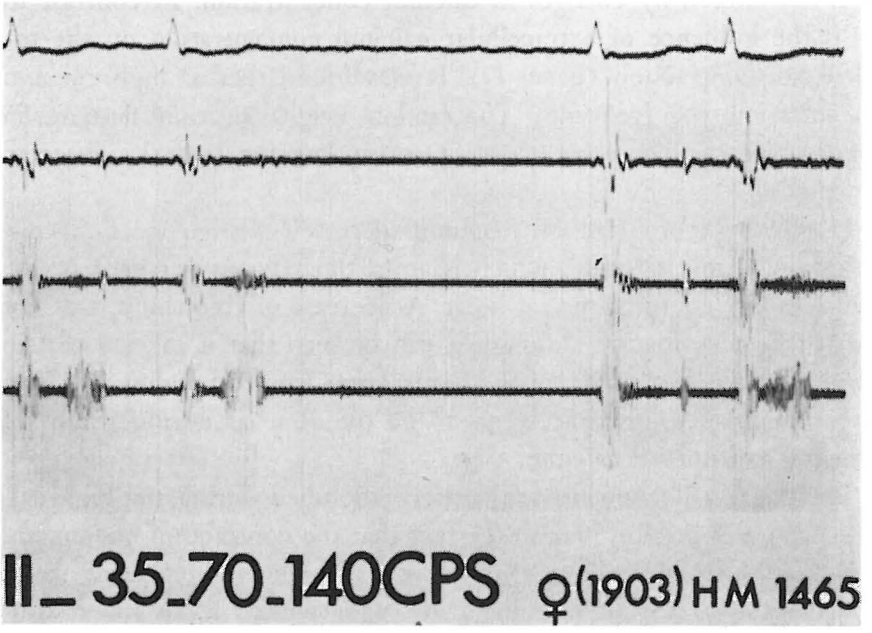

Fig. 7. Phonocardiogram recorded at the apex of a 61-year-old patient with auricular fibrillation and a late systolic murmur due to mitral incompetence. For further details see text.

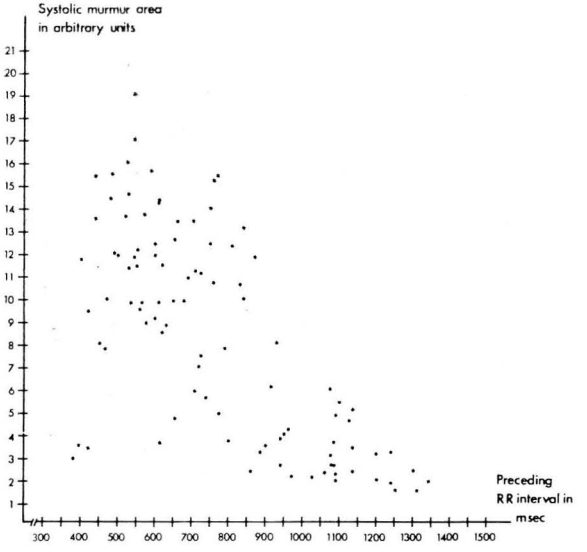

Fig. 8. Relation between murmur area and preceding cycle length in the same patient (Figure 7 mitral incompetence, auricular fibrillation). It can be seen that the amplitude and duration of the murmur (represented by the murmur area) varies inversely with the duration of the preceding cycle length.

Clinical Aspects

Paired stimulation as a diagnostic means. The knowledge that the contractile force of the heart can be enhanced by means of paired stimulation can be of help for cardiac diagnosis. Late systolic murmurs are often related to different types of mitral incompetence. One type of mitral incompetence can occur when the (normal) mitral valves do not close adequately because of contractile failure of one or both papillary muscles and/or the whole heart.

In a patient of 61 years with auricular fibrillation a late systolic murmur was heard.

Auricular fibrillation gives rise to an irregular cardiac action and during auscultation it was noticed that the loudness of the murmur was not related to the duration of the cardiac cycle.

