Synchronized Repolarization After Defibrillation Shocks
A Possible Component of the Defibrillation Process Demonstrated by Optical Recordings in Rabbit Heart

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Background. It is currently believed that defibrillation shocks act primarily by stimulating excitable myocardium to abolish wave fronts. Recent studies have shown that shocks applied during pacing not only stimulate excitable myocardium but also prolong the depolarization and refractoriness of myocardium already in a depolarized state. This study investigates the effects of shocks on fibrillation action potentials.

Methods and Results. Recordings of membrane action potentials free of shock artifact were obtained using the voltage-sensitive dye WW781 during defibrillation of isolated rabbit hearts. These records showed that the shocks caused an additional phase of depolarization beginning with an initial rapid depolarization of the optical signal followed by a slow phase of repolarization. This occurred throughout all phases of the fibrillation action potential from just after completion of the upstroke to a time of near maximal repolarization. Defibrillation shocks, however, had the additional effect of causing the myocardium to repolarize at a constant time after the shock regardless of its prior electrical activity—the constant repolarization time response. This effect was not dependent on the presence of D600 (methoxyverapamil) or continuous coronary perfusion. It was accompanied by a similar constancy in the return of myocardial excitability. Recordings taken from multiple adjacent recording sites also showed a constant repolarization time among them.

Conclusions. A simple model of reentry is used to illustrate how the constant repolarization response, in addition to wave front termination and refractoriness extension, could play a role in the successful termination of fibrillation by electrical shock. (Circulation 1992;85:1865–1878)

Key Words • repolarization • dye, voltage-sensitive • defibrillation • fibrillation, ventricular

Electrical defibrillation has long been used to terminate ventricular fibrillation; this technique, as accomplished by automatic, implantable devices, is now recognized as one of the most important means for the prevention of cardiac death. Despite the critical role this technique plays, it is not yet known how electrical shocks terminate ventricular fibrillation. Implicit to all current theories is the assumption that the multiple wave fronts causing fibrillation are abolished during defibrillation, a process based on the belief that defibrillation shocks act as stimulating agents. Gurvich and Yuniev proposed that defibrillation shocks stimulate the ventricle and abolish fibrillation wave fronts in the same manner that induced extrasystoles abolish reentry in rings of myocardial tissue. Because it has been found that both pacing and defibrillation thresholds exhibited the same hyperbolic time and strength dependence, it is believed that defibrillation shocks should be considered a form of mass tissue stimulation similar to pacing stimuli but of higher intensity because of the larger mass of ventricle to be excited. Ideker and coworkers recently proposed that defibrillation shocks are also capable of exciting graded responses as well as all-or-none action potentials. Another recent study indicated that the extension of refractoriness by defibrillation shocks may be due to the production of a graded response, which, as shown in studies of cell aggregates, prolongs the time the myocardium remains depolarized. Like pacing stimuli, defibrillation shocks are thought to have no effect on absolutely refractory myocardium but only to excite myocardium after the recovery of excitability.

Defibrillation is challenging to understand because of the complexity of fibrillation and the difficulties in obtaining electrical recordings of cardiac electrical activity during and after the application of high-voltage shocks. Special electrodes and electronic instrumentation have permitted electrographic recording in experiments studying the effects of high-voltage shocks but these techniques cannot be used to record electrical activity during the shock or for several milliseconds afterward. However, when combined with a computerized mapping system, these techniques have yielded valuable insights into the defibrillation process. Although cardiac mapping permits studies of impulse

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propagation, it is unable to provide information about the cardiac action potentials underlying this activity, information that may be important to understand defibrillation mechanisms. The microelectrode technique has been used to investigate the damaging effects of high-voltage shocks applied to excised myocardium or myocardial cultures, preparations not capable of fibrillation. Recently, a “floating” microelectrode has been used to record action potentials during the application of high-voltage stimuli in the open-chest dog during a paced rhythm. To circumvent the problems of shock voltage artifact and to obtain membrane action potential recordings in an intact heart during defibrillation, the author developed a technique of optical recording using fiber optics. This approach uses a voltage-sensitive dye to transduce the cardiac membrane potential into a fluorescent emission and fiber optics to acquire these optical signals, thus permitting action potentials to be recorded without interference by the large interstitial electrical field produced by defibrillation shock.

Using this technique, it was previously reported that defibrillation shocks not only stimulated normal action potentials but also had a marked effect on the repolarization of myocardium by causing an additional period of depolarization that effectively prolonged the action potential duration and the effective refractory period. This phenomenon was observed during steady pacing of the ventricle at times when the myocardium is ordinarily considered to be absolutely refractory, and it was proposed that it might also occur during defibrillation. The present study demonstrates not only that defibrillating shocks produce an additional period of depolarization during repolarization of the action potential in fibrillation, but also that it causes the myocardium to repolarize synchronously after a shock. This behavior is called the constant repolarization time (RT) phenomenon, and it is proposed that it, along with other processes, plays an important role in the defibrillation process. These results have been presented in preliminary form.

**Methods**

**Experimental Preparation**

The effects of defibrillation shocks on action potentials were investigated in hearts of 23 New Zealand White rabbits (weight, 4–5 kg). Rabbis were intravenously injected with pentobarbital 40–50 mg/kg body wt and 5,000 units of heparin. The hearts were removed through a midsternal incision and immersed in cold Tyrode’s solution. They were then mounted on a Langendorff apparatus, and the coronary system was continuously perfused via a cannula in the aortic root with Tyrode’s solution under a pressure head of 53 mm Hg. The coronary and cavitary blood was first flushed out after the heart was connected to the perfusion system. The Tyrode’s solution consisted of the following (mM): NaCl 130, NaHCO3 24.2, KCl 4, CaCl2 1.8, MgCl2 0.6, NaH2PO4 1.2, and dextrose 11.1. Solutions were continuously gassed with a 95% O2/5% CO2 mixture, giving a pH of 7.35–7.40. Solution temperature was controlled with a thermostatic water bath, and the left ventricular endocardial temperature was monitored by a thermistor and maintained in the range of 36–38°C. During perfusion of the first nine hearts, the coronary effluent was collected, filtered, and returned to the perfusion reservoir. A total volume of approximately 1.6–2 l of Tyrode’s solution was continuously recirculated throughout these experiments. In the last 14 hearts, the coronary effluent was discarded, and fresh Tyrode’s solution was added to the perfusion system. This latter perfusion method did not produce any noticeable differences in the behavior of the hearts but simplified the experimental procedure. The left ventricle was drained through tubing inserted through the mitral valve. All hearts were weighed at the end of the experiment. Hearts used in this study weighed an average of 14±2.4 g, with a range of 10.1–17.8 g.

