Increased Excitability of the Heart Induced by Electrical Stimulation in the Absolute Refractory Period*

S. Ragel, M.D.** and Y. Hasin, B.Sc.†

A series of experiments were designed to study the possible effects of electrical stimuli, delivered during the absolute refractory period, on the threshold of excitability in the relative refractory period. They were carried out in dogs with complete A-V block or with intact conduction system. It was found that such stimuli, which previously were regarded as ineffective, may convert a subthreshold current to a depolarizing one. This effect was shown to be dependent on the time-relation between the “ineffective” and the test stimuli from the driving stimulus and also on the strength of the stimulations. The mechanism of the effectiveness of the ineffective stimulus was demonstrated to be a threshold-reducing, locally induced, anodal, all-or-none phenomenon.

Application of electrical stimuli during the absolute refractory period does not evoke propagated depolarization of the heart. It is claimed, therefore, that stimulation occurring at such period is ineffective and harmless. This assumption was utilized for the development of certain pacing methods. However, there are some hints pointing to a possible effectiveness of such “ineffective” stimuli.

This study evaluates the role of electrical stimuli delivered during the absolute refractory period, on the threshold of excitability of the heart in its relative refractory period.

Material and Methods

Twelve mongrel dogs (8 to 15 kg) were anesthetized with intravenously administered pentobarbital (30 mg/kg). Artificial respiration was maintained by positive pressure breathing. The chest was opened by a longitudinal sternal split. In eight dogs, following transient inflow obstruction, the A-V node was destroyed by electrocoagulation and complete A-V block was produced. A pair of steel hook-electrodes, with an inter-electrode interval of 2 mm, was attached to the right ventricular wall, close to the apex, for subsequent bipolar stimulation. Unipolar stimulation was applied through use of one of these electrodes, the indifferent electrode being a wide plate (2 cm times 4 cm) buried under the abdominal skin. The marked difference in the size of the electrodes and their distant location let us assume true monopolar stimulation. Surface lead electrocardiogram was continuously recorded and displayed on an American Optical monitor.

The heart was stimulated by a specially designed triple-pacemaker* which is capable of producing three consecutive stimuli (S₁, S₂ and S₃). The second (S₂) and the third (S₃) stimuli may be set at variable time intervals after S₁ and are of independently adjustable intensity. S₁ was always set at a current which was twice the threshold value and served as steady stimulus at rates between 50 to 114 per minute. The current used was about 1 to 3 mA and of 2 msec duration. S₂ was applied 80 to 180 msec following S₁ (absolute refractory period in the different dogs). Currents up to 8 mA were used but QRS was never evoked. S₃ was delivered 150 to 400 msec following S₁. This interval was shown to be within the relative refractory period or in the early diastolic period since it was possible to initiate depolarization if sufficient current level was used. In most dogs S₂ or S₃ or both were applied following every driving S₁ stimulus, and in all dogs a series of S₂ or S₃ or both were given only after every second driving stimulus.

In four additional dogs the A-V conduction system was left intact. Atrial driving was carried out through a pair of silver clips attached to the right atrial appendage. The stimuli (S₁) were delivered at a rate sufficient to suppress sinus activity. S₂ was an anodal stimulus, applied to the right ventricle, at such an interval as to fall within the QRS complex (about 40

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*Kindly supplied by American Optical Co.
to 60 msec following the onset of the QRS complex). This was achieved by coupling the S2 stimulus to the atrial S1. Similarly, S3 was triggered by S1, but with a delay of 150 to 170 msec, to stimulate in the relative refractory period. The relative current levels of S2 and S3 were about the same as described earlier for the dogs with A-V block. In the different dogs S2 and/or S3 were applied following each or following every second S1.

Results

Complete A-V Block

In all dogs the ventricles were driven at steady rates by S1. In a series of experiments S2 was applied 80 to 180 msec following S1, but no QRS was produced, the heart being stimulated within the absolute refractory period. In another series, in all dogs, S1 was followed only by S3. This is a stimulating current applied within the relative refractory period at such level as to remain subthreshold.

