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# PHYSIOLOGICAL ASPECTS OF PAIRED STIMULATION

F.L. MEIJLER and D. DURRER

Department of Cardiology and Clinical Physiology, University of Amsterdam,
Wilhelmina Gasthuis, Amsterdam, The Netherlands

Starling's law of the heart states that "the energy of contraction, however measured, is a function of the length of the muscle fibre" (Starling, 1915). This physiological property of myocardial and skeletal muscle enables the heart, within certain limits, to eject during each systole the amount of blood that enters it during diastole. It follows that this mechanism plays an important role in the regulation of the circulation.

The significance of Starling's law has tended to obscure other important adaptive mechanisms of the heart. Almost everyone has experienced the feeling of a premature beat; as a rule, it is not the premature beat which is felt but rather the contraction following it, the so-called post-extrasystolic beat. Until recently, this enhanced beat was explained on the basis of Starling's law, namely that the long pause following the extrasystole increased diastole filling and thus enhanced the post-extrasystolic beat. However, it has been demonstrated time and again that the same effect takes place without filling playing any part in it (Meijler, Van de Bogaard, van der Tweel and Durrer, 1962; Siebens, Hoffman, Cranefield and Brooks, 1959).

Fig. 1 demonstrates the potentiating effect of a premature beat in an isolated perfused rat heart preparation. The contractions were recorded isotonically (Meijler *et al.*, 1962).

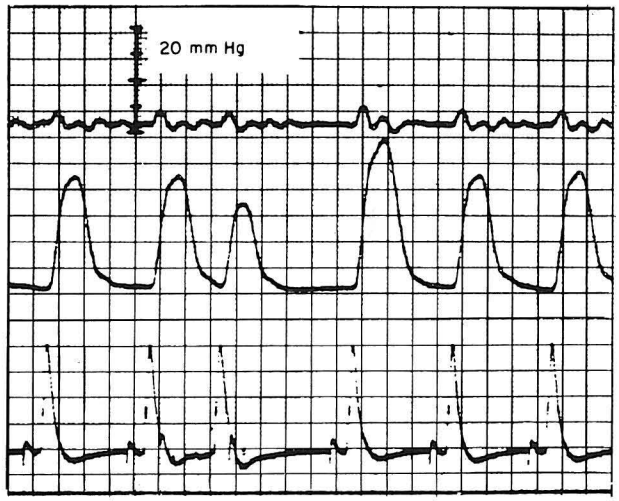


*Fig. 1.* Left intraventricular pressure (upper tracing), contractions (middle tracing) and electrocardiogram of an isolated rat heart with opened ventricular cavities and interrupted coronary perfusion. Note that there is insignificant intraventricular pressure, however, the postextrasystolic contraction is enhanced at a constant end-diastolic length. Bipolar stimulation of the right atrium. Stimulation rate 2.5/sec. Delay of the extra stimulus 280 msec. Paper speed: 50 mm/sec. From Meijler *et al.* (1962).

A filling effect was excluded by opening both ventricular cavities. The left ventricular pressure was recorded at a high sensitivity to demonstrate that the left ventricular cavity was indeed open. This mechanism is called "post-extrasystolic potentiation". It has thus been shown that the interval between beats itself (or rather, the time between R waves) has a strong effect on the strength of the succeeding contraction. A personal study of the relationship between interval and contraction was started about 10 years ago. This relationship is now generally called the interval-force relationship of myocardial muscle.

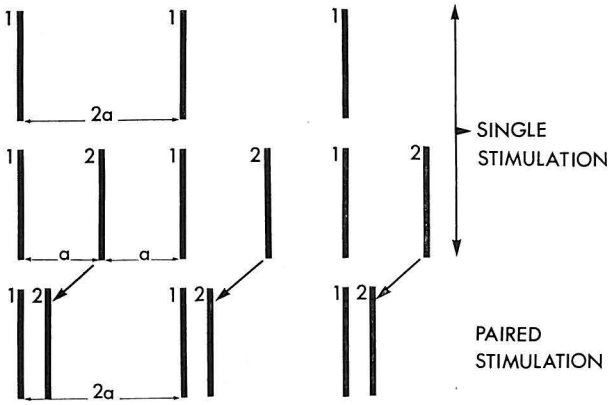


*Fig. 2.* Schematic representation of the transformation of single stimulation into paired stimulation. From *Ned. T. Geneesk., 109*, 1628, 1965.