**Experimental Protocol**

The experimental setup, fiber-optic recording system, and defibrillation apparatus used in this study were identical to those described in an earlier study of the effects of shocks applied during pacing. A voltage-sensitive dye, WW781, was used to optically record action potentials from the epicardial surface of the left and right ventricles. This dye was present in the Tyrode’s solution at a concentration of 1.3–2.6 μM. The optical recordings were obtained using a fiber-optic pickup placed in contact with the epicardial surface. This pickup sensed the aggregate electrical activity of a population of cells within a volume several hundred micrometers deep and approximately 700 μm in diameter. An “electrocardiogram” was recorded between an electrode on the aortic root and an electrode within the right ventricular cavity.

Defibrillation shocks were delivered through a pair of stainless steel mesh electrodes applied to the base and apex of the heart. Defibrillation shocks were generated by a Model 2326 Medtronic high-energy stimulator. At the start of each experiment, the defibrillation threshold (DFT) of the heart was determined. Fibrillation was initiated by rapid pacing (25 Hz, 1–4-second train duration), and a defibrillation shock was applied 30 seconds after fibrillation induction. If the shock failed to defibrillate, the same strength shock was reapplied or the next highest strength was tested. Successive episodes of fibrillation and defibrillation were repeated until the lowest shock strength capable of reliably defibrillating on the first attempt was found. The criterion for reliable defibrillation was three consecutive defibrillations on the first attempt. The standard Bournand22 defibrillation protocol was not used in this study because the shock generator could not produce the necessary gradations in shock strength. Three minutes were allowed to elapse between attempts. Coronary perfusion was maintained throughout fibrillation except in a series of experiments in which it was desired to produce ischemia by turning off the coronary flow (see “Results”).

The experimental protocol involved recording optical action potentials from the epicardium of the left or right ventricle during the application of defibrillation shocks. Each optical recording typically encompassed several fibrillation action potentials preceding the shock followed by the shock response. The return of cardiac excitability after the shock at the optical recording site was determined by using stimuli applied through platinum bipolar electrodes flanking the optical pickup. These stimuli were 2 msec in duration and set to eight times the diastolic pacing threshold. The optical record-
ing was used to monitor the effect of these extrastimuli on the membrane voltage to see whether they were able to excite a local action potential. The coupling intervals (CIs) of these stimuli with respect to the shock were changed in 5-msec steps.

Although cardiac contraction was greatly diminished during fibrillation, it was easiest to obtain good recordings when contractility was further suppressed by the addition of D600 (methoxyverapamil, Sigma Chemical Co.). This agent was used in most experiments and was present in the perfusate at a concentration of 2 μM. In addition to suppressing contraction, D600 also increased the coronary flow of Tyrode’s solution. Optical recordings obtained in seven hearts not treated by D600 were compared with those taken in the presence of D600, and, as will be described later, no qualitative differences were found.

Data Analysis

The optical calibration bars shown in the figures in this article indicate a 1% change in the optical signal with respect to the background fluorescence level. The optical signal cannot be interpreted to give either a direct or relative indication of transmembrane voltage. The height of the upstroke as a percentage of the background fluorescence varies from recording site to recording site and with time at the same site. This is because of nonuniform staining by the dye, dye washout, and bleaching of the dye by the laser light.

Figure 1 shows an example of the recordings acquired during a typical defibrillation episode and is used to describe the measurements made in this study. The “electrocardiogram” (trace a) shows the disorganized electrical activity characteristic of ventricular fibrillation. A defibrillation threshold–strength shock promptly overloaded the amplification system, and electrode polarization artifacts caused the amplifier to swing between its positive and negative limits long after the shock. (It must be noted that these shock artifacts were exacerbated by the placement of the recording electrodes. Closely spaced bipolar electrodes would show recovery within tens of milliseconds after the shock.) The time courses of the truncated exponential shock voltage (V) and current (I) waveforms are shown in the inset below trace a. Trace b shows four consecutive action potentials recorded immediately before the defibrillation shock was applied shortly after the fourth action potential upstroke. These action potentials varied in height and duration and were typical of microelectrode recordings taken during fibrillation.23-25 The shock CI was measured as the time from the midpoint of the action potential upstroke immediately preceding the shock to the onset of the shock. The shock caused a prompt upward deflection on the optical trace that led to a prolonged depolarization of the membrane that smoothly repolarized back to resting potential. The focus of this study was on the effects of the shocks on the time course of action potential repolarization during defibrillation. The RT was measured as the time difference between the onset of the shock until the moment of complete repolarization. Total depolarization time (TDT) was the time from the midpoint of the upstroke preceding the shock to the moment of complete repolarization after the shock.

The figures in this article were prepared by converting the acquired data into a format acceptable to a graphics software package (Chart by Zenographics). This software was used to create and label figures portraying optical traces and was also used to compose plots of the numerical data.

Results

Characteristics of Defibrillation in Rabbit Heart

Figure 2 is representative of recordings consistently obtained throughout this series of experiments. It shows