However, if S2 and S3 are both applied after S1, at the same location and in the same intensity as described above, the previously ineffective S2 may convert the previously subthreshold S3, leading to the appearance of S3-induced QRS complex. This phenomenon can be produced both by unipolar anodal or by bipolar stimulation, but not by cathodal stimulation. S2 and S3 should be applied through the same electrodes to obtain activation.

A representative tracing of the above phenomena is illustrated in Figure 1. It is taken from an experiment where S2 or S3 or both were applied following every second S1. The results are equal to those obtained by similar stimulations following each driving stimuli.

In an attempt to elucidate the mechanism responsible for the described activation of a subthreshold stimulus, the role of the intervals between the various stimuli and their strength was further investigated.

Interval-strength relationship for anodal stimulation was determined according to the method described in a previous study from this laboratory. The upper limit of threshold (TV) is defined as the minimal current just sufficient to evoke immediate and continuous depolarizations at various intervals following S1. Such TV curves were built for S3 when it is applied without previous S2. It can be seen in Figure 2 that the shape of TV is similar to the usual anodal threshold curve. If, however, strength-interval relationship is plotted for S3 following ineffective S2 stimulations, the resultant curve shows reduced threshold levels (TVR) (Fig 2). This was achieved by applying S2 140 msec following S1, with an intensity of 2 mA. The values of TV and of TVR were obtained at

![Figure 1](http://journal.publications.chestnet.org/pdaccess.ashx?url=data/journals/chest/21525/)

**Figure 1.** Upper tracing: S1 is driving the heart and S2 is applied following every second S1. Previously subthreshold S3 becomes effective if preceded by S2. Middle tracing: Subthreshold S3 follows every second driving stimulus. S3 becomes effective only if preceded by S2. Lower tracing: Same as above in a single tracing.
The threshold diminishing effect of $S_2$ and its relation to its timing is shown in B of Table 1. Application of $S_2$ at 90 msec following $S_1$, did not alter the level of $T_1$ of $S_3$, irrespective of the strength of $S_2$. However, when $S_2$ was applied somewhat later (100 to 120 msec after $S_1$) it lowered $T_1$ to about half of its previous level (from 4.2 mA to 2.0 mA).

Similar results were obtained in all eight dogs studied. It is to be noted that once $T_{UR}$ was obtained at a given timing of $S_2$ and at a certain strength of $S_2$, further increase of $S_1:S_2$ interval or $S_2$ intensity were not accompanied by further alteration of $T_{UR}$ of $S_3$.

II Normal Conduction

In four dogs with intact conduction system the atria were driven by $S_1$. This stimulus triggered another pacemaker to deliver anodal $S_2$ during the inscription of the QRS complex. The interval between the onset of the QRS and $S_2$ was kept short and similar to that obtained by using certain commercially available pacers. A representative tracing from such an experiment (Fig 3) shows that $S_3$ becomes effective only if it is preceded by $S_2$, which in its present location has, therefore, a threshold reducing effect. In this figure the $S_2$ or $S_3$ stimuli were delivered only following every second QRS complex. It is also to be seen that certain $S_3$ may remain subthreshold even following $S_2$. This is probably due to spontaneous variations in the threshold of excitability, as described earlier from this laboratory.¹⁰

### Table 1—Representative Figures from Two Experiments to Emphasize the Importance of the Intensity (A) and of Timing (B) of $S_2$ in its Threshold Reducing Effect.

<table>
<thead>
<tr>
<th></th>
<th>$S_1$</th>
<th>$S_2$</th>
<th>$S_1:S_2$</th>
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<tbody>
<tr>
<td>A</td>
<td>Interval Intensity</td>
<td>Interval</td>
<td>of $S_2$</td>
<td>of $S_1$</td>
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<td>msc*</td>
<td>mA</td>
<td>msc</td>
<td>without $S_2$</td>
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<td>150</td>
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<td>205</td>
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*The width of the QRS is 150 msec.
**The width of the QRS is 120 msec.

