Reentrant ventricular rhythms in the late myocardial infarction period: prevention of reentry by dual stimulation during basic rhythm

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ABSTRACT Stimulation at two ventricular sites during basic rhythm as a means of preventing the induction of ventricular arrhythmias in the postinfarction heart was investigated. Isochronal maps of ventricular epicardial activation from dogs were analyzed 4 days after ligation of the left anterior descending coronary artery. Activation patterns were obtained by use of a computerized data acquisition system recording from 62 sites. Effective refractoriness and conduction time during basic paced rhythm (S1) for each site were summed to construct isochronal maps of recovery time. The patterns of recovery time on the heart were eccentrically layered, with a narrow zone of differentially prolonged recovery time along one border of the infarct. The formation of an arc of functional conduction block after premature stimulation (S2) was correlated with regions of differentially prolonged recovery time (59 ± 30 msec, mean ± SD) between recording sites spaced 5 to 10 mm apart. The recovery time difference between sites that did not block (17 ± 14 msec) was significantly shorter. The spatial distribution of recovery time on the heart could be modified by application of stimuli at two sites during the basic rhythm. Reentry was prevented by appropriate placement of the secondary site in the ischemic zone and the temporal sequencing of the paired stimuli. Stimulation at the secondary site "peeled back" refractoriness in the ischemic zone. Prevention of reentry was a result of either: (1) a shift in the arc of conduction block toward the ischemic zone, (2) a reduction in the extent of the continuous arc, (3) early activation of regions distal to the arc, or (4) a combination of the above. In two dogs, the arc of block was abolished entirely after dual stimulation. This report illustrates the criteria for effective prevention of reentry, applied to a well-described verifiable model of reentrant activation.


THE "FIGURE 8" MODEL of reentry has evolved through a series of investigations that have elucidated a physiologic and anatomic substrate for reentrant ventricular rhythms in the canine postinfarction heart. An arc of functional conduction block, resulting from premature stimulation and slow conduction preceding reactivation, occurs in a layer of electrophysiologically abnormal epicardial tissue overlying the infarct. A recent study has examined the functional physiologic properties of the model. This study showed that refractoriness is spatially distributed on the ventricular surface as eccentrically layered contours that increase monotonically toward the core of the infarct. The results demonstrated a strong correlation between the spatial patterning of refractoriness and the position of arc of functional conduction block. Subsequent reentrant activation is dependent on both the extent of the arc of block and the conduction delay incurred distal to block.

The present report describes a method of preventing the induction of reentry based on the understanding of a well-described, functional model of reentrant activation. We will show that logical application of properly sequenced stimulation at two selected sites during basic rhythm can modify the spatial distribution of recovery of excitability in a way that prevents the induction of reentry. Preliminary reports from this laboratory have shown that dual stimulation can prevent the initiation of reentry. The present report will characterize the mechanism of prevention and identify criteria for optimal dual stimulation.

Methods

Surgical preparation. Experiments were performed on 21 mongrel dogs weighing 15 to 20 kg in which the left anterior
descending coronary artery had been ligated distal to the anterior septal branch. Details of the surgical technique have been reported previously. 

Four days after ligation, each dog was reanesthetized with sodium pentobarbital, 30 mg/kg iv, with supplemental doses as necessary. The dogs were ventilated with room air through a cuffed endotracheal tube via a Harvard Apparatus positive-pressure respirator. Supplemental anesthetic and saline were administered through a catheter placed in the cephalic vein. Electrocardiographic lead II and aortic blood pressure (Statham) were continuously monitored on an Electronics for Medicine DR10 monitor. The heart was exposed through a left thoracotomy. Core temperature and intrathoracic temperature were monitored with two electronic thermometers (Yellow Spring Instruments). A bipolar plunge electrode for control stimulation consisting of two hooked stainless steel wires (enamel coated, 0.005 inch diameter) was inserted into the right ventricle with a 23-gauge hypodermic needle. Additional bipolar stimulation could be delivered at sites on the ventricular surface through silver electrode pairs on a sock electrode array (described below). Programmed electrical stimulation was provided by a Bloom DTU-101 digital stimulator. To slow the sinus rate, a Grass S88 stimulator was used to stimulate the right and left vagosympathetic trunks through two pairs of Teflon-coated silver wire (0.010 inch diameter) with square-wave pulses of 0.1 to 0.5 msec duration at a frequency of 20 Hz at 1 to 10 V.

Isochronal mapping. A sock electrode array was placed on the ventricular surface for simultaneous recording at multiple epicardial sites. The sock electrode array consisted of 62 individually sewn bipolar electrodes constructed from sutured silver wire (0.005 inch diameter) with an interpolar distance of 1 to 2 mm. The electrode arrangement and recording technique have been detailed and reported previously. 

After the surgical preparation, the ribs were approximated and the chest cavity was closed. Once the core temperature had stabilized, programmed stimulation was applied to the control site, which was generally the right ventricular base. In three experiments the control site was located at the midlateral right ventricular free wall. The control stimulation sequence consisted of a train of eight basic driven beats $(S_2, S_2$ or $360$ to $400$ msec) at twice diastolic threshold, followed by a premature stimulus, $S_2$. The premature stimulus was introduced at decreasing coupling intervals, beginning at $260$ msec, until unstimulated ventricular responses were induced. Only those hearts in which a single extrastimulus, $S_2$, initiated spontaneous ventricular rhythms were studied.