FIGURE 1. Electrical and optical recordings obtained during a typical defibrillation episode and illustration of how shock coupling interval (CI), repolarization time (RT), and total depolarization time (TDT) were measured. Trace a is the “electrocardiogram”; calibration bar to its left shows 15 mV. Shock time and duration are shown by the black bar labeled “shock” under trace b. Inset between traces a and b shows time course of shock voltage (V, left side) and current (I, right side) waveforms at an expanded time scale. Time calibration bar indicates 5 msec; shock voltage and current calibration bars are 100 V and 2 A, respectively. Trace b is the optical recording showing fibrillation action potentials and response to shock. Upstrokes of the four action potentials preceding shock are indicated by arrowheads numbered 1–4. A large depolarizing deflection was registered at the moment of shock (shock response). Shock CI is taken as time from midpoint of preshock upstroke to onset of shock. RT is the time from onset of shock to moment of complete repolarization after shock. TDT is the time from upstroke to complete repolarization and is computed from the sum of the CI and RT. Shock CI was 33 msec, RT was 79 msec, and resulting TDT was 112 msec. Optical calibration bar for trace b indicates 1% change in fluorescence. Defibrillation threshold and shock were both 1.0 J. D600 was not present in the perfusate.
optical recordings during fibrillation induction by rapid pacing and subsequent defibrillation attempts with shocks of increasing strength. Trace a shows fibrillation induction by 1 second of rapid stimulation (40-msec cycle length). The left part of the trace shows a normal action potential caused by excitation by the first stimulus of the train. A second action potential was stimulated shortly after repolarization of the first action potential. This second action potential did not fully repolarize before a third action potential was stimulated. Subsequent action potentials arose from depolarized membrane potentials and, as stimulation continued, action potential amplitude diminished. This pattern of action potential generation continued after the last stimulus as the ventricle underwent rapid, repetitive activation characteristic of ventricular fibrillation.\(^{23}\) The optical recordings show that the membrane action potentials accompanying fibrillation were rapid and varied in height, CI, and duration. Trace b shows the result of a defibrillating attempt with a 0.05-J shock applied 16 seconds after fibrillation induction. The time of the shock is indicated by the black arrowhead placed under trace b, and it is seen that a minute deflection is simultaneously registered on the optical trace. Traces c–e show other unsuccessful defibrillation attempts resulting from application of 0.1-, 0.5-, and 1.0-J shocks. Trace f shows that a 2.0-J shock applied 63 seconds after fibrillation induction was able to defibrillate the heart.

The average defibrillation threshold found in this study was 0.062±0.033 J per gram heart. This is 22% higher than the defibrillation threshold of 0.051±0.026 J/g found for the in situ canine heart in a study using combinations of atrial and ventricular apex defibrillation electrodes.\(^{26}\) This difference may be due to the different defibrillation protocols used in these studies. However, the fact that the rabbit heart exhibited a defibrillation threshold in this and other studies\(^{17,27,28}\) indicates that it was not on the verge of spontaneous defibrillation despite its small mass.\(^{29}\)

**Defibrillation Shocks Cause Stimulation of Repolarized Myocardial Cells and Additional Depolarization of Depolarized Myocardial Cells**

In a previous study, it was shown that defibrillation shocks prolonged the depolarized state and effective refractory period of paced action potentials.\(^{17}\) For this effect to be considered as a possible mechanism for defibrillation, it is necessary to show that it also occurs when shocks are applied during fibrillation. Figure 3 shows optical recordings obtained from a single site during 24 successive and successful defibrillation episodes with shocks 1.4×DFT and is representative of

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**FIGURE 2.** Optical recordings obtained during fibrillation initiation by rapid pacing and subsequent defibrillation attempts by progressively stronger shocks. Trace a shows onset of rapid pacing (stimuli at times indicated by arrows) followed by development of fibrillation. Traces b–f show optical traces during application of shocks (at times indicated by arrowheads under traces) having 0.05-, 0.1-, 0.5-, 1.0-, and 2.0-J strength, respectively. Shocks in traces b–f were delivered at 16, 27, 39, 50, and 63 seconds after fibrillation induction shown in trace a. Trace f shows successful defibrillation. All optical calibration bars represent 1% change in fluorescence.

**FIGURE 3.** Optical recordings of 24 successive defibrillation episodes. Times of shocks are indicated by vertical dotted lines drawn through each column of six traces. Optical calibration bars on each trace show size of 1% fluorescence change. Shock strength was 1.4×defibrillation threshold (1.25 J). See “Results” for discussion.
results obtained from the 23 hearts used in this study. Defibrillation shocks were delivered at a fixed time, 30 seconds after fibrillation induction, but, because of the disorganized nature of ventricular activation during fibrillation, they occurred at random times with respect to the beginning of any ongoing action potential. In all cases, the shock gave rise to a prompt depolarizing deflection that rose above the level of the preceding action potential upstrokes. This was true whether the shock came late in the repolarization phase of the ongoing action potential such as in traces b, d, i, j, k, or q or soon after the upstroke of an action potential such as in traces a, h, n, p, r, s, t, u, or w. In 11 of the 24 defibrillation episodes (traces c, e, i, l, m, n, o, p, r, v, and x), the membrane repolarized to a steady, quiescent level after the shock-induced depolarization, indicating prompt termination of fibrillation. The remaining traces (a, b, d, f, g, h, j, k, q, s, t, u, and w) show an upstroke that arose before or shortly after complete repolarization of the shock-induced depolarization, after which fibrillation terminated. These action potentials could be due to the ectopic activity after defibrillation shocks before eventual resumption of a normal rhythm.11,12,30

In the examples in Figure 3, in which shocks came late in repolarization (traces b, d, i, j, k, and q), it is presumed that the shock stimulated an action potential upstroke because the myocardium was nearly repolarized and thus its inward sodium current system should have largely recovered from depolarization-induced inactivation. The prompt shock responses had a large amplitude and rose above the levels attained by the upstrokes of the previous action potentials. The larger size of the shock-induced depolarization could be due to the greater stimulating power of the defibrillation shock relative to that of the fibrillation wave fronts. These continuous (i.e., unaffected by shock artifact) recordings directly demonstrate that defibrillating shocks applied to a fibrillating heart act as excitatory stimuli.

A different situation is represented by the responses to shocks applied shortly after the action potential upstroke (traces a, h, n, p, r, s, t, u, or w). At these times, the membrane is depolarized, and the inward sodium current system responsible for the action potential upstroke should be inactivated.31 Despite this, the shocks gave rise to responses that were similar to those evoked in much more repolarized myocardium (described above). The most significant difference is that the prompt shock-induced depolarizations were smaller in magnitude than those of the previous group, but, because of their higher, more positive take-off potentials, attained similar levels of depolarization. These shocks caused an extended period of depolarization during the action potential, the net effect of which was to prolong the duration of depolarization normally experienced by the fibrillation action potentials.