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Discussion

It is a widely accepted phenomenon that application of a stimulus at a certain time within the relative refractory period may cause repetitive firing and fatal arrhythmias.\textsuperscript{10-17} This is described in cases with competition between fixed rate pacemaker and spontaneous cardiac activity as well as in cases with spontaneous R/T phenomenon.\textsuperscript{1,2,7-9,12-16} These observations hold true for stimulus strength far above the threshold of excitability.\textsuperscript{13} Stimuli of lower current levels falling into any part of the absolute or the relative refractory period of the cycle are regarded as ineffective and harmless.\textsuperscript{5-6,11,14} Based on the assumption that stimulation in the absolute refractory period is not accompanied by any untoward effects, noninhibiting standby pacemakers were developed. These are R-triggered pacemakers which deliver electrical stimuli very shortly following spontaneous R waves. It is stated in the description of such pacing methods that “this impulse falls ineffectively within the absolute refractory period and so cannot cause a competing rhythm nor stimulate during the vulnerable period”.\textsuperscript{14}

However, some recent studies indicate that stimuli applied 10 to 40 msec following the onset of QRS, i.e. within the absolute refractory period, may unmask digitalis intoxication by uncovering repetitive ventricular discharge.\textsuperscript{2} Similarly, Castellanos and co-workers\textsuperscript{4} have claimed that “stimuli falling in the so-called refractory period are apparently ineffective. Yet, various investigators have been aware that they need not always be so.”

In a previous study we have shown that premature depolarizations may reduce the threshold of excitability for the next stimulations.\textsuperscript{10} It was also shown that the threshold, at different time intervals within the relative refractory period, changes widely between an upper limit \( (T_c) \) and a lower limit \( (T_i) \). It was the purpose of the present work to define whether electrical stimuli, applied during the absolute refractory period, have any effect on these parameters.

The results described above indicate that the so-called “ineffective stimuli” are in fact effective. This seems to be proved by converting a stimulus with a subthreshold current level to a depolarizing one with the help of such an ineffective stimulation. This may be explained by a threshold reducing effect of \( S_2 \). Indeed, strength-interval relationship of \( S_2 \) following \( S_1 \) illustrates lower \( T_i \) level \( (T_{U,R}) \) for anodal stimulation throughout the relative refractory period when compared to \( T_i \) of \( S_2 \) without previous ineffective \( S_2 \). It was also found that the magnitude of such increased excitability does not depend on the delay and intensity of \( S_2 \)—once a threshold reducing effect was reached. This may point to an all-or-none phenomenon.

In the present study the intervals expressed in msec between \( S_1-S_2-S_3 \) are somewhat misleading. They represent the time elapsed between two stimulation artifacts, but do not necessarily indicate the location of a stimulus within the cardiac cycle. If one takes into account the time lag between the stimulus artifact and the corresponding depolarization, as well as the different widths of the QRS complexes, it is evident that a certain \( S_1-S_2 \) interval may represent various locations of \( S_2 \) in the cardiac cycle. Close inspection of the tracings revealed that the effectiveness of \( S_2 \) is dependent only on its relation to the QRS complex and not on its relation to \( S_1 \). This may explain the marked variations in the timing of \( S_2 \) in the experiments with A-V block and wide ventricular complexes as compared to the narrow QRS of normal conduction.

It may, therefore, be concluded that placement of electrical stimuli during or shortly after the QRS and thus with no generalized depolarization of the heart, may lead to a locally increased excitability which becomes evident during the vulnerable period. Observing such threshold reducing effect under the above conditions may be of practical importance regarding the clinical use of the various types of artificial pacemakers.

ACKNOWLEDGMENT: We wish to express our sincere thanks to Dr. Y. Mahler for his valuable help and criticism.
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In Praise of the Art of Painting

Of all the imaginative works of man, the most appealing, it seems to me, is great painting. Nothing in the other arts offers itself so directly to the mind, or opens up, in such small compass, so many avenues of interest. For painting reveals itself as a whole, not as a succession of parts, it stands before us in all its glory, apprehensible and undisguised, a complete statement of the infinite surmises and adventures of the human spirit. It weds the past to the present and conceives the future; it deals with experiences as old as time, and always, when it is living and useful, in the terms of some special civilization; always casting its materials in the predominant pattern of the period, but tracing into that pattern the individual variations of genius which make the behavior of the race endlessly dramatic and fascinating throughout the ages.