Once a reproducible rhythm could be initiated, computer-generated electrode recordings were obtained and used to construct isochronal maps of epicardial activation. Isochrones were delineated by closed contours at $20$ msec intervals beginning with the earliest detected time of activation. A difference in activation time between adjacent recording sites of greater than $40$ msec or electrotonic deflections representing distant activation were considered to represent functional unidirectional conduction block. A continuous line could be drawn through these regions and is defined as an arc of functional conduction block. 

If the resultant isochronal activation maps revealed that the reentrant circuit could be bridged in both space and time on the ventricular epicardial surface, effective refractory periods at each of the $62$ recording sites were determined. The effective refractory periods were measured at twice diastolic threshold after a train of $8$ basic driven beats (the cycle length was equal to the rate used to initiate reentry) by the extrastimulus method. Vagal stimulation was applied during effective refractory measurement when applied during the control stimulation sequence. Refractory measurements were made at $10$ msec increments. This interval is greater than previously reported effects of vagal stimulation on effective refractory periods. The effective refractory period of the premature beat, ERP2, was determined at selected sites in the region of reactivation for the $S_2$, interval, which resulted in an unstimulated reentrant response. ERP2 was measured at twice diastolic threshold after a train of $8$ basic driven beats and two extrastimuli. The coupling period of the first extrastimuli for each site was set equal to the measured response interval of the $S_2$, delivered from the control site. Further details of the refractory period measurement technique have been reported previously. 

Isochronal maps of refractoriness were constructed and delineated by closed contours at $20$ msec intervals.

Dual stimulation. Dual site ventricular stimulation was applied at various sites during the basic driven beats to prevent the initiation of reentry at the same premature interval that resulted in unstimulated responses during the control sequence. The secondary site was located in the ischemic zone, distal to the arc of functional conduction block, as determined from the control $S_2$ activation map. An average of $12$ sites ($12$ $\pm$ $4$, mean $\pm$ $SD$) was tested for each experiment. Simultaneous dual-site stimulation was applied only during the basic driven beats, $S_1$, and the premature stimulus was delivered from the control site. If simultaneous dual-site stimulation failed to prevent reentry, asynchronous dual stimulation was applied. The paired asynchronous pulses were delivered with the ischemic site preexcited with reference to the control site. The ischemic site was increasingly preexcited in $10$ msec increments until either (1) the preexcitation interval exceeded the activation time interval measured during control, or (2) the preexcitation interval exceeded $60$ msec. Computerized electrogram recordings for each protocol were obtained and the $S_1$, stimulus to activation time intervals were computed and tabulated.

Recovery time maps. Recovery time was also determined at each of the $62$ recording sites for each stimulation protocol. Recovery time was defined as the earliest time after a stimulus that a site could be reactivated. Recovery time was computed by the sum of the activation time (stimulus artifact to response during $S_1$) plus the effective refractory period of each site. The basic cycle length remained constant for each stimulation protocol. Therefore, the modified variable in each experiment for determining recovery time was the $S_1$, activation time. In all experiments there was a $1:1$ conduction at each of the recording sites during the basic drive. The resulting recovery time determinations were used to construct isochronal maps of recovery time. The maps were also delineated into closed contours of $20$ msec.

Statistical analysis. The difference in recovery time between adjacent epicardial sites were tabulated for eight hearts. The composite results are summarized in table 2. Recovery time difference between sites that did not block during $S_2$ was 

<table>
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<th>Table 1</th>
<th>Recovery time difference at sites of block vs sites of no block and sites of block vs sites that did not block after dual stimulation</th>
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| 59 ± 30| 17 ± 14                                                                   
| (n = 476)| (n = 77)                                                                 |
| Block control | No block dual stimulation                                                                                                     |
| 38 ± 18| 11 ± 19                                                                   
| (n = 42) |                                                                                                                          |

Values are mean ± SD.

Group A: unpaired Student's t test, $p < .001$.

Group B: paired Student's t test, $p < .001$. 

430
pared with the recovery time differences at sites of block during control with use of unpaired Student's t test. The recovery time values at those sites which blocked during control and not during dual stimulation were also compared. These values were compared with use of paired Student's t test.

The recovery time difference across the control arc of block after each dual-stimulation protocol was compared with control values with use of the paired Student t test. The difference was computed with the subtrahend being the site located towards the normal zone. Unless otherwise indicated, a confidence level of 95% was considered indicative of statistical significance.

**Results**

A total of 21 dogs was studied. In five hearts, S3 stimulation was necessary for the initiation of reentry, in one heart reentry could not be induced by premature stimulation and in two hearts epicardial activation maps of a reentry circuit were unsatisfactory. Effective refractory periods at the recording sites were determined in eight of the 13 dogs in which S2 stimulation resulted in reentrant responses.

Basic mechanism by which dual-site stimulation prevents reentry. The isochronal activation maps shown in figure 1 demonstrate the ability of dual pacing to prevent the initiation of reentry. The isochronal maps are presented as polar projections of the epicardial ventricular surface. The center of the map corresponds to the apex of the heart and the outer perimeter represents the atrioventricular annulus. As shown in the S1 map, the left anterior descending artery is depicted by the dashed line, which originates at the two o'clock position on the map, with the left ventricular surface originating below the line. The surviving epicardial layer, overlying the infarct, is contained within the closed dashed contour. The left anterior descending artery and the outline of the surviving epicardial layer, which orient the position of the heart, are shown only in this first figure.