The effects of shocks on the ventricular action potential during fibrillation are shown in detail in Figure 4, which also compares these effects with the effects of shocks on action potentials during steady pacing at a 300-msec cycle length. Seven of the traces from Figure 3 are reproduced on the left side of the figure, and seven recordings obtained from the same site during steady pacing are shown on the right side. The same shock strength was used in both sets of recordings (1.4 × DFT). Traces a–f in Figure 4 correspond to traces b, w, u, z, o, i, and d, respectively, in Figure 3. In traces a–d, dashed, curved lines derived from the repolarization phase of the preceding action potential are used to indicate the likely RT course had the shock not been applied. The traces are arranged so that the shock CI increases from top to bottom. In trace a, the shock comes just 1.4 msec after the upstroke, and so the shock response blends into the upstroke. When the dashed curve is compared with the actual waveform that arose as a result of the shock, it is apparent that the shock not only depolarized the membrane potential positive to the level of the optical action potential before the shock but also prolonged the period of depolarization beyond that usually associated with the fibrillation action potential. Traces b, c, and d, in which shocks also came early after the upstroke, show similar results; the shocked action potential remained in the depolarized state longer than

**Figure 4.** Optical recordings show comparison of shock responses obtained at the same site during fibrillation and pacing. Traces b, w, u, z, o, i, and d from Figure 3 are reproduced here as traces a–g (fibrillation). Traces h–n (pacing) were recorded at same site during application of shocks while pacing the ventricle at 300-msec cycle length. In all traces, shock times and durations are indicated by thick black bars underlying traces; filled arrowheads indicate upstroke immediately preceding shock. Open arrowheads in traces a–d mark dashed curves showing likely time course of repolarization had the shock not been applied. Curves were copied from the preceding action potential. In traces h–l, dashed curves, indicated by open arrowheads, show repolarization phase derived from the preceding unshocked action potential. Vertical dashed lines running through traces a–g and h–n indicate earliest repolarization time. Optical calibration bars on each trace show size of 1% fluorescence change. Shocks were 1.25 J in both sets of traces.
the fibrillating action potential. In succeeding traces, the shock arrived later and later in repolarization until the shock apparently excited an action potential in traces f and g. It was always found that shocks of defibrillation threshold strength or higher caused prolongation of the depolarization phase of the action potential. The amount of prolongation increased as the shock CI increased.

The shock CI dependence of the additional depolarization caused by the shock is similar to that seen during pacing. Traces h–n show responses to shocks applied during a paced rhythm (300-msec basic cycle length). The shock CI increases from top trace to bottom trace, and the action potentials are offset in time so that the shock appears at the same point in each figure. The dashed curves in traces h–l are the repolarization phases of unshocked action potentials. The asterisk on trace m marks the upstroke of a spontaneous extrasystole that arose after repolarization of the shocked action potential. The shocks in traces h–k caused an additional depolarization that led the action potential to repolarize later than the normal. The delay of repolarization of paced action potentials, as indicated by the separation between the trace and the dashed curve, also increased with increasing CI. Shocks applied at the latest two CIs, traces m and n, caused stimulation of a new action potential. These data clearly demonstrate that the prolongation of the depolarization phase of the action potential by shocks occurs during pacing and fibrillation.

**Defibrillation Shocks Cause a Constant Postshock RT**

Figure 4 also shows an unexpected result that was consistently found in all experiments. The time for repolarization after the shock was always the same among the recordings at each site, no matter when the shock was delivered, in relation to the action potential upstroke. For example, repolarization occurred at the same time after the shock in all of the 24 episodes shown in Figure 3. The vertical dashed line running through traces a–g in Figure 4 is positioned 100 msec after the shock and intersects all of the traces just as they fully repolarize. This constancy is surprising because each fibrillation episode had a unique history, and because the shocks arrived over a wide range of CIs with respect to the previous action potential. The ability of the defibrillation shock to cause these consistent RT courses is called the constant RT phenomenon. This differs from the case in which shocks were applied during the paced rhythm as demonstrated by the vertical dashed line running through traces h–n. This line is positioned 122 msec after the shock and intersects traces i, j, k, and l just as they repolarize. This line also intersects traces h, m, and n before these traces show full repolarization and therefore indicates an inconstant postshock RT.

The two sets of optical traces shown in Figure 4 are superimposed on each other in Figure 5 to compare the postshock RT courses. The top half of the figure shows recordings obtained during pacing and the bottom shows superimposed recordings obtained during fibrillation. In the case of the paced rhythm, the shock caused responses that repolarized at times over a range of 122–155 msec after the shock. The longest RT was shown by trace n (in Figure 4), in which the shock stimulated an action potential. The four shortest RTs were from traces i, j, k, and l in Figure 4, in which the shock came during the middle plateau of the phase. Traces h and m registered a medium RT, the shock in these cases arriving just after the upstroke and just before complete repolarization. The shock responses of traces h and n achieved nearly the same peak amplitude, yet repolarized from these points at different times. In contrast, the high degree of overlap in the terminal portions of the seven defibrillation episodes (bottom of Figure 5) indicates a nearly constant postshock RT. Considering the erratic and nonuniform electrical activation during fibrillation, this consistency of the shock responses is striking. The indicated RT of 100 msec was based on the average RT of 99.7±2.3 msec (n=24) found for all traces shown in Figure 3.

Figure 6 summarizes the effects of shocks on the action potentials from the experiments illustrated in Figure 4 by plotting the dependence of TDT and RT on the shock CI for defibrillation episodes (panel A) and for shocks applied during pacing (panel B). In panels A
FIGURE 6. Plots. Panel A plots the dependence of total depolarization time (TDT) and repolarization time (RT) on the shock coupling interval (CI) during defibrillation. Data points were obtained from the 24 defibrillation episodes shown in Figure 3. Solid line is drawn through RT data points (filled circles). Seven RT data points are labeled by the letter of the corresponding optical trace shown in Figure 4. RTs for all 24 defibrillation episodes clustered around a fixed value of 99.7 ± 2.3 msec; this indicates that constancy indicated in Figure 4 is representative of the remaining defibrillation episodes. Dashed line is drawn through TDT data points (unfilled circles). Panel B plots the dependence of TDT and RT on the shock CI during pacing at 300-msec pacing cycle length. Data were obtained from recordings taken from the same site as those used in panel A with the same shock strength. Seven RT data points are labeled by the letter of the corresponding optical trace shown in Figure 4. Solid line is drawn through RT data points (filled circles); dashed line is drawn through TDT data points (unfilled circles).

