Early Afterdepolarizations Induced In Vivo by Reperfusion of Ischemic Myocardium

A Possible Mechanism for Reperfusion Arrhythmias

Silvia G. Priori, MD, Massimo Mantica, MD,
Carlo Napolitano, MD, and Peter J. Schwartz, MD

Recent studies in vitro have shown that afterdepolarizations may develop during reperfusion after hypoxia, thus suggesting that these afterdepolarizations may contribute to the genesis of reperfusion arrhythmias. We recorded monophasic action potentials (MAPs) during myocardial ischemia and reperfusion to investigate whether afterdepolarizations develop in vivo when reperfusion arrhythmias occur. In 15 anesthetized cats, 24 trials of 10 minutes of occlusion of the left anterior descending coronary artery were followed by reperfusion. In 13 of 24 (54%) trials, afterdepolarizations developed at the moment of reperfusion, with a mean amplitude of 2.4±1.1 mV (13±8% of MAP amplitude). When cycle length was either increased by vagal stimulation or decreased by atrial pacing, early afterdepolarization (EAD) amplitude was modified, according to what has been described for EAD in vitro, with a positive linear correlation between cycle length and EAD amplitude (\( r=0.91, p<0.0001 \)). The occurrence of EAD was not related to rapid changes in left ventricular pressure. In the eight of 13 (62%) cases in which EAD development was associated with reperfusion arrhythmias, the coupling interval of the EAD and of premature ventricular contractions showed a significant correlation (\( r=0.86, p<0.0001 \)). However, in five of 13 (38%) cases, occurrence of reperfusion arrhythmias was not accompanied by the presence of EAD on the MAP recording. In two animals, a 2:1 block of EAD conduction was observed, and this was reflected on the intracavitary electrocardiogram as T wave alternans. Thus, EADs occur frequently after reperfusion in vivo, with a time course that parallels the onset of reperfusion arrhythmias. This finding further supports the role of triggered activity in the genesis of reperfusion arrhythmias in vivo. (Circulation 1990;81:1911–1920)

Reperfusion of the ischemic myocardium is often associated with the development of malignant ventricular arrhythmias. Attention to the role of afterdepolarizations comes from experimental observations, several clinical reports have suggested a role for these arrhythmias either during spontaneous reperfusion after coronary spasm or after thrombolysis subsequent to acute myocardial infarction.

The mechanisms for reperfusion arrhythmias have not been fully elucidated, even though it has been suggested that nonreentrant mechanisms, such as automaticity or triggered activity, may have a predominant role. Investigation of the electrophysiological changes that occur immediately after reperfusion may give insight into the understanding of arrhythmogenic mechanisms. In vitro studies with microelectrode recordings have described the occurrence of afterdepolarizations as a consequence of reoxygenation after hypoxia. However, hypoxia is only one of several components of ischemia, and in vitro reproduction of the metabolic and neurohormonal factors that play a critical role during in vivo reperfusion is complex.

Analysis of the modifications of action potentials in vivo, as reflected in monophasic action potential (MAP) recordings, may add new information to previous studies concerning the electrophysiological alterations after reperfusion in the intact heart.

The aim of the present study was to investigate the occurrence of afterdepolarizations with MAP recording during reperfusion of the ischemic heart in vivo and to characterize the dependence of afterdepolarizations on cycle length, their time course, and their potential implications in the genesis of reperfusion arrhythmias.

From the Unità' di Studio delle Aritmie, Centro di Fisiologia Clinica e Ipertensione, Ospedale Maggiore, Istituto di Clinica Medica Generale e Terapia Medica, Università di Milano, Italy. Address for correspondence: Peter J. Schwartz, MD, Centro di Fisiologia Clinica e Ipertensione, Pad. Sacco, via F. Sforza, 35, 20122 Milano, Italy.

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Methods

Surgical Preparation

Experiments were performed on adult cats (2.4–3.9 kg) sedated with ketamine (20 mg/kg i.m.) and anesthetized with α-chloralose (70 mg/kg i.v.). Ventilation was maintained by a tracheal cannula connected to a respirator (model 607, Harvard Apparatus, South Natick, Massachusetts). Tidal volume and respiratory rate were adjusted to keep blood gases and pH within the physiological range throughout the experiment. Body temperature was recorded continually by a thermistor probe (model YSI 43TA, Yellow Springs Instr. Co., Yellow Springs, Ohio) and maintained in the normal range with a heating pad and an infrared lamp. Polyethylene catheters were inserted into the femoral artery and vein for blood pressure recording (model 4-327-C Beckman transducer, Beckman Instrs., Inc., Schiller Park, Illinois) and chloralose administration. The second to fifth ribs on the left side were removed, and through this opening, the heart was exposed and suspended in a pericardial cradle. The left anterior descending coronary artery was carefully isolated at its origin, a suture was gently passed around the vessel, and its extremities were inserted into polyethylene tubing. The vagosympathetic trunk on the right side was carefully dissected, and the right cervical vagus was prepared for electric stimulation. A bipolar plunge electrode was positioned in the right atrium for atrial pacing, and in selected experiments, a silk suture was gently passed underneath the thoracic aorta to perform graded aortic constriction.