As shown in the upper portion of figure 1, after an S1 drive at 380 msec, a premature stimulus, S2, delivered from the same site, gave rise to an unstimulated beat, V1. The premature coupling interval was 180 msec. Within 40 msec, the S2 activation wavefront encountered an arc of functional unidirectional con-

**FIGURE 1.** Isochronal activation maps of reentrant activation and the prevention of reentry resulting from dual-site S1 stimulation. The maps shown are polar projections of the ventricular epicardial surface with the atrioventricular anulus at the perimeter and the apex at the center. The left anterior descending artery is shown by the dashed line, with the left ventricular surface originating below the line. The surviving epicardial layer overlying the infarct is contained within the dotted line, shown in the S1 map. Stars denote stimulation sites. Lead II electrocardiograms are shown in the lower right corner. **Top,** Control. Premature stimulation (S1-S2, 180 msec) from a single site induces a single unstimulated beat, V1. **Bottom,** S1 stimulation was delivered from the same control site plus a site located in the ischemic zone. S2 delivered only from the control site at the same coupling interval failed to reenter.
FIGURE 2. Mechanism by which dual stimulation prevents reentry. Selected electrograms traversing the arc of block are shown for the same experiment as in figure 1. Effective refractory periods are shown within the shaded boxes. Expanded views of the S2 activation maps are shown to the right. Top, Control. Site A activated during S2 while site B was refractory and conduction block occurred. Retrograde activation at B arrived at the tail end of refractoriness (ERP2) for site A and reactivation occurred. Bottom, Dual stimulation. S1 activation at site B preceded that at site A. The peeling back of refractoriness at B allowed antegrade conduction during S2. Conduction block occurred between sites B and C. Activation arrived at the distal site, C, 60 msec later and reactivation was impossible.

duction block. The arc is demarcated by the heavy line in the S2 map. Two circulating wavefronts travelled clockwise and counterclockwise around the arc of conduction block, joined distal to the arc and conducted slowly through the ischemic region. The common reentrant wavefront reexcited a region on the proximal border of the arc 180 msec later. The difference in conduction time across the arc, in the region of reactivation, was 120 msec.

In the dual-stimulation mode, a second site was selected and paced simultaneously with the control site during the basic driven beats (S1). The secondary site was located distal to the arc of block shown on the control S2 map. After dual stimulation, the length of the arc of block was reduced and the position of the arc, opposite the control stimulation site, receded toward the core of the infarct. Although the entire epicardial surface was again activated in 180 msec, the maximum difference in activation time across the arc of block was reduced to only 80 msec. The difference in activation time across the arc at the site of reactivation during control was reduced to less than 60 msec. Therefore, reactivation was impossible at any site proximal to the arc of conduction block.

Figure 2 details electrograms from sites that traversed the arc of block during control and dual-site stimulation. Expanded views of the same S2 activation sequences shown in figure 1 are presented in the right portion of figure 2. The response interval for site A during control was equal to the S1-S2 interval of 180 msec. The refractory period at site A was 160 msec. Site B was activated 62 msec after the onset of the S1.
stimulus artifact. Coupled with a refractory period of 190 msec, the expiration of refractoriness, or the recovery of excitability, for site B was 252 msec after S1. S1 activation at site A was 34 msec. This interval added to the S1-S2 interval of 180 msec corresponds to S2 activation at site A 214 msec after S1. Therefore, site B had not recovered excitability from the previous S1 stimulation at the time site A was activated by the S2 wavefront. As a result, unidirectional conduction block occurred between the two sites. The activation wavefront circumvented the arc of block and activated site B 120 msec later. The effective refractory period of S2, ERP2, measured at site A was 125 msec. As shown by the electrograms in figure 2, activation at site B followed upon the expiration of ERP2 for site A. The reentry wavefront was able to reactivate a region proximal to the arc, in the vicinity of site A.

When dual stimulation was applied, the S1 activation sequence was modified such that S1 activation at site B preceded site A by 16 msec. S1 activation at site B was 17 msec, a reduction of 45 msec from control. As a result, the recovery of excitability for site B, relative to the S1 stimulus, was reduced to 207 msec. S1 activation at site A was 33 msec, a reduction of only 1 msec from control. Therefore, dual stimulation shifted the expiration of refractoriness at site B to the leftward in time, relative to site A. The same S1-S2 coupling interval of 180 msec was applied from the control site. Conduction from site A now proceeded antegrade to site B. However, the activation wavefront arrived at site B before recovery of excitability at site C. An arc of block formed between sites B and C. The reentrant wavefront traveled around the arc of block and activated site C 47 msec after activation at site B. This interval was far too short to permit reactivation of site B. Dual stimulation prevented reentry by shifting the arc of conduction block and allowing sites distal to the arc to activate before recovery of excitability proximal to the arc.

Recovery time (S1 activation + effective refractory period) was determined at all sites on the ventricular surface. Figure 3 compares configurational changes in the arc of block with differences in recovery time at several sites during control and dual stimulation. The arcs of block, shown with the recovery time values, are from the same experiment shown in figures 1 and 2. During control, conduction block occurred between sites A and B, D and E, F and G. The difference in recovery time between the three pairs was 58, 72, and 40 msec, respectively. After dual stimulation the difference was 14, 51, and 11 msec, respectively.