and B, the TDT data points (left axis) and RT data points (right axis) are plotted; RT data points corresponding to the optical tracings in Figure 4 are pointed out. In panel A (fibrillation), a solid horizontal line is drawn through the RT data points at the level of 99.7 msec on the right axis, showing the constant RT. The dashed line, fitted to the TDT data points, shows a positive, monotonic dependence of TDT on shock CI. The shortest TDT, obtained at the shortest shock CI, was longer than the average ventricular fibrillation cycle length in this experiment, taken as the time between successive upstrokes, of 86.9 ± 5.3 msec (n = 52). Because the rapid activation rate in ventricular fibrillation prevented the action potential from fully repolarizing, the average ventricular fibrillation cycle length was slightly less than the action potential duration that would result when full repolarization occurred. Panel B of Figure 6 summarizes the finding demonstrated in Figure 4 that the postshock RT during pacing depends on the shock CI. The solid line drawn through the data points in this plot trace out a U-shaped dependence that has its maxima at late and early CIs, differing markedly from the constant RT seen during defibrillation. The TDT during pacing showed a positive and monotonic dependence on the shock CI just like that demonstrated in an earlier report. This dependence of TDT is similar to that seen during fibrillation (Figure 6A) and is due to the additional depolarization caused by the shock-induced depolarization; thus, although the effects of shocks on the RT when applied during pacing versus fibrillation differ, it is seen that in both circumstances, the shocks give rise to similar responses on the optical recordings, and they both show the same progressive increase in TDT with shock CI.

Figure 7 shows plots of TDT and RT dependence on shock CI obtained in experiments on six other hearts. Like the plot shown in Figure 6, the shocks 1.0 × DFT in these six examples caused a constant RT and a positive, monotonic dependence of the TDT on the shock CI. A constant postshock RT was found at all of the epicardial recording sites in the 23 rabbit hearts examined in this study. Because endocardial and septal sites were not examined in this study, it is not known whether the constant RT always occurred in these areas. It is possible that the effective shock strength in these deeper structures may not have been sufficient to elicit the constant RT response during defibrillation.

Constant RT Is Accompanied by Constant Time Until Return of Excitability

The time course of recovery of excitability after defibrillation shocks was determined at 15 sites on six hearts with a single local stimulus (see “Methods”). Traces a–e in Figure 8 show five defibrillation episodes with DFT-strength shocks from a site exhibiting a constant RT. The stimulus CIs were 85, 90, 95, 100, and 105 msec with respect to the shock (traces a–e). Trace a shows that the earliest extrastimulus at 85 msec caused a small membrane depolarization but did not excite an action potential. The next extrastimulus (90 msec, trace b) caused a similar slight depolarization but was followed after a significant latency by a slowly rising upstroke and a poorly formed action potential. The next extrastimulus (95 msec) caused a larger depolarization followed with a slight latency by an action potential with a slow upstroke. The next-longest coupled extrastimulus (100 msec, trace d) excited an action potential with a continuous upstroke. The last extrastimulus (110 msec, trace e) also excited an action potential but with a faster upstroke than that in trace d. This progression in myocardial responsiveness with increasing CI is similar to that seen by others6,7,32,33 and is taken as an indication that the myocardium recovered its excitability in concert with the optically indicated membrane potential. It also demonstrates that the prolongation of depolarization by defibrillation shocks causes a prolongation of the effective refractory period. Myocardial excitability was not depressed by the sort of shock-induced trauma demonstrated by others13,14 because it would have significantly
delayed the recovery of excitability beyond repolarization of the shock response.

Constant RT is Seen Among Multiple Adjacent Sites

The constant RT response was demonstrated by recording successive defibrillation episodes at a single site. This protocol was sufficient to ascertain the independence of RT from the phase of action potential depolarization at the time of the shock. The following protocol demonstrates that this RT was also constant among adjacent recording sites within a small area. Instead of remaining fixed at the same site, the fiberoptic pickup was repositioned after each defibrillation episode. This protocol yielded similar results in each of the three hearts in which it was executed. In one example (illustrated in Figure 9A), 14 sites were arranged on a rectangular grid having 1-mm spacing between rows and columns. Figure 9A shows optical recordings taken from five of these sites arranged so that the shock CI increased from top to bottom. Despite the differences in both shock CI and recording site, the optical recordings show a constant time until complete repolarization from shock response. This constancy is highlighted by the vertical dashed line running through all of these traces just as they repolarize. The average RT found for these sites was 72.4±1.6 msec (n=14). This experiment and others in two additional hearts demonstrate that the RT remains constant among a number of adjacent sites within a small area.

Constant RT Phenomenon is Not Dependent on D600 or Nonischemic Conditions

The original protocol of recording successive defibrillation episodes at a fixed site was repeated in various hearts under different conditions to determine whether the experimental procedures used in this study were responsible for the constant RT. The first factor investigated was the use of the calcium channel-blocking agent D600. Figure 9B illustrates one of the 17 sets of recordings obtained from four hearts in which D600 was omitted from the perfusing solution. To obtain usable recordings, it was necessary to find optical recording sites that produced no contraction artifact. Figure 9B shows traces recorded from the same site during defibrillation episodes that used shocks 1.2×DFT. The dashed vertical line was placed 76 msec after the shock. These traces, despite the absence of D600, are very similar to those shown in Figure 4, in which D600 was used. As before, the shock gave rise to prompt depolar-
ing deflections and a constant RT after the shock. In all experiments in which no D600 was used, all sites showed prolongation of depolarization in response to defibrillating shocks, and, as was the case for D600-containing solutions, these sites demonstrated the constant RT phenomenon.

All of the examples shown thus far have been obtained from hearts that remained perfused during the period of fibrillation. The in situ heart, however, becomes ischemic during fibrillation because of the fall of cardiac output. Therefore, four experiments were performed using three hearts in which ischemia was produced during fibrillation by shutting off the coronary perfusion system after the induction of fibrillation. This method did not fully reproduce all of the hemodynamic conditions present during fibrillation, such as equilibration of arterial and venous pressures and cardiac swelling. This means that ischemia did not occur immediately upon cessation of perfusion because the coronary system was free to drain through the coronary sinus. This drainage was complete within seconds and represented only a small fraction of the total duration (30 seconds) of nonperfusion. D600 was not present in the perfusion solution. Figure 9C shows five traces recorded from the same site during defibrillation episodes using shocks 1.0×DFT. The combined effect of ischemia and absence of D600 did not cause any qualitative differences in the responses of the heart to defibrillation shocks. Both shock-induced prolongation of depolarization and a constant RT are evident in Figure 9C, just as in Figure 4. This same result was found in recordings from the four sites in three hearts in which this protocol was executed.