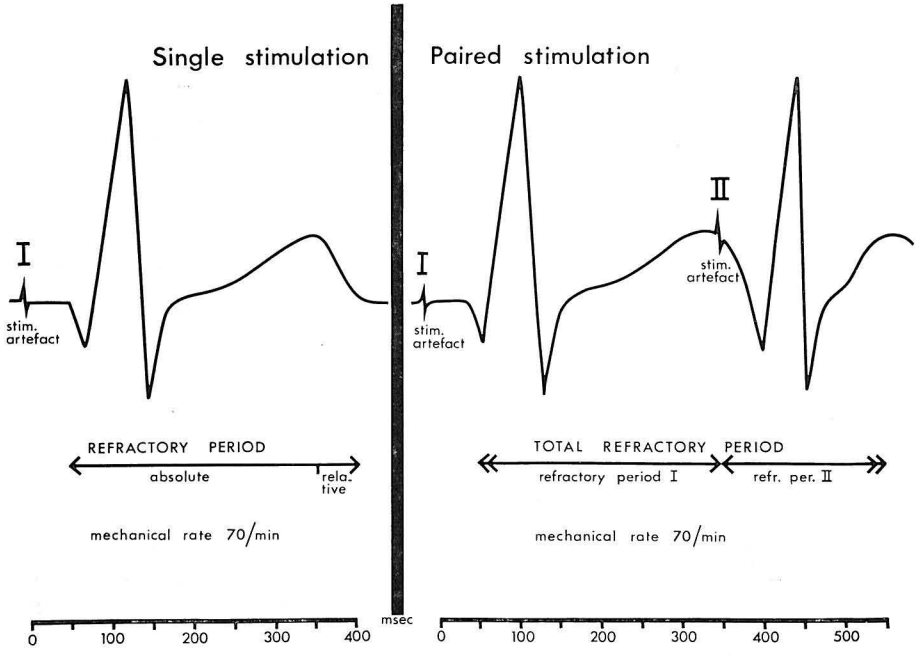


*Fig. 3.* Schematic representation of the increase of the effective refractory period by means of paired stimulation, the so-called chinidine-like effect.

The effect of paired stimulation on the contractile state of the myocardium is a result of this interval-force relationship. What is meant by paired stimulation? The development of artificial pacemakers in the treatment of total heart block has focused clinical interest on the excitability of the heart and the circulatory response during artificial stimulation: this type of stimulation can be called single stimulation. Paired stimulation of the heart entails the method of delivering two closely-spaced stimuli to the heart instead of one. Fig. 2 gives a schematic representation of how paired stimulation can be effected. It can be seen that single stimulation is transformed into paired stimulation by gradually moving every second impulse closer to the preceding one, or by giving two stimuli instead of one.

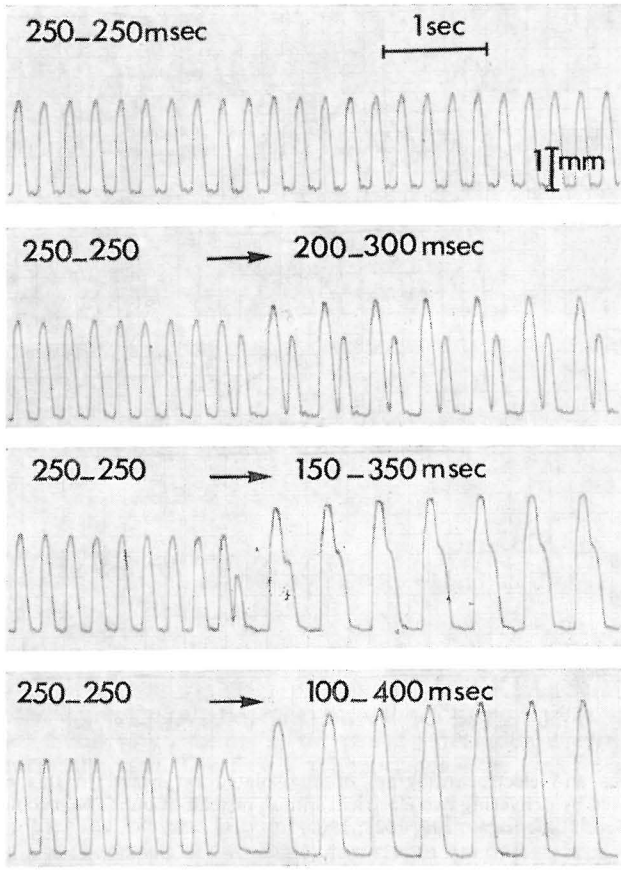


*Fig. 4.* Contractions of an isolated rat heart. The effect of paired stimulation (100-400) is obtained by gradually moving every second impulse closer to the preceding one: The number of electrical impulses remains the same; the effective mechanical rate is halved. The increase in oxygen demand due to this type of stimulation is shown in Fig. 7. From *Ned. T. Geneesk.*, *109*, 1628, 1965.