After dual stimulation, conduction block did not occur between sites A and B and shifted the arc toward the ischemic core, between sites B and C, where the recovery difference was 60 msec. There was no shift in the arc of block between sites D and E. Since the recovery time difference between sites D and E was sufficiently long during control (72 msec), the 21 msec reduction in recovery time difference to 51 msec induced by dual stimulation did not prevent conduction block. Dual stimulation was able to eliminate conduction block when the recovery differences between adjacent sites was smaller during control, such as seen between sites F and G. The 40 msec recovery time difference between these sites during control was reduced to only 11 msec after dual stimulation. Most of the arc that passed between sites F and G during control disappeared after dual stimulation.

The difference in recovery time between all adjacent sites that did and did not exhibit functional conduction block during control was determined for eight experiments and compared as stated in Methods. The recovery time differences at sites of block that did not block

FIGURE 3. Comparison of recovery time values with configurational changes in the arc of block after dual stimulation. Recovery time values are shown for several sites with the value after dual stimulation in parentheses. The control arc of block is depicted by the heavy solid line and the dashed line represents the arc after dual stimulation. The arcs shown are from the same experiment shown in figures 1 and 2. Dual stimulation resulted in a shift in the arc of block from between sites A and B to B and C. The difference in recovery time before and after dual stimulation between sites A and B was 58 and 14 msec, respectively. The difference in recovery time between sites B and C was 60 msec during dual stimulation. There was no change in the site of block between sites C and D, where the difference in recovery time was 72 and 51 msec before and after dual stimulation. The arc of block that passed between sites F and G was abolished after dual stimulation. The recovery time difference between these sites was reduced from 40 to 11 msec.
during dual stimulation were also determined and compared. The composite results and statistical comparisons are shown in table 1. The recovery time difference at sites of block was 59 ± 30 msec (mean ± SD), which was significantly different from that at sites that did not exhibit conduction block (17 ± 14 msec, p < .001). After application of dual stimulation, 42 of the 476 paired sites that blocked at control conducted without block. The recovery time differences for these sites, 38 ± 18 msec, was less than the mean value for all sites of block. Dual stimulation significantly reduced the recovery time difference of all previously blocked sites to 11 ± 19 msec (p < .001).

**Recovery time maps.** To understand in a global sense the role of nonuniform conduction and refractoriness in the initiation of reentry, isochronal maps of recovery time were constructed. Figure 4 illustrates the construction of the isochronal recovery time maps for the two stimulation modes shown in figures 1 and 2. The effective refractory period of S₁ (RP₁) was added to the S₁ activation interval at each site to generate isochronal recovery maps for the control and dual-stimulation modes. The basic cycle length was identical for both stimulation modes. Since refractoriness is independent of the site or number of sites of stimulation, the refractory maps are identical in both instances. Each isochrone of recovery (RT₁) defines a 20 msec interval when contiguous regions on the heart surface have recovered excitability from the last S₁ stimulus.

The isorefractory map (RP₁) of figure 4 shows a 100 msec dispersion in refractoriness. Two isochronal contours separated adjacent recording sites between the 200 and 240 msec isochrones of RP₁. This region corresponded with the position of the arc opposite the stimulating site, as seen in the control S₂ maps of figures 1 and 2. With the addition of S₁ activation time, the dispersion in recovery time was 180 msec. The upper right panel of figure 4 shows that, during control, a steep gradient of recovery time (RT₁) was present between the normal and ischemic zones. Along this border the recovery time difference between adjacent sites (5 to 10 mm) was 47 ± 16 msec (mean ± SD).

![FIGURE 4. Construction of recovery time maps. Top, Control. S₁ activation times (S₁ stimulus artifact to response) for single-site stimulation were added to the effective refractory periods to determine recovery time maps (RT₁). Bottom, Dual stimulation. After dual stimulation, the ischemic region was activated earlier than control after S₁. ERP map is identical to control. The recovery time map shows a reduced gradient and dispersion of recovery time.](http://circ.ahajournals.org/content/136/7/434)
and corresponded with the position of the arc of functional conduction block shown in figures 1 and 2. The recovery time difference between adjacent sites that did not block was significantly shorter (20 ± 19 msec, mean ± SD) than the sites along the arc. The dispersion in recovery time on the ventricular surface was 200 msec.

The bottom row of figure 4 shows recovery time determination after dual stimulation. During control, the regions of longest refractoriness corresponded approximately with the region of late S1 activation. After application of dual S1 stimulation, this region was activated much earlier and then corresponded with early S1 activation. As a result of dual stimulation, prolonged recovery of excitability in the ischemic zone, due to prolonged refractoriness, was not exacerbated by delayed activation during S1. There was a significant reduction in recovery time difference (30 ± 16 msec) at those sites that blocked during control. The lower right panel of figure 4 shows that there was a reduction in the gradient of recovery time in the region that blocked during control. In addition, the dispersion in recovery time was reduced to 160 msec.

