Editorial

Paired Electrical Stimulation of the Heart: A Physiologic Riddle and a Clinical Challenge

IT HAS BEEN appreciated for many years that both the rate and rhythm of the heart exert strong influences on the strength of cardiac contractions. In 1871 Bowditch wrote that "the interval between a contraction of the heart and the preceding beat is of such importance for the strength of the contraction that a study of this effect is a prime necessity." Many investigators then studied the effects of premature beats on cardiac contractility and by the turn of the century, Woodworth had clearly demonstrated in isolated cardiac tissue that the contraction following an extrasystole is usually stronger than that which preceded it, a phenomenon now generally termed "postextrasystolic potentiation." Since then considerable effort has been directed toward analyzing in detail the influence exerted by the intervals preceding and following the premature beat on the degree of postextrasystolic potentiation, and this entire subject has recently been reviewed in detail.

During the past two years both cardiovascular physiologists and clinical investigators have renewed their interest in studying the effects of postextrasystolic potentiation. Particular attention has been directed to investigating the effects of paired electrical stimulation, a technic introduced by Lopez, Edelist, and Katz, which consists of repetitively delivering pairs of stimuli to the heart in a manner so that the second stimulus of each pair is delivered immediately after the termination of the refractory period resulting from the first depolarization. This second stimulus initiates a propagated depolarization which is not followed by an effective second contraction. The resultant stimulation of myocardial performance is sustained for as long as paired electrical stimulation is continued and is unusually pronounced, the positive inotropic effect, in our experience, exceeding that which results from the administration of any pharmacologic agent, including the catecholamines, sympathomimetic drugs, and digitalis glycosides. Since this augmentation of the heart's contractile state is induced electrically rather than pharmacologically, we have termed it "electroaugmentation."

Paired electrical stimulation has been shown to stimulate cardiac contraction in every circumstance in which this mode of stimulation has been examined. For example, electroaugmentation may be induced in the isolated cat papillary muscle, studied in vitro in a myograph (fig. 1). Similar observations in our laboratory have been made on papillary muscles that were removed from the left ventricles of patients with congestive heart failure and that were found to be depleted of their norepinephrine stores. In open-chest dogs paired electrical stimulation more than dou-

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Tracings obtained from a cat papillary muscle contracting from a constant initial muscle length against an afterload held constant at 2.0 Gm. With this technique the contraction is isometric until the force developed exceeds the afterload, and thereafter it is isotonic. From the top downward are shown the stimulus artifact (STIM.), force of contraction, displacement (or muscle shortening), and the rate of shortening (dl/dt). At the arrow (D.P.) paired (double) electrical stimulation was begun. Note the pronounced increases in the rate of force development, the extent of shortening, and the velocity of shortening induced by paired stimulation.

The salutary effects of paired electrical stimulation on the hearts of intact, conscious human subjects have also been observed. In studies in which the paired stimuli were delivered by means of a bipolar catheter introduced into the right ventricular cavity, it was observed that the rate of intraventricular pressure rise, the mean systolic ejection rate, and the velocity of ventricular shortening increased, while the ventricular end-diastolic pressure generally declined (fig. 2).

In addition to the striking alterations of the mechanical activity of the ventricle enumerated above, paired electrical stimulation also exerts important effects on the electrical properties of the heart, as well as on its metabolism. The introduction of an electrical stimulus shortly after the termination of the absolute refractory period associated with the previous depolarization results in a second depolarization which is, of course, also accompanied by a refractory period. Since the two refractory periods are consecutive, the time during which the ventricles are unresponsive to other stimuli is effectively doubled and the number of effective ventricular contractions per minute may thus be reduced. Sinus tachycardia may be slowed, paroxysmal atrial and ventricular...

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tachycardia may be suppressed, as may the ectopic rhythms induced by digitalis intoxication.

Paired depolarizations may also be produced by allowing the normal, spontaneous ventricular depolarization to take place and to act as the first depolarization of the pair. A single electrical stimulus, triggered by and coupled to the spontaneous QRS complex, but adjustable delayed so that it occurs near the peak of the T wave, produces the second depolarization. This mode of stimulation has been referred to as "coupled pacing" and usually simply reduces the ventricular rate in half. Since two ventricular depolarizations occur, electroaugmentation results from coupled pacing. Among the advantages of this method are that the normal temporal relationship between the atrial and ventricular contractions is retained and that the first ventricular depolarization wave spreads over normal pathways. It is also possible to slow the

**Figure 2**

*Effects of discontinuing paired electrical stimulation in a patient with left ventricular failure due to a cardiomyopathy. In the top panel paired stimuli were delivered with the shortest possible interval between the stimuli (300 msec.). Following discontinuation of paired electrical stimulation the left ventricular end-diastolic pressure, indicated by the arrows, rose from 9 to 23 mm. Hg. In the bottom panel the interval between the stimuli was 320 msec. and two discrete contractions are evident. It is evident that paired electrical stimulation lowered the left ventricular end-diastolic pressure even when the contractions were not well fused, as in the bottom panel.*

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ventricular rate by delivering pairs of stimuli to the atrium.\textsuperscript{4-7} If the second of these reaches the atrioventricular conduction system while it is still refractory, ventricular slowing will occur without two ventricular depolarizations, and therefore without electroaugmentation.