In the phonocardiogram a late systolic murmur of the crescendo-diminuendo type, very localized to the apex beat, was found. Measured at 140 cps. at the apex beat, the width of the first heart sound amounted to 70 msec. The electromechanical interval was 50 to 60 msec. Very small but definite initial systolic variations were visible. The amplitude and duration of the murmur varied *inversely* with the length of the preceding cycle (Figures 7 and 8). This implies that the degree of mitral incompetence also varies inversely with the length of the preceding cycle. Braunwald *et al.*[15] demonstrated that the left ventricular characteristics in patients with auricular fibrillation are closely related to the length of the preceding cycle. In the isolated rat heart we could demonstrate that the area under contraction is closely related to the length of the preceding cycle, if the heart is stimulated with an irregular rhythm simulating the irregularity during auricular fibrillation (Figure 9). This indicates that during auricular fibrillation the contractility per beat varies directly with the preceding cycle length. Thus it was thought possible that in the patient the mitral incompetence was caused by inadequate contractions of the papillary muscle. A strong contraction (after a long pause) is accompanied by a slight mitral incompetence, a weak contraction (after a short pause) by a more seriously mitral incompetence.

To test the presence of an intrinsic myocardial factor independent of filling, an electrode catheter was introduced into the right ventricle and the heart was driven with single and paired impulses (Figures 10 and 11). Another catheter was placed in the left ventricle to check the

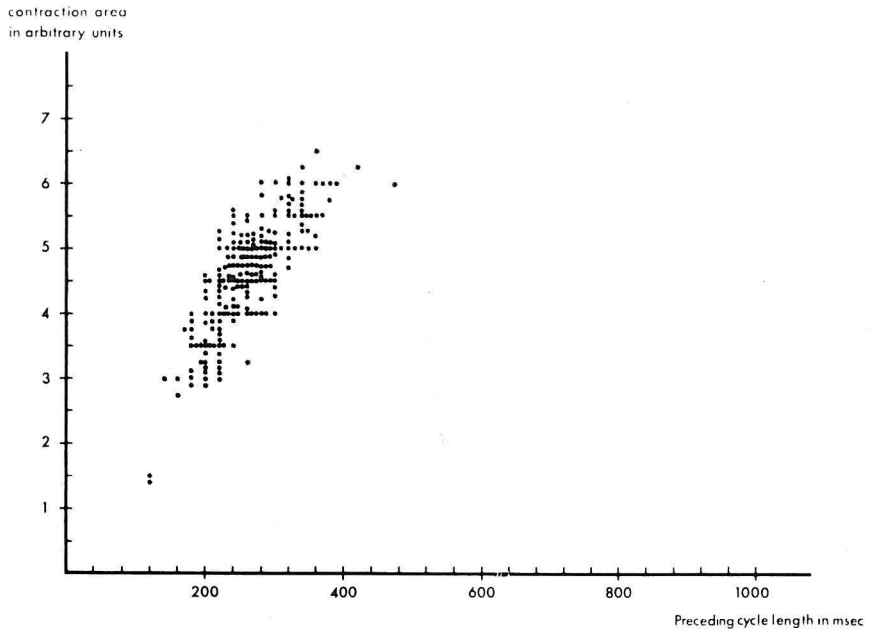

Fig. 9. Relation between contraction area and preceding cycle length in the isolated perfused rat heart. The heart was stimulated with an irregular rhythm simulating ventricular irregularity during auricular fibrillation.

contractile response to paired stimulation. The phonocardiogram at the apex beat together with the left ventricular pressure recorded via the Telcocatheter was registered (Figures 10 and 11). During single stimulation (Figure 10) the first heart sound had a duration of 40 to 50 msec. The late systolic murmur was distinctly visible and, since all cardiac cycles were the same, showed a constant pattern. The rising time of the ascending limb of the left ventricular pressure curve amounted to 110 msec.

During paired stimulation (Figure 11) the first heart sound still had a width of 40 to 50 msec. but the amplitude was strikingly enlarged. The rise time of the left ventricular pressure was diminished by as much as 90 msec., and the late systolic murmur had disappeared. These observations led to the conclusion that in this patient the mitral incompetence was originated by an inadequacy of the contraction of one of the papillary muscles. The latter could be improved by paired stimulation. In case of a structural alteration of the mitral valves the incompetence