Role of secondary site in the prevention of reentry. Figures 5A and 5B illustrate the criteria for selection of the optimal secondary site. The top row of figure 5A shows the control beats in which reentry was initiated. The three sites chosen for dual stimulation are shown on the S1 map as filled squares. Sites a, b, and c were distal to the arc of block, as revealed by the control S2 map, and were located in regions of prolonged recovery time (greater than 300 msec). The control stimuli were delivered from the right ventricular base for all trials and at the same basic cycle length. The S2 activation map shows that reentry occurred within 200 msec. The S1-S2 coupling interval was 180 msec. The arc of block occurred along a border of markedly graded recovery time, corresponding to a recovery time difference of 78 ± 26 msec. The recovery time difference between those sites that did not block was 16 ± 12 msec. The dispersion in recovery time was 160 msec.

The activation and recovery time maps after dual stimulation at site a, which prevented reentry, are shown in the lower half of figure 5A. Site a was located

**FIGURE 5A.** Effect of secondary site on the prevention of reentry. Three sites (a, b, c) were selected as the secondary sites for simultaneous dual stimulation and are landmarked for reference by the filled squares. **Top,** Control. Sites a to c were distal to the arc during S2. The steep gradient of recovery time (RT1) correlated with the location of the arc in S2. **Bottom,** Dual stimulation at site a prevents reentry. Modification of the recovery time distribution resulted in a reduced arc of block and early activation of sites distal to the arc.
in the last 20 msec isochrone during control S₁. The site was also located near the region that reactivated during control, distal to the arc of block. The S₁ activation map, after dual stimulation, shows that a large portion of the region distal to the arc activated within 40 msec. The resultant recovery time map shows that there was a 40 msec reduction in the maximum recovery time and a 40 msec reduction in the dispersion of recovery time. There was a statistically significant reduction in recovery time difference (60 ± 36 msec) between those sites that blocked during control. The recovery time map shows reduced isochronal crowding and a shift in the border of maximally graded recovery time toward the ischemic core. This was accompanied by a shorter arc of block during S₂. Activation distal to the arc occurred within 160 msec. The maximum difference in conduction time across the arc was less than 120 msec and did not result in a reentrant response.

Figure 5B examines dual stimulation at two other sites, b and c, which failed to prevent reentry. Site b, which was distal to the arc during control, activated during the first 20 msec isochrone of control S₁. After dual stimulation, there was only a slight penetration of the S₁ activation wavefront into the ischemic zone. The reduction in recovery time difference along the control arc of block (68 ± 29 msec) was not statistically significant. The dispersion in recovery time was reduced by only 20 msec from control. Since the spatial distribution of recovery time was only modified slightly, no appreciable change in the arc after S₂ was evident. The S₂ activation wavefront reached the entrance to common reentrant pathway within 80 msec. This interval was 20 msec earlier than control. However, conduction through the retrograde reentrant pathway was sufficiently impaired due to prolonged recovery time distal to the arc. Reactivation occurred within 200 msec, as in control.

Site c was activated during the last isochrone of the control S₁ beat and was distal to the arc of block, yet failed to prevent the initiation of reentry. Site c was located near the entrance to the common reentrant pathway during the control S₂ beat and was distant from the reentrant exit site. During the first 20 msec isochrone of S₁, activation arising from site c engaged
only a small portion of the region with prolonged recovery times. The area distal to the arc, near the reentrant exit, was again activated late after \( S_1 \). Although recovery time was reduced in the vicinity of the secondary site, the maximum isochrone of recovery time was only reduced by 20 msec, to 340 msec. Dual stimulation at site c did not result in any significant reduction in recovery time difference (76 ± 26 msec) at the sites of block. As in the preceding example, activation reached the entrance to the common reentrant pathway within 80 msec. Impaired conduction within the common reentrant pathway and an extensive arc of block provided sufficient delay for reactivation to occur within 180 msec.

**FIGURE 6.** Effect of synchronous excitation of the ischemic zone. Sites of stimulation are landmarked for reference by filled squares in \( S_2 \) and \( RT_1 \) maps. **Top,** Control. Recovery time map shows markedly graded recovery time, with a maximum recovery time of 400 msec at the core of the ischemic zone. Reactivation during \( S_2 \) occurs within 200 msec. **Middle,** Simultaneous dual stimulation. Simultaneous dual stimulation results in early activation of a small portion of the ischemic zone. A shift in the recovery time gradient near the dual site which results in an abolishment of the arc is encountered by the counterclockwise \( S_2 \) wavefront. Reactivation still occurs in 200 msec. **Bottom,** Asynchronous excitation of the ischemic zone. After asynchronous dual stimulation, with a 40 msec delay, activation of the ischemic zone precedes the normal zone. After \( S_2 \), the arc of block shifts toward the secondary site. Reduced recovery time distal to the arc allows early \( S_2 \) activation and reentry is prevented.
Asynchronous excitation of the ischemic zone. Simultaneous dual stimulation was successful in 9 ± 1% of all sites tested (n = 96 sites) in eight hearts. In three hearts, simultaneous dual stimulation was ineffective regardless of the site selected. In these instances, the gradient of refractoriness alone provided a sufficient barrier to conduction. Reentry was initiated regardless of any improvements in recovery time distribution by simultaneous dual stimulation. In these instances, the expiration of refractoriness distal to the arc was shifted further to the left by preexcising the ischemic area. Preexcitation was implemented through asynchronous application of dual S1 stimuli. The ischemic zone was stimulated first. Asynchronous dual stimulation dramatically improved the success rate in preventing reentry. The combination of simultaneous and asynchronous stimulation sites that prevented reentry accounted for a 34 ± 13% success rate.