**Discussion**

**Optical Recordings Show Electrophysiological Responses of Fibrillating Myocardium to Defibrillation Shocks**

Optical recordings permit membrane action potentials to be obtained without any artifactual distortions caused by the large interstitial electrical fields presented by the defibrillation shock. It was found, as long believed, that shocks were able to stimulate an action potential in fibrillating myocardium. Although it had previously been shown that high-voltage shocks excited action potentials in cultured cell or isolated tissue preparations and in the open-chest dog, the present study was conducted in a heart actually undergoing fibrillation. Using optical recording, however, it was found that, in addition to action potential stimulation, defibrillation shocks produced an additional period of depolarization in myocardium already depolarized by previous excitation. This shock-induced prolongation of depolarization and refractoriness may in part underlie the manifestation of a postshock “isoelectric interval” because it would act to transiently suppress electrical activity after the shock. The present study also demonstrated that defibrillation shocks unexpectedly gave rise to a constant postshock RT. This phenomenon was evident in the optical recordings taken from the same site during successive defibrillation episodes. It was also found that optical recordings from adjacent and nearby sites showed the same constancy in postshock RT. This implies that the constant RT response is able to greatly reduce or eliminate the spatial dispersion in refractoriness present in fibrillation because myocardium within small areas would repolarize synchronously after the shock. This phenomenon may have been responsible for the “repolarization homogenization” (i.e., synchronous T waves after the shock indicative of simultaneous repolarization) seen on direct-current electrogram recordings during defibrillation of the canine heart.

The immunity of the optical recording technique to interstitial shock voltage gradients derives from the use of a voltage-sensitive dye to directly transduce cellular membrane voltages into an optical signal. The fluores-
Figu**re 9.** Optical records demonstrating constant repolarization time (RT) phenomenon under various conditions. In each panel, time and duration of shocks are indicated by thick black lines underlying each trace. Preshock upstrokes are indicated by filled arrowheads; vertical bars indicate 1% change in background fluorescence. Shocks were applied over a range of coupling intervals (CIs) from early in the plateau to nearly full repolarization. Synchrony in RT among traces in each panel is highlighted by dashed vertical line intersecting them just as they fully repolarize, indicating, as in Figure 4, that shock caused constant RT. Panel A: Optical recordings obtained from sites within a 26-mm² rectangular area on the left ventricle near basal defibrillation electrode during separate defibrillation episodes. Traces a–e cover range of CIs from early in the plateau to nearly full repolarization. In this instance, shocks 1.5×defibrillation threshold (DFT) (1.0 J) were applied so that defibrillation always succeeded. Average RT was 72.4±1.6 msec (n=14). Panel B: Constant RT phenomenon did not require perfusion with D600-containing Tyrode's. Average RT was 75.7±3.5 msec (n=12); shocks 1.2×DFT (1.0 J) were used. Recording shows that constant RT response was not due to an electrophysiological alteration brought about by the use of D600. Panel C: Constant RT among traces recorded during ischemic fibrillation and with D600-deficient Tyrode's. Average RT was 79.7±3.2 msec (n=15); shocks 1.0×DFT (1.25 J) were used. Recording demonstrates that ischemia does not inhibit production of constant RT response.

C-1 cent oxonol dye WW781 (dye XXV of Gupta et al.\(^\text{21}\)) was used in this study and was shown to give rapid, linear responses to changes in membrane potential caused by membrane potential–driven shifts of dye molecule populations between the membrane and bathing solution phases.\(^\text{35}\) Axon voltage clamp experiments demonstrated that WW781 transduced only the changes in membrane voltage despite variations in other membrane properties such as ionic permeability and transmembrane ionic fluxes.\(^\text{36}\) The wide voltage range and linearity of the response of another oxonol dye, an analogue of WW781, was shown in experiments in which the membrane potential of lipid vesicles was varied over a range of 500 mV.\(^\text{37}\) The insensitivity of the optical signal to extracellular voltage gradients was demonstrated in studies in which a voltage-sensitive dye was used to map the changes in membrane potential induced in a single cell exposed to external electric fields\(^\text{38,39}\) whose strength in one report\(^\text{39}\) exceeded 40 V/cm; thus, in this study of defibrillation, the optical signals registered during and after a shock relate only to myocardial membrane voltage changes. This was verified by the correlation between the optically recorded prolongation of action potential depolarization and the prolongation of the effective refractory period that occurred during shock application.\(^\text{17}\)

The optical technique should not be considered a replacement for or superior to the intracellular microelectrode because these techniques provide different information. For example, the intracellular microelectrode is able to record the absolute transmembrane voltage and to sense the electrical activity of a single cell, whereas the optical technique cannot yield either an absolute or relative measurement of membrane potential. Furthermore, the optical technique senses the aggregate electrical activity of a population of cells. The fact that the optical signal is derived from a population of cells gives rise to a complication in that, despite the insensitivity of the optical signal to interstitial shock voltage gradients, it is difficult to interpret the optical signal change occurring during the shock. A portion of the shock current applied to the heart flows through the cells of the myocardium; this current flow gives rise to the cellular voltage changes, which, in turn, elicit electrophysiological responses. Thus, although the optical signals generally show a depolarizing deflection during the shock, this probably does not represent the true membrane voltage change caused by the shock because the optical signal registers only the average membrane voltage change experienced within and among cells. Computational modeling shows that externally applied currents such as defibrillation shocks induce mixed hyperpolarizing and depolarizing voltage changes within a single cell in addition to an overall electrotonic polarization of the cell.\(^\text{40,41}\) These complexities arise from the syncytial nature of the myocardium and dis-
continuities in intercellular conductivity caused by gap junctions. In addition, nonlinear membrane conductances cause the magnitude of shock-induced voltage changes to vary, depending on the polarity and strength of the shock currents crossing the cellular membrane. The optical signal recorded during a shock occasionally showed a small transient hyperpolarization preceding the depolarizing shock response. In these cases, the same electrophysiological responses ensued, but such examples, though atypical, illustrate the difficulties in interpreting the optical signal changes seen during the application of a shock. This study is concerned with the electrophysiological events arising after the shock.