An absolute condition for the occurrence of the effect of paired stimulation is the fact that both applied stimuli are followed by an excitation of the heart. Thus not the stimuli themselves, but the electrical responses originated by these stimuli are responsible for the dramatic effect of paired stimulation.

Paired stimulation in its effect is similar to coupled pacing. During paired stimulation both electrical responses of the heart are originated by an applied stimulus, while during coupled

pacing the first electrical response is spontaneous and only the second originated by a stimulus delivered after a chosen delay following the QRS complex.

It is evident that the second impulse has to occur after the absolute refractory period following the first QRS complex. Thus, if both stimuli produce electrical activity of the heart, the total duration of the period for which the muscle is effectively refractory for other impulses is increased. It is suggested that this effect of paired stimulation is called a chinidine-like effect (Fig. 3). In both instances, the number of apparent contractions is 70/min. The chinidine-like effect of paired stimulation can be used in the treatment of certain cardiac arrhythmias.

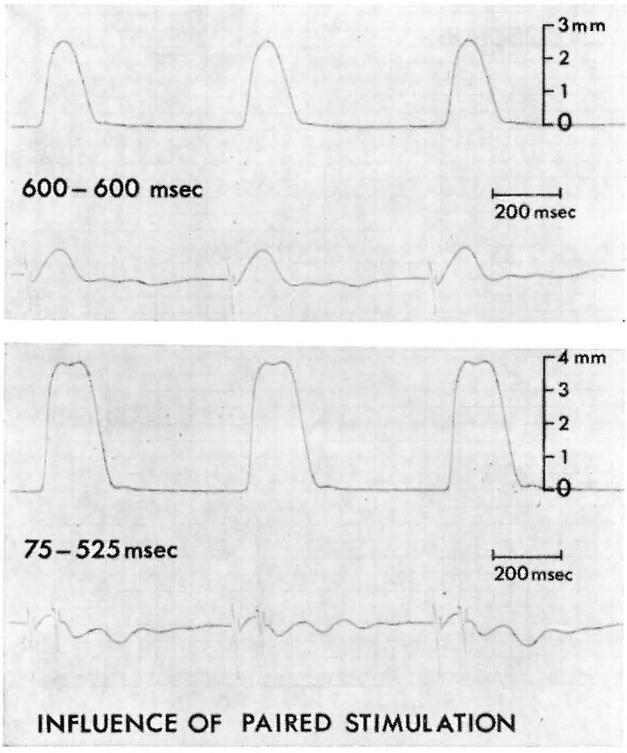


*Fig. 5.* Contractions and electrocardiogram of an isolated rat heart. In this experiment paired stimulation is effected by delivering two electrical stimuli instead of one. The mechanical rate remains unaltered. From *Ned. T. Geneesk.*, *109*, 1628, 1965.

The effect of paired stimulation on the contractility of the heart is shown in Fig. 4, which comprises graphs of contractions of an isolated rat heart. In the first row the heart is stimulated with a regular rhythm with 250 msec interval, which is gradually changed into a bigeminal rhythm and finally complete fusion of two beats is reached at intervals of 100-400 msec. It can be seen that the second contraction becomes smaller and the first becomes larger. Thus by using the same number of electrical stimuli but by altering their mutual spacing, the contractile response of the heart can be profoundly altered and the number of contractions halved. The remaining fused contraction, however, is larger and lasts longer than the original one.

Another way of applying paired stimulation is demonstrated in Fig. 5. These are also contractions of an isolated rat heart. In the upper row, the heart is stimulated with single impulses; in the second row with paired impulses. In this case, the number of apparent

(mechanical) contractions, of course, remains constant. However, the contractions registered with the same sensitivity of the recorder are much larger. The dramatic effect of this type of stimulation has not only been demonstrated in an isolated perfused heart performing hardly any physical work, but also in dogs and man. Fig. 6 demonstrates the effect of paired stimulation on the left ventricular pressure and stroke volume of an open chest dog: the increase in left ventricular pressure, aortic pressure and stroke volume can be seen. It is suggested that this effect of paired stimulation should be called an epinephrine-like effect.