Paired electrical stimulation increases myocardial oxygen requirements. When stroke volume, arterial pressure, and the number of ventricular contractions are held constant, paired stimulation increases the heart’s oxygen requirements by an average of 35 percent of control levels.\textsuperscript{5} Of course, if the heart rate is slowed simultaneously, myocardial oxygen consumption may not change.

It is generally agreed that electroaugmentation is a sustained form of postextrasystolic potentiation. The magnitude of the potentiation of cardiac contraction following an extrasystole is proportional to the degree of its prematurity, while the contractile response produced by the extrasystole itself varies inversely with its prematurity.\textsuperscript{11,12} Consequently, it is not surprising that paired electrical stimulation produces a particularly marked degree of augmentation. The fundamental mechanism that underlies postextrasystolic potentiation has not been elucidated. Since the potentiation of contraction is related to the preceding extra excitation, it is possible that an examination of the events that are involved in the coupling of excitation to contraction might provide the key to the solution of this intriguing problem. There is increasing evidence that calcium ions play a central role in excitation-contraction coupling, and perhaps the extra depolarization during paired stimulation increases the influx of calcium to the intracellular contraction sites. Regardless of whether or not augmented calcium influx is causally related to postextrasystolic potentiation, it is likely that elucidation of its basic mechanism will provide important insight into the intracellular conditions that control the contractile state of the myocardium. The mechanism responsible for the increase in myocardial metabolism induced by paired electrical stimulation is also of considerable interest. Recent experiments point to the augmented velocity of cardiac contraction as the primary cause of the stimulation of the heart’s oxygen requirements.\textsuperscript{5,13} It is likely that further studies with paired electrical stimulation will help to elucidate the manner in which alterations in the heart’s contractile state influence its metabolism.

In addition to these important theoretical considerations, which are now being brought into sharper focus by utilizing paired electrical stimulation in the experimental laboratory, the clinical investigator is challenged by the exciting possibility that this technic may be useful in a variety of clinical circumstances. In this regard it is important to emphasize that paired electrical stimulation is not without hazard. After all, the second stimulus of each pair is delivered during, or close to, the so-called vulnerable period. Although we have not personally encountered any serious or persistent arrhythmias, ventricular fibrillation has often occurred in the dog, and we have learned of the occurrence of this arrhythmia in a patient. The most impressive hemodynamic change that occurs during paired electrical stimulation is an increase in the velocity of cardiac contraction. However, what, if any, clinical benefits will accrue from this acceleration of the contractile process are not yet clear. It has been disappointing that the cardiac output has not risen consistently during paired electrical stimulation, even in patients with myocardial failure. On the other hand, the decline of the elevated ventricular end-diastolic pressure (fig. 2) may be of potential clinical benefit. The increase of myocardial oxygen consumption resulting from paired electrical stimulation of the ventricles suggests that this technic should not be applied in patients with coronary artery disease in whom myocardial ischemia might be intensified, unless the ventricular rate is simultaneously reduced. Moreover, the potential hazards of paired electrical stimulation of the hypoxic myocardium have not been defined. Although both paired electrical stimulation and coupled pacing may be used to slow the ventricular rate and to suppress a variety of arrhythmias,
it must be appreciated that these methods of stimulation are not curative and are effective for only as long as they are applied.

From the considerations presented above it appears that although paired electrical stimulation has profound effects on the electrical, mechanical, and metabolic properties of the myocardium, the most propitious manner in which this technic may be used clinically has not yet been defined. Nonetheless, important steps will have been taken if the physiologist solves the riddle of the mechanism of postextrasystolic potentiation and if the clinical investigator finds a practical way of utilizing the profound changes induced by paired electrical stimulation in the treatment of disturbances of cardiac contraction or rhythm.

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Theory and Fact
I take the view that a theory should be a policy and not a creed, that its most important work is to suggest things which can be tried by experiment, and for this the theory should be one that is easily visualized.—J. J. Thomson.
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