Proposed Mechanism of Constant RT Response

It was shown that neither D600 nor maintained coronary perfusion was needed for the production of the constant RT response (Figures 9B and 9C). A previous investigation showed that shock-induced prolongation of depolarization was not due to use of the voltage-sensitive dye WW781 or to the fact that the optical recording technique senses activity in a population of cells. Also, the prolongation in refractoriness accompanying the additional depolarization evoked by the shock during pacing and fibrillation were not due to the type of events depicted in other studies that showed long-lasting (several seconds) membrane depolarization that was perhaps due to cellular damage. The optically recorded membrane potential gave no evidence of such maintained depolarizations; Figure 8 shows that cellular excitability returned in concert with repolarization of the membrane potential.

The postshock RT seen during pacing varied with CI and therefore failed to meet the criteria for a constant RT (top of Figure 5). However, a constant postshock RT could be produced at the same site during defibrillation (bottom of Figure 5). The period of rapid action potential generation preceding the shock may be the cause of this difference if it is also assumed that the shock acted to reinitiate an action potential during all action potential phases. This hypothesized restimulation process is believed to be a result of the ability of external electrical fields to induce hyperpolarizing as well as depolarizing voltage changes, which, in turn, reactivated the fast sodium channels of the hyperpolarized cellular membranes (see Figure 10 in Reference 17; also see Swartz et al. for an alternative restimulation mechanism). The action potential duration is known to vary with activation rate, and, in the case of premature excitation during pacing, with the CI of the extrastimulus. Thus, action potentials restimulated by shocks during the depolarized phase of a paced action potential would also be expected to vary in duration. Fibrillation, in contrast to pacing, would be expected to cause the shock-restimulated action potential to attain a quasi-steady-state duration, which, as a result of the high activation rate, would change little during the course of each fibrillation action potential. Because the duration of the restimulated action potential corresponds to the postshock RT, the result is the constant postshock RT response demonstrated in this study.

Although the use of D600 did not alter the qualitative character of the myocardial responses to shocks, it had other effects. When used during a study of shock application to a paced heart, it was found that the addition of D600 enhanced the additional depolarization evoked by shocks applied during the plateau phase. In this study, it was noted that the average action potential duration in fibrillation increased after the application of D600. These changes apparently resulted from the primary and secondary electrophysiological effects arising from the use of D600, which, at the dose used in this study, was found to block 90% of the calcium current in cat ventricle. Even though blockade of the calcium current led to a decrease in plateau amplitude, the total action potential duration was unchanged because of a reduction in the outward current. This latter effect may explain both the enhancement of additional depolarization by D600 and also the prolongation of the fibrillation action potential. The time course of repolarization from the peak of the shock response is determined by the balance between depolarizing and repolarizing currents. The depolarizing calcium current, even in the absence of D600, is reduced by voltage-dependent inactivation occurring during the period of depolarization preceding the shock. On the other hand, the repolarizing potassium current is indirectly reduced by the use of D600. Thus, in the presence of D600, the decrease in repolarizing potassium current may more than offset the loss of the partially inactivated depolarizing calcium current and lead to a longer phase of postshock RT than that seen in the absence of D600. Because of these electrophysiological effects, D600 could not be used in any study seeking to quantitatively evaluate the effects of defibrillation shocks. However, because it has been shown that the constant RT response remains intact in the absence of D600, the use of this agent does not invalidate the findings and conclusions of this study. This insensitivity is consistent with our hypothesis that strong shocks are able to reactivate the fast sodium current in depolarized myocardium, a process that should be unaffected by blockade of the calcium current.

Role of Constant RT Response in the Defibrillation Process

Experimental observations by Wiggers led him to believe that all traces of fibrillatory activity must be abolished by single or multiple shocks to successfully defibrillate the ventricle. Several decades later, it was observed that ventricular fibrillation could be halted if electrical activity in a portion of the ventricle was abolished by chemical or electrical means. This led to the formulation of the "critical mass" hypothesis, which stated that defibrillation shocks need only abolish activity in a portion of the ventricle, so that the remaining wave fronts are too few to perpetuate fibrillation on their own. The more recent "upper limit of vulnerability" hypothesis differed in that it was believed that electrical shocks could abolish all propagating wave fronts in the ventricle without necessarily defibrillating it. This is because the shock itself conditions the ventricle to produce new wave fronts that refibrillate it shortly after wave front abolition. Only when shocks are made sufficiently strong, i.e., approach the "upper limit of vulnerability," is defibrillation thought to succeed, because the shock can no longer refibrillate the ventricle. However, Witkowski and colleagues have recently conducted an investigation supporting the "critical mass" hypothesis, which, in contrast to the "upper limit of vulnerability" hypothesis,
they believe showed residual fibrillatory activity to be responsible for unsuccessful defibrillation. The data presented in this study do not support or challenge either of these hypotheses, and a discussion of the role of the constant RT response in the defibrillation process uses concepts common to both, as illustrated by the following example.

It is almost universally accepted that fibrillation is a result of reentrant excitation. Figure 10 shows a hypothetical situation in which a single impulse undergoes reentrant propagation around a ring of myocardial tissue having uniform membrane properties. Although fibrillation is not characterized by impulse reentry around an anatomic obstacle, this model serves to simply illustrate several principles applicable to reentrant excitation in general. Most of this ring is shaded black to denote depolarized myocardium, and a short portion of the ring is filled with hatching to indicate that it could be excited by electrical stimulation or a propagated impulse (excitable gap). The electrical activity at four sites on this ring are chosen for consideration. A single shock, analogous to a defibrillation shock, terminates the reentrant activity in this ring. Three different shock effects are examined, one in which the shock causes a constant RT response such as described in this article and two others in which the shock either stimulates an action potential or, in addition, stimulates a graded response. Traces representing the membrane voltage waveforms recorded from the four sites in each of these scenarios are also shown in Figure 10; they portray the last few action potentials generated during the reentrant rhythm. As represented here, the action potentials do not completely repolarize between successive activations as is generally the situation in fibrillation (see “Results”). Shock delivery time is indicated above each set of traces, and it is supposed that the effective shock strength is uniform throughout the ring of myocardium.

The traces on the left side of Figure 10 show that the shock evokes a rapid depolarization followed by synchronous repolarization from the peak of the shock response. The shock was able to cleanly terminate all propagating activity in this hypothetical situation because it brought all of the myocardial tissue to a uniform electrical state and allowed it to synchronously repolarize. This hypothetical synchronous repolarization over a local area is based on Figure 9A of the results, which shows that adjacent sites repolarize synchronously after a shock. If any point on this ring were depolarized by an impulse during repolarization, it would result in either uniform conduction of an impulse in both directions around the ring or failure to excite a propagated response. The absence of spatial gradients in RT and hence, refractory period (see Figure 8) would make this ring resistant to the reinduction of reentry by single stimuli.