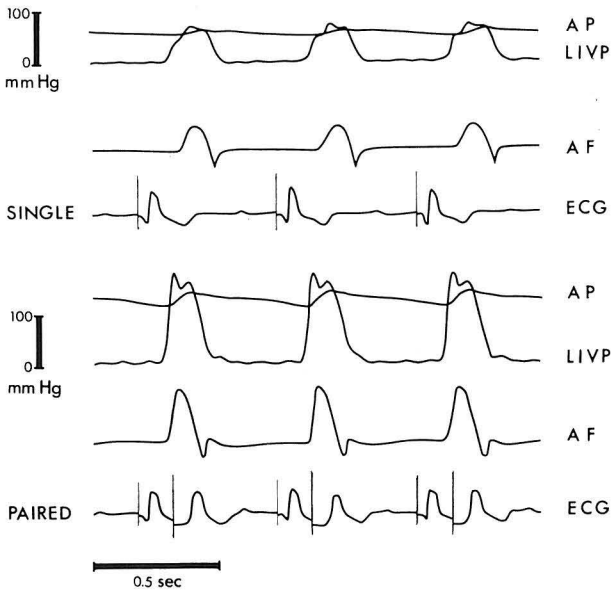


*Fig. 6.* Aortic pressure (AP), left intraventricular pressure (LIVP) and aortic flow (AF) during single and paired stimulation in the open chest dog. "Epinephrine-like" effect. From *Bull. N.Y. Acad. Med.*, *41*, 575, 1965.

This type of stimulation seems to enable the physiologist and the clinician to regulate the force of contraction of the heart. However, it should be realized that during paired stimulation the oxygen consumption of the heart increases. Fig. 7 demonstrates that alteration of the spacing of the stimuli which results in the paired stimulation effect gives rise to an increase of oxygen consumption. This fact is of importance if the use of paired stimulation is considered in patients, say with an inadequate coronary system.

Now it is known that the increase in number of electrical responses, the peculiar spacing of these responses, and the fusion of two beats, give rise to the potentiation of contractility. Some authors talk of sustained post-extrasystolic potentiation (Cranefield, 1966). Personal studies (Nieuwendijk, 1966; Nieuwendijk, Meijler and Durrer, 1967) suggest that the calcium ion is the direct link between the RR interval and the force of the beat. During low calcium perfusion there exists a so-called electrical-mechanical dissociation (Fig. 8). The muscle is still excitable but exhibits no mechanical responses. If under these conditions paired stimulation is introduced, contractions can be recorded after a few seconds, again illustrating the dramatic effect of paired stimulation. After cessation of paired stimulation, a number of contractions continue for a short time although originated by single stimulation. It is thus shown that paired stimulation has a strong effect on the contractile response and excitability of the heart, and as a consequence on the circulation as a whole. Its clinical applicability is evident for diagnostic as well as for therapeutic use. Its application, however, is beset with a number of difficulties which have not yet been completely solved. These difficulties are dealt with by Durrer and Meijler (1966).

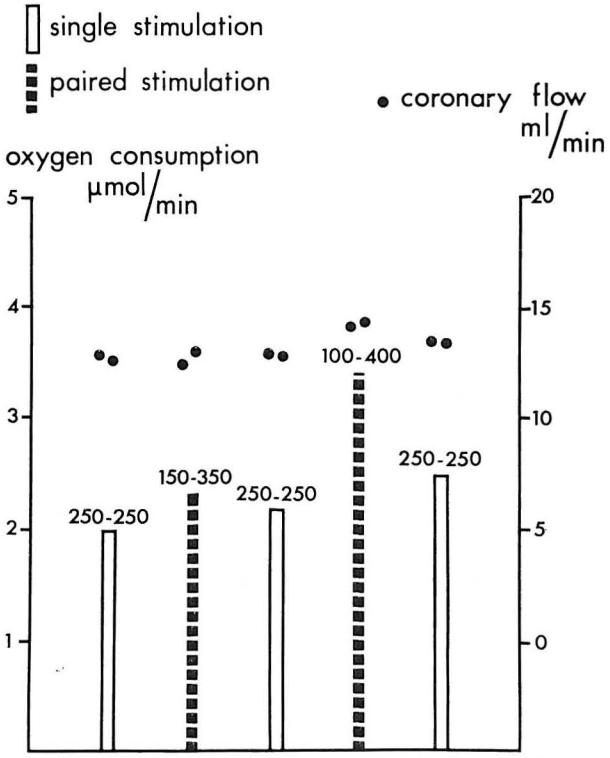


*Fig. 7.* Oxygen consumption and coronary flow of an isolated rat heart during single stimulation (250-250) and paired stimulation (150-350 and 100-400). When this diagram is compaired with the contraction record shown in Fig. 4, it can be seen that despite the effective mechanical rate during paired stimulation, there is a large increase in oxygen consumption.

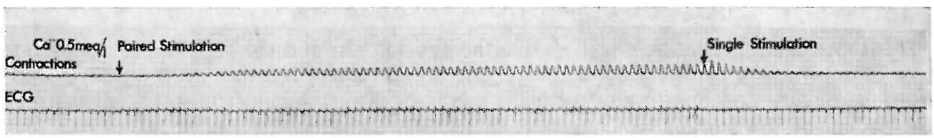


*Fig. 8.* Effect of paired stimulation during low calcium perfusion of an isolated rat heart. This record shows the dramatic influence of this type of stimulation on myocardial contractility.

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