Figure 6 shows that when dual simultaneous stimulation at a site failed to prevent the initiation of reentry, preexcitation of that site by 40 msec during S1 succeeded in preventing reentry. The top row of maps shows the single site stimulation mode in which an S1-S2 coupling of 180 msec initiated reentry. The position of the arc of conduction block opposite the stimulation site correlated with a steep gradient of recovery time corresponding to a recovery time difference of 80 ± 39 msec. The difference between sites that did not block (23 ± 20 msec) was significantly shorter. Reactivation proximal to the arc of block occurred within 200 msec.

Simultaneous dual stimulation, shown in the middle row of figure 6, failed to prevent the initiation of reentry. The secondary stimulation site was distal to the arc of block as revealed by the control S2 map. The S1 activation map shows that only a small portion of the ischemic zone was activated during the first 20 msec isochrone. The remaining activation sequence for the majority of the heart surface was similar to the control S1 map. As a result, the recovery time map for simultaneous dual stimulation differed little from control. There was a slight and statistically insignificant reduction in the recovery time difference (70 ± 33 msec) along the control arc. The dispersion in recovery time was 180 msec, a reduction of only 20 msec from control. A slight reduction in recovery time in the vicinity of the dual stimulation site enabled the counterclockwise limb of the reentrant wavefront to penetrate a region that had blocked during control. Conduction through this region, however, was sufficiently impaired and the reentrant wavefront reactivated the same region as seen in the control map. Reactivation occurred again within 200 msec.

The lower row of figure 6 shows that reentry was prevented when the secondary site was preexcited by 40 msec. After asynchronous dual stimulation the dispersion in recovery time was reduced to 160 msec. There was a significant reduction in recovery time difference (59 ± 25 msec) from control along the arc of block. A uniform reduction in the spatial distribution of recovery time within the ischemic core can be seen in the lower right map of figure 6. The gradation of recovery time, albeit diminished, was still steep enough to support a reasonably extensive arc of block after S2 activation. Conduction within the normal zone, or 0 to 80 msec during S2, differed little from the two preceding examples. The location of the arc and the degree of slow conduction distal to the arc encountered by the clockwise limb of the activation wavefront were similar to those with the two preceding stimulation modes. This was because those regions were insufficiently preexcited during S1. On the other hand, there was a noticeable shift in the arc, which receded toward the ischemic zone, encountered by the counterclockwise limb of the activation wavefront. This was due to a shift in the recovery time gradient toward the secondary site. As a result of reduced recovery times distal to the arc, the counterclockwise activation wavefront reached the entrance to the reentrant pathway in 80 msec. Regions distal to the arc that had either blocked or conducted slowly in the two preceding examples had recovered earlier and activated before recovery of excitability proximal to the arc. Therefore, reentry was prevented.

Figure 7 illustrates that dual stimulation prevents reentry by differentially reducing recovery time in the ischemic zone. Figure 7 shows the recovery time of selected sites that traverse the arc of block during the three stimulation modes shown in figure 6. Recovery time maps appear in the top row. Expanded views of the S2 activation maps, along with recovery times of selected sites a to e, are shown in the bottom row of the figure. The effective refractory periods of the premature stimulus interval, ERP2, for sites on the proximal border of the arc of block are shown in parentheses. In all three examples, the proximal sites, a, c, and e were activated within 20 msec after recovery of excitability. During control, the difference in recovery time between sites across the arc of block ranged from 64 to 144 msec. Since the proximal sites activated early during S2, the recovery time difference was a sufficient barrier to conduction to support the formation of an arc of functional unidirectional conduction block. The difference in recovery time at the site of reentry (between
d and e) was 134 msec. This interval was greater than ERP$_2$ (120 msec), at the earliest site of reactivation, e. Recovery time difference across the arc was less than ERP$_2$ for those sites that did not correspond to earliest reactivation.

After application of dual simultaneous stimulation, the maximum recovery time difference across the arc was reduced by only 14 msec. The recovery map in the middle column of figure 6 shows that simultaneous dual stimulation did not result in any appreciable modification of recovery time distribution near the site of reentry. The values of recovery time proximal to the arc (sites a, c, and e) were similar to control. The reduction in recovery time distal to the arc was minimal. The difference in recovery time across the arc, between sites d and e, was 121 msec, which was still greater than ERP$_2$ at the site of reentry.

When asynchronous dual-site stimulation was applied with a 40 msec delay interval, the recovery times of the proximal sites (a, c, e,) were similar to control values. However, there was a marked reduction in recovery time distal to the arc. As explained above, asynchronous dual-site stimulation had shifted the gradient of refractoriness such that the lower appendage of the arc receded toward the ischemic zone. The reduction in recovery time distal to the arc of block allowed those regions to activate earlier during S$_2$. Recovery time at site d was reduced by 49 msec from control and activation occurred within 100 msec during S$_2$. The difference in activation time across the arc was no more than 120 msec. The maximum difference in recovery time between any two sites across the arc was 91 msec. This interval was less than the ERP$_2$ for any potential site of reentry on the proximal border of the arc. Although recovery time does not determine when activation occurs, when the maximum recovery time difference across the arc was substantially less than the ERP$_2$ proximal to the arc, reentry was less likely.
FIGURE 8. Abolition of the arc of functional conduction block by dual stimulation. Top, Control. \( S_1 \) activation occurred within 60 msec. A gradient of recovery time between the 190 and 230 msec isochrones supported the formation of an arc of block during \( S_2 \). Bottom, Dual asynchronous stimulation. When the dual ischemic site was preexcited by 40 msec, no two adjacent sites differed in recovery time by more than 20 msec. A zone of graded recovery time that could support functional conduction block was not present. An arc of conduction block did not form.