Monophasic Action Potential Recording

To allow endocardial recording of MAP, a 4F silver–silver chloride contact electrode (custom-made by Meditec, Parma, Italy) was introduced through a stab wound in the free wall of the left ventricle. The recording pole of the electrode had a 1 mm diameter, and the reference electrode, located 5 mm proximal to the recording end, had a 0.5 mm diameter. The recording tip was placed against the distal end of the septum, and the catheter was secured to the epicardial surface by a silk suture. In some experiments, a left ventricular epicardial recording was also obtained with a MAP catheter; in these experiments, continuous contact of the tip and the epicardial surface was provided by a spring-loaded mechanism similar to that described by Franz et al. and electric continuity between recording and reference electrodes was maintained by a foam rubber cylinder soaked with saline solution. The MAP signals were amplified with a DC-coupled differential amplifier (model 9853C, Beckman Instrs., Inc.) and stored on magnetic tape (Recall Store type 7DS, Southampton, England) for subsequent analysis.

MAP phases were defined according to the definitions used for transmembrane action potential. MAP amplitude was defined as the difference between phase 2 and diastolic resting potentials; the action potential duration (APD) was measured from the base of the action potential trace to 50% (APD50) or 90% (APD90) repolarization. Early afterdepolarizations (EADs) were defined according to descriptions of in vitro occurrences during conventional transmembrane recording. The coupling interval of the EAD was defined as the interval between phase 0 of the action potential and the peak or shoulder of the afterdepolarization trace. APD50, APD90, cycle length, coupling interval, and EAD amplitude were measured with a digital oscilloscope (Statham model 1425, Gould, Inc., Cleveland, Ohio) equipped with data storage analysis functions and a movable cursor (moved at intervals of 0.5 msec).

EAD amplitude was defined according to the various methods used in the literature to analyze potential disparities between the different techniques. First, the change in slope of the repolarization curve induced by EAD, expressed as the ratio H=bc/ac (Figure 1A), was measured. Second, EAD “area” was calculated by drawing lines that extended phase 3 of the action potential and the line of the resting membrane potential until they intersected (Figure 1B) and by counting the 1×1-mm graticules on the recording paper between the two lines or by planimetry. Finally, EAD “height,” defined as the difference between the peak EAD amplitude and the base of phase 0, was measured (Figure 1C).

Stability of Recording

Distinction of afterdepolarizations from recording artifacts is critical in the experiments using MAP recording. Therefore, at the beginning of the experiments, control MAP recordings were made for at least 20 minutes in each animal to identify a stable baseline; after this control period, sudden changes in cycle length were induced by right vagal stimulation or rapid atrial pacing to evaluate maintenance of a stable baseline during changes in diastolic intervals. When this was not the case, the recording site was changed, and the experimental protocol was started only after a constant shape of the MAP with a stable diastolic resting potential was consistently recorded. Additionally, in three animals that did not enter the occlusion-reperfusion protocol described below, stability of the MAP recording and the temporal relation between MAP and changes in intraventricular pressure were assessed by sequentially performing vagal stimulation, atrial pacing, and an increase in afterload induced by graded aortic constriction while simultaneously recording left ventricular pressure and its first derivative (dP/dt) with a Millar 4F tip pressure transducer (Millar Instrs., Houston, Texas), and MAP from the epicardium and endocardium.

Experimental Protocol

In 22 animals, reversible occlusion of the left anterior descending coronary artery was obtained by pulling the two ends of the suture and by securing the
ligature with a bulldog clamp. The occlusion was maintained for 10 minutes, and no attempts were made to defibrillate those animals in which ventricular fibrillation (VF) occurred during ischemia. Reperfusion was produced by releasing the clamp and the suture. Reperfusion was easily confirmed within seconds by the return to a reddish color of the previously ischemic tissue. In those animals that survived reperfusion and had stable hemodynamic conditions, a second coronary artery occlusion was performed after a 30-minute interval, followed by a second reperfusion.

At the end of each experiment, Monastral blue dye (type BXE HD, ICI Milan, Italy) was injected into the left descending coronary artery to obtain a gross estimate of the ischemic area; the heart was then removed and opened to identify the endocardial lesion produced by the tip of the MAP catheter and its relation to the ischemic area.

To further investigate the nature and characteristics of afterdepolarizations, thirteen in three animals in which reperfusion afterdepolarizations developed, atrial pacing (cycle length, 182–333 msec) and vagal stimulation in short bursts (1–5 mA, 4-msec duration, 10 Hz) were performed to evaluate changes in amplitude of afterdepolarizations secondary to cycle length modifications. Also in a further series of experiments, the occlusion-reperfusion protocol was performed while simultaneously recording MAP from the endocardium and from a left ventricular epicardial site, as well as monitoring intracavitary left ventricular pressure and dP/dt with a Millar 4F tip pressure transducer (Millar Instrs.), with vagal stimulation and atrial pacing performed either in the presence and or absence of EAD. These experiments allowed us to determine the temporal relation between EAD during reperfusion and changes in left ventricular pressure.