The right side of Figure 10 shows waveforms generated during the termination of reentry through stimulation by the shock. This situation demonstrates the process of wave front abolition envisioned by traditional and current defibrillation hypotheses: it is based on the belief that fibrillation wave fronts must continually enter regions of excitable myocardium to perpetuate fibrillation. A defibrillation shock would deprive these wave fronts of excitable pathways and thus abolish them by prematurely stimulating action potentials in these areas. In accordance with this mechanism, trace a shows that the shock was able to evoke an action potential in the excitable segment of the ring just before it was about to undergo excitation once again by the head of the reentrant wave front. This action effectively terminated the reentry because this previously excitable segment of the ring became depolarized and thus blocked the propagation of the wave front. The shock was strong enough to excite all of this area at once and so terminated reentry instead of advancing the head of the impulse through the hatched area (i.e., resetting the reentry).

Because the shock affected only the excitable portion of the ring, it left the remainder to continue repolarization unperturbed. Thus, there is an increasing gradient in RT in the counterclockwise direction around the ring. This leaves it temporarily vulnerable to the reestablishment of reentrant excitation during the period of

**Figure 10.** Diagram of termination of hypothetical reentrant rhythm by a shock having three different possible effects. Reentrant excitation is due to circular movement of an impulse in a ring of tissue schematically illustrated in center of diagram. Depolarized portion of the ring is shaded black; excitable portion is hatched. Impulse circulates counterclockwise. Four sites on ring are indicated by the letters a–d. Hypothetical optical recordings from these sites are shown. Left set of traces indicates outcome of shock that produces constant repolarization time (CRT response). Middle and right side show outcomes of shock having stimulatory effects producing either action potential stimulation alone (AP stimulation) or action potential and graded response stimulation (graded response). Time of shock is indicated by labeled arrow. Arrow (↓) above trace b on right and middle set of traces indicates time when depolarizing stimulus should be able to initiate reentry after its termination by the shock. See “Discussion.”
repolarization after the shock. For example, if an impulse arrives at site b late in the repolarization phase of that site, it would then likely be blocked in the clockwise direction but be able to propagate in the counterclockwise direction. This impulse would continue around the ring and once again establish the circus movement reentry. Reentry could thus be restarted by the application of an impulse during a window of time after the shock at a variety of sites on the ring.

The middle set of traces in Figure 10 shows both wave front abolition and refractoriness enhancement. It accounts for recent studies suggesting that shock-stimulated graded responses, by prolonging the period of myocardial depolarization and hence, enhancing refractoriness, may promote defibrillation. Whereas trace a showed that a shock was able to stimulate an action potential in excitable myocardium, trace b shows that the shock caused a local graded response that failed to evolve into a propagated action potential. Traces c and d show that shock arriving during the early phase of action potential depolarization had no effect on their repolarizing time courses. The ability of a shock to stimulate a graded response could increase the likelihood of successful defibrillation because it would extend the refractoriness of myocardium that would otherwise become available to support impulse propagation soon after wave front abolition.

As was the case for wave front abolition by a shock (Figure 10, right traces), the middle set of traces shows that stimulation of an action potential at site a and a graded response at site b also had the side effect of causing asynchronous repolarization within the ring. If excitation arrives at or is delivered to site b during repolarization, it could generate an impulse that would be blocked clockwise but able to propagate in the counterclockwise direction and subsequently undergo circus movement. The temporal window for reentry reinitiation is smaller in this instance than that for a shock that only abolishes wave fronts because of the additional refractoriness caused by the graded response. The graded response also serves to limit the physical extent of the ring, where impulses could restart reentry. Reentry reinitiation could also occur if the graded response at site b eventually gave rise to a propagated impulse that also underwent circus movement.

The above model can be used to understand the possible effects of electric shocks on fibrillating ventricle. The erratic propagation of multiple wave fronts in fibrillating ventricle creates an extremely inhomogeneous spatial distribution of refractory states. A shock that only abolished wave fronts would condition the ventricle to produce disorganized reentrant propagation of any impulse that arose after the shock. This is because the shock would not affect myocardium already depolarized by prior activity (myocardium that would continue to repolarize out of synchrony with adjacent areas). The ventricle would remain vulnerable to postshock impulses (for example, spontaneous postshock impulses or surviving preshock wave fronts) until continued repolarization of the myocardium reduced the spatial inhomogeneity in refractoriness. This situation would be ameliorated if a shock, in addition to abolishing wave fronts, also produced a transient phase of refractoriness such as by stimulation of a graded response. Although this response would not completely eliminate the dispersion in refractoriness present in fibrillating ventricle, it would reduce the tendency toward prompt reinitiation by transiently prolonging myocardial refractoriness toward spontaneous postshock impulses or surviving preshock wave fronts. The greatest level of protection is afforded by a shock that causes a constant RT, because, as depicted in Figure 4, it would not only extend myocardial refractoriness but also eliminate local differences in RT. Even if the shock did not produce the same RT throughout the entire ventricle, the reduction in the disparity of RTs on the microreentrant circuit size scale would greatly reduce the ability of postshock impulses to undergo reentry, leading again to fibrillation.

The data presented in this article make it clear that the constant RT response occurs during defibrillation, and the above discussion uses a simplified example to make a case for the participation of constant RT response in the defibrillation process. This does not imply, however, that it is regarded as the sole or most important mechanism of defibrillation. It could be possible for a shock to produce all of the processes illustrated in Figure 10 at once throughout different parts of the ventricle. This would arise as a result of the nonuniform distribution of effective shock strength through the ventricle because of the nonideal nature of defibrillation electrode systems. Our unpublished data showed that, as shock strength was increased, the range of shock effects progressively evolved from action potential stimulation alone to include the production of additional depolarization in depolarized myocardium by graded responses and reinitiated action potentials and finally to the production of a constant RT. Another unresolved issue is the origin of the impulses that reinitiate the heart in cases of failed defibrillation, whether they are simply surviving preshock wave fronts or impulses generated de novo by the shock. A more detailed and thorough study of defibrillation with multiple recording sites will be required to determine whether the constant RT response acts in the way described above and, if so, its significance regarding other processes.

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