In all the examples shown previously, dual-site stimulation succeeded in preventing the initiation of reentry by modifying the position and extent of the arc of functional conduction block and/or allowing sites distal to the arc to activate earlier during \( S_2 \). The example shown in figure 8 illustrates a case in which dual stimulation abolished the arc of functional conduction block. The upper row shows an \( S_2 \), at a coupling of 180 msec, which initiated a reentrant rhythm. Reactivation occurred within 180 msec. The control recovery time map shows a border of graded recovery time opposite the stimulation site between the 190 msec and 230 msec isochrones. The difference in recovery time between adjacent sites in the vicinity of block was 27 ± 12 msec. This range was sufficient to support the formation of an arc of conduction block. Values for sites that did not block (13 ± 10 msec) were significantly shorter.

Asynchronous dual stimulation was applied, with the ischemic site preexcited by 40 msec. Although the surface of the heart was activated in 100 msec during \( S_1 \), compared with 80 msec for control, the areas of longest recovery time were activated before activation at the control site. The maximum recovery time was reduced to 270 msec. More importantly, the distribution of recovery time was modified such that the recovery time difference at sites along the control arc was only 13 ± 27 msec. As a result, an arc of block did not form after premature stimulation. The entire ventricular surface was activated within 80 msec.

Discussion

Spatial distribution of recovery time. The results presented in this report demonstrate the value of the spatial distribution of recovery time in understanding both the initiation and prevention of reentry. A border of markedly disparate recovery time was found to correlate with the position of a continuous arc of functional conduction block. The arc of block corresponded with a zone of differentially prolonged recovery time (59 ± 30 msec), which was clearly illustrated by a continuous border of crowded contours in the recovery time maps. The recovery time differences found within these regions were far greater than those in regions where block did not occur.

The contours of recovery time shown on the maps were constructed from 62 epicardial sites, spaced 5 to
Reducing the difference in activation time across the arc of block to a value less than ERP$_2$ proximal to the arc is the hallmark of the protective efficacy of dual stimulation. While it is true that sites may not activate at the time of their recovery interval, reentry is prevented when the difference in recovery time across the arc is less than ERP$_2$ (figure 7). Careful selection of dual stimulation sites that reduce the global dispersion of recovery time may reduce the risk of reentry without necessitating identification of the sites of conduction block and reactivation. In other words, reentry will be less likely if no two sites on the heart differ in recovery interval by more than the shortest ERP$_2$.

Peeling back of refractoriness. Effective dual stimulation required a reduction in the difference in recovery time across the arc of block through a differential reduction in recovery time within the ischemic zone. The differential shift in the expiration time of effective refractoriness has also been termed “peeling back of refractoriness” by Moe et al.\textsuperscript{9} It is important to note that the concept of peeling back of refractoriness has been associated with facilitated conduction.\textsuperscript{9,10} In the present study, conduction did improve in some regions due to earlier recovery of excitability. However, the mechanism of successful dual stimulation also depended on the ability to modify the extent and position of the arc of functional conduction block. In most of the hearts studied, regions distal to the arc recovered excitability before the reentrant wavefront arrived. In these instances, it was the arc of block that provided the additional barrier to conduction. In all the hearts studied, activation arrived at the distal border of the modified arc of block after dual stimulation. A zone of conduction block in the common reentrant pathway was not observed in any experiment, after successful dual stimulation. Therefore, it was the progressive reduction in the excitable gap after dual stimulation that protected the heart against reentry.

Choosing the secondary stimulation site. Differential prolongation of recovery time in the ischemic zone was responsible for conduction block. Since changes in the S$_1$ activation sequence resulted in the prevention of the control reentrant response and since prolonged refractoriness within the ischemic zone is an important factor in the formation of an arc of conduction block, the most appropriate secondary site should be within the ischemic zone. In all instances that resulted in the prevention of reentry, the secondary site was distal to the arc of block that formed during the control S$_2$ beat. The secondary site should be in an area of long refractoriness, which activates late during the basic driven beat. However, the site of longest recovery time may not be
the site of choice. Regions of markedly prolonged recovery time may block during the premature beat, as shown in figure 6. These regions are unrelated to the reentrant pathway. Therefore, earlier recovery of those regions by dual stimulation may be of little value.

Location of the secondary stimulation site in relation to the reentrant pathway is also critical. As illustrated in figures 5A and 5B, the secondary site should be located near the terminal portion of the common reentrant wavefront. Activation emanating from the secondary site must engage a reasonable mass of tissue in the ischemic zone before activation arrives from the control site. Stimulation at the secondary site must ensure both a reduction in recovery time difference across the arc and early recovery of regions encountered by the distal reentrant wavefront.