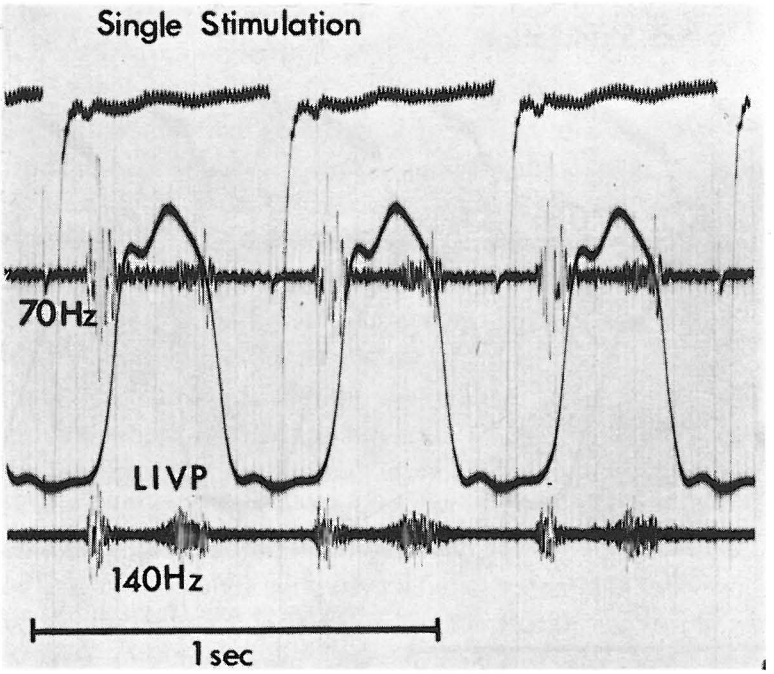

Fig. 10. Electrocardiogram, phonocardiogram, and left intraventricular pressure in the same patient (Figure 7) during single stimulation. The late systolic murmur is still present.

would have been increased by paired stimulation.

The use of paired stimulation can help to differentiate between functional (inadequate contractions) and organic mitral (and probably also tricuspid) incompetence. This type of mitral incompetence, to the best of our knowledge, has not been described before and can be regarded as a syndrome that can be found easily in patients with auricular fibrillation. The underlying mechanism can be demonstrated or ruled out by paired stimulation. The use of catecholamines for the demonstration of this type of valvular incompetence seems not to be indicated since not only is the contractile force increased but also the frequency. The latter might confuse the issue and therefore lead to a false interpretation.

Paired stimulation as a therapeutic means. The augmenting effect of paired stimulation on myocardial contractility might be used for the improvement of cardiac insufficiency.

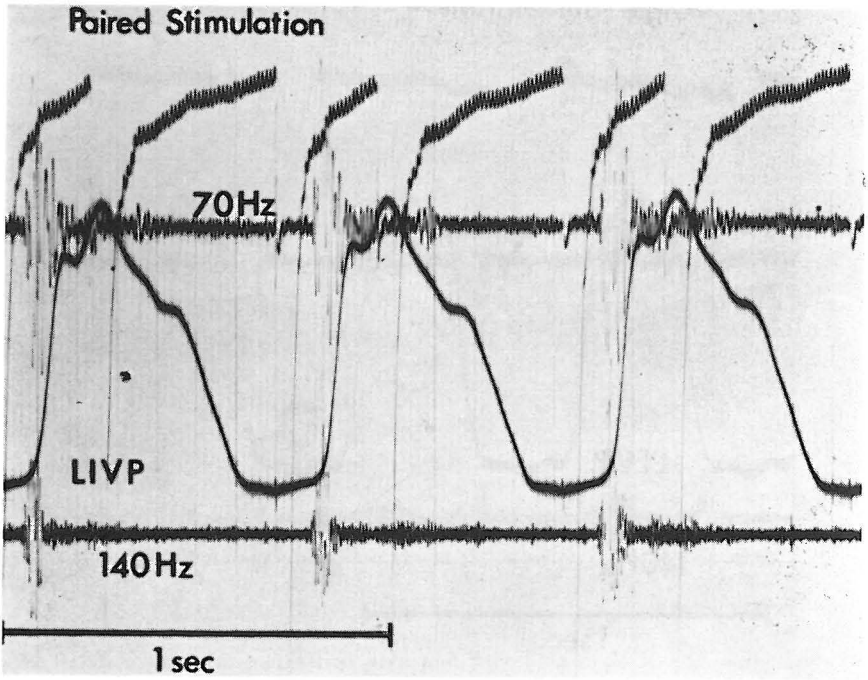

Fig. 11. As Figure 10 during paired stimulation. The systolic murmur has disappeared. For further details see text.

The patient was a 53-year-old housewife who had had an attack of rheumatic fever in 1929 with recurrence in 1948. In 1952 commissurotomy was performed for mitral stenosis but chorda rupture occurred, resulting in a "slight" degree of mitral insufficiency.