Properly applied dual stimulation differentially peels back recovery time in the ischemic zone. Figure 7 illustrates that preexcitation of the ischemic zone can reduce the difference in recovery time with little effect on recovery time values within the normal zone. Choosing the secondary site in a normal zone, proximal to the arc, can result in a differential reduction of recovery time in the normal zone. This may result in enhanced conduction on the proximal border, along with increased recovery time dispersion across the arc of block. The arc will be enhanced if the premature wavefront encounters areas of graded recovery time at an earlier interval. Without a reduction in recovery time in the ischemic zone the difference in activation time across the arc will increase and reentry will remain inducible. This converse situation is, in effect, a peeling of refractoriness in the zone of potential reactivation. Similar observations have been made of supraventricular reentrant rhythms involving concealed accessory pathways. When the basic beat is delivered close to the reentrant pathway in a region of short refractoriness, the tachycardia zone is widened.11

Asynchronous excitation of the ischemic site. If dual simultaneous stimulation fails to prevent the initiation of reentry, preexcitation of the ischemic zone may succeed. Asynchronous dual stimulation was successful at a greater number of sites (34% vs 9%) than was simultaneous dual stimulation. However, it should be pointed out that the number of sites tested in each heart was limited by the number of available positions on the sock electrode array and that all available sites distal to the arc were included in the determination.

In the same fashion that dual simultaneous stimulation peeled back refractoriness in the ischemic zone, asynchronous excitation of the ischemic zone further peeled back refractoriness. Preexcitation can conceivably reduce recovery time to a value that is less than the refractory period of the site. This may be appropriate in cases in which the recovery time gradient is so extreme that dual simultaneous stimulation from any site fails to prevent reentry. When a less-than-optimal site resulted in failure to prevent reentry after dual simultaneous stimulation, success was achieved by increasing the degree of preexcitation.

Asynchronous excitation of the ischemic zone can dramatically reduce the dispersion of recovery time. This may be necessary in depressed myocardium where conduction is impaired or if the critical zone of reentry is too large to be sufficiently preexcited. The example shown in figure 6 demonstrates this situation. After simultaneous dual stimulation, the activation wavefront travels slowly across the ischemic zone. Although conduction is impaired after asynchronous dual stimulation, the ischemic zone is activated early relative to the normal zone.

Asynchronous stimulation has been used for the treatment of supraventricular reentrant tachyarrhythmias in humans.12 Permanent atrioventricular sequential pacemakers have been successful in treating atrioventricular nodal reentrant tachycardias and those involving accessory pathways. The proposed mechanism of the technique is that preexcitation of a limb of the circuit will render it refractory to the returning impulse. In reentry of this type the critical zone may be situated such that preexcitation ensures that recovery time in the entire zone is sufficiently reduced. Conduction block still occurs, but without the presence of alternate reentrant exits. Success in these cases is possible with less attention paid to location of the stimulating sites. This differs from the model of reentrant activation studied in the present report; in this model, suppression of one reentrant pathway does not preclude the appearance of an alternate pathway.5, 13

Preexcitation has been used in a similar fashion to either reduce or abolish the window of premature coupling that induced ventricular macroreentry.14, 15 Increasing the degree of atrioventricular delay forces preexcitation of the critical zone for reentry. After premature ventricular stimulation, the window of reentry is reduced due to enhanced conduction in the His-Purkinje system. The mechanism of prevention may differ from that of the present report since Mahmud et al.14, 15 noted a fixed site of conduction block in most instances.

Clinical implications. Prevention of the initiation of reentrant tachyarrhythmias by appropriate electrical stimulation is a more appealing concept than current antitachycardia stimulation techniques.16, 17 One pos-
possible method has been reported. The authors showed that a subthreshold preconditioning stimulus can inhibit capture of a subsequent premature stimulus. As a result, there is an increase in the effective refractory period of the preconditioned tissue. This differs from results of the present study in which dual stimulation prevented reentry by allowing a region of depressed myocardium to recover excitability earlier.

Synchronous pacing at multiple sites has been suggested as a method for reducing the possibility of reentry based on the premise that synchronous activation of the heart should reduce the dispersion of recovery of excitability and thus the probability that reentry will occur. The present study demonstrated that proper placement and temporal sequencing of only two stimuli effectively reduced the dispersion of recovery of excitability.

While it is recognized that the mechanism of ventricular reentrant rhythms in man may be disparate recovery of excitability in the heart, the precise role of dispersion recovery, either temporal or spatial, has not been adequately described. However, selective application of a second pacing lead for dual S1 stimulation may protect the heart against the possibility of subsequent reentrant activation due to disparate recovery of excitability during the premature response. This technique could potentially be applied in those patients who are pacemaker dependent and who also have recurrent ventricular tachyarrhythmias initiated by spontaneous or induced premature beats. Although our study only considered premature stimuli delivered from the control site, the ideal dual stimulation arrangement should prevent reentry when premature beats arise from any site in the heart. This will be examined in a future study.

In the same way that dual S1 stimulation reduced the spatial dispersion of recovery, dual stimulation during a sensed premature beat may also prove to be helpful in preventing reentry. It is possible to envision a strategically positioned electrode that senses a spontaneous premature beat, which may initiate a reentrant tachyarrhythmia, and soon thereafter stimulate the underlying myocardial zone. This dual premature stimulation can possibly prevent the perpetuation of reentry and have an even wider application than dual S1 pacing.

In conclusion, dual ventricular stimulation is a potentially valuable method for the prevention of reentrant tachyarrhythmias. Electrical treatment of cardiac arrhythmias can be both reliable and effective when based on a well-characterized model of cardiac activation.

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