After a short period of improvement she gradually became dyspneic during exercise. Her condition gradually deteriorated. In the following years she was hospitalized for the treatment of congestive heart failure many times. When mitral annuloplasty or correction of the chorda rupture became surgically possible, it seemed inadvisable to submit her to a major surgical procedure.

In April 1964 she entered the Cardiology Department with extreme cardiac cachexia, severe congestive failure, pulmonary congestion, severe mitral and tricuspid insufficiency with pulsating liver and veins of both legs, extreme cardiac enlargement, and frank ascites. She had three tablets of digoxine, one fourth mg., daily. The heart rate was about

140/min., irregular, with auricular fibrillation and ventricular premature beats. After treatment with strict saltless diet and mercurial diuretics, a slight improvement occurred, and she was discharged at her own request.

Again the situation gradually deteriorated and she re-entered our department September 11, 1964, the same findings as in April 1964 being present. A rigorous treatment with severe salt restriction, digoxine, fursemid 80 mg. given on alternate days, did not improve the patient's condition to the extent that surgery was possible. This patient therefore appeared to be an instance of intractable congestive heart failure. We considered the possibility of paired stimulation as a method of improving the cardiac status enough to persuade the surgeon to accept this patient for cardiac surgery.

Because no coronary arterial insufficiency appeared to be present, it was concluded that a trial with paired stimulation was justified. After explaining the implications of this treatment to the patient she consented and collaborated perfectly. The presence of a severe degree of mitral insufficiency made it necessary to shorten the ejection time as much as possible by appropriate shortening of the delay between the first and the second of a pair of pulses.

After a short unsuccessful trial on November 30, an electrode catheter was introduced on December 8 via the right superficial jugular vein into the right ventricle. Paired stimuli with an interval of 300 msec. between the first and second pulse were given with a frequency of 60/min. During the 12-day period of paired stimulation the patient felt better, was active and interested in her surroundings, and wanted to eat and drink more, which could not be allowed because of the dietary regimen necessary for the evaluation of this treatment. It was clear, however, that the signs of tricuspid insufficiency also became more marked. Because the situation was not improved after the 12 days, paired stimulation was discontinued. She was discharged December 24 because she wanted to be at home at Christmas.

Immediately after stopping the paired driving a nodal rhythm occurred, and after 10 min. the conduction between atrium and ventricle was restored. No deterioration of the cardiac conduction was manifest either at discharge or several weeks later.

It can be stated that paired stimulation failed to improve the patient to an extent enabling the cardiac surgeon to perform surgery. The en-

hancement of the contractile force of the heart which was evident from the increase in dp/dt in both left and right ventricle also enlarged the tricuspid incompetence and possibly also the mitral incompetence.

During the second trial it was impossible to evaluate a change in the cardiac condition by quantitative measurements. It would have been necessary to have one electrode catheter in the right ventricle to stimulate the heart, another catheter in the pulmonary artery for measuring cardiac output, and another in the left ventricle to measure left intraventricular pressure. During our first trial on November 30, these catheters were properly positioned but we failed to get a good stimulation pattern and response. On December 8, for medical reasons, it was impossible to repeat the same procedure. This patient demonstrated that indeed it is possible to continue paired stimulation during an extended period of time without any permanent harm. The use of this technique can be of value for the treatment of cases of congestive heart failure. Appropriate measures should be taken to prevent the electrical calamities that can occur during this treatment.

Summary

In this paper some physiological and clinical aspects of paired stimulation are discussed.

1) The augmenting effect of paired stimulation on myocardial contractility is due to potentiation (increase in speed of restitution) and fusion of two contractions.

2) While using paired stimulation the oxygen demand of the heart is increased to an extent surpassing the gain in contractility.

3) The calcium ion plays an important role in the "translation" of potentiation into the actual change of myocardial shortening.

4) In a patient with mitral incompetence due to an insufficient contracting papillary muscle, the presence of an intrinsic myocardial factor independent of ventricular filling was demonstrated with the aid of paired stimulation.

5) A patient with a severe congestive heart failure due to rheumatic heart disease who did not respond to conventional treatment was treated with paired stimulation for 12 days. Although the patient felt better no objective improvement could be demonstrated since the tricuspid and possibly also the mitral incompetence increased by the augmented dp/dt of the right and left ventricles.

Acknowledgment

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