Data Analysis

Intracavitary and surface electrocardiograms (ECGs), blood pressure, MAP, and left ventricular pressure were continuously recorded on paper (Beckman model R612, Beckman Instrs., Inc.) and stored on magnetic tape (Racall Store type 7DS) for subsequent analysis.

Arrhythmias occurring within 2 minutes from release of the coronary occlusion were defined as reperfusion arrhythmias and were classified as follows: VF; VT, ventricular tachycardia (≥4 consecutive premature ventricular contractions, either sustained [VTs], if lasting >30 seconds, or nonsustained [VTNS], if lasting <30 seconds); and PVCs, single premature ventricular contractions.

Statistical analysis was performed with a one-way analysis of variance followed by Tukey's test for multiple comparisons for evaluation of blood pressure, APD90, APD90, and MAP modifications during ischemia and reperfusion. The relations between cycle length and EAD amplitude, and between PVC coupling interval and EAD in the beat immediately preceding occurrence of the arrhythmia were assessed by linear-regression analysis. Data are expressed as mean±SD.

Results

Of the 22 animals entering the occlusion-reperfusion protocol, seven were excluded because of VF during the first coronary artery occlusion (n=5) or hemodynamic deterioration (n=2). In six cats, only one occlusion-reperfusion trial was analyzed because of the occurrence of VF during reperfusion (n=4) or during the second coronary artery occlusion.
(n=2). Thus, analyzable data were obtained for two occlusions in nine animals and for one occlusion in six animals. Overall, 24 trials of ischemia and reperfusion were performed in 15 cats.

During occlusion, systolic blood pressure decreased from 135±34 mm Hg before ischemia to 106±27 mm Hg (p<0.01) at the moment of reperfusion, whereas cycle length did not change (from 313±53 to 309±57 msec). Within a few seconds after onset of reperfusion, resolution of ECG signs of ischemia was accompanied by an increase in systolic blood pressure, from 106±27 to 135±31 mm Hg (p<0.01), whereas cycle length was not modified (from 309±57 to 319±56 msec). Between the first and the second occlusions, no difference was observed in the total incidence of arrhythmias (95% vs. 91%, p=NS) and in the incidence of combined VT and VF (54% vs. 64%, p=NS).

Reperfusion arrhythmias occurred in 15 of 24 (62%) trials, with a mean time of onset of 18±15 seconds. VF was observed in four of 24 (17%) cases, VTS in none, VTNS in five of 24 (21%), and PVCs in six of 24 (25%); in nine (38%) cases, no arrhythmias developed. At the moment of reperfusion, blood pressure and heart rate were similar between animals that developed complex (VF or VT) versus simple or no arrhythmias, and no difference in the incidence of reperfusion arrhythmias was observed between the first and the second coronary artery occlusions.

**Monophasic Action Potential Recording**

Signals accepted for the protocol were stable for 1 hour without requiring any further change in electrode position. During this control period, modifications of the shape of phase 4 were never observed with abrupt changes in cycle length. Also, modifications in dP/dt induced by changes in heart rate or afterload did not induce a signal artifact on the epicardial and endocardial MAP recordings that resembled EADS (n=3). In animals undergoing occlusion-reperfusion, the catheter tip was located within or at the border of the ischemic area, as indicated by postmortem verification of the recording site.

During ischemia, MAP amplitude was reduced from 19±7 mV (range, 13–35 mV) to 13±5 mV (range, 9–25 mV, p<0.01), whereas its duration varied slightly either at APD90 or at APD90 (APD90 from 172±53 to 167±21 msec, p=NS; APD90 from 198±25 to 193±23 msec, p=NS).

Within a few seconds after release of the occlusion and just before the occurrence of afterdepolarizations, MAP amplitude increased to 17±8 mV (range, 9–33 mV, p<0.01 vs. ischemia); APD90 and APD90 were not significantly modified (APD90 from 167±21 to 172±26 msec; APD90 from 193±23 to 197±29 msec).

In 13 of 24 (54%) trials, afterdepolarizations rapidly developed after reperfusion, with a mean time of onset of 28±18 seconds, and lasted for 106±43 seconds (range, 32–180 seconds). The mean amplitude measured as the height of the afterdepolarization (see below) was 2.4±1.1 mV, that is, 13±8% of MAP amplitude, and remained constant in each experiment unless sudden changes in cycle length were introduced as described below. In all cases, afterdepolarizations interrupted phase 3 of the repolarization and were therefore interpreted as high-potential EADs (Figure 2).

In eight of 13 (62%) cases, EAD development was accompanied within seconds by the occurrence of reperfusion arrhythmias. In six cases, EADs overlapped arrhythmias by 10–180 seconds, whereas in two cases, EADs disappeared when the arrhythmias subsided. The coupling interval of the EAD and that of the premature beats were consistent in each experiment and showed a significant (r=0.86, p<0.0001, Figure 3) correlation. In five (38%) cases, EADs were
not associated with reperfusion arrhythmias; the amplitude and coupling interval of these EADs were similar to those accompanied by arrhythmias.

Figure 4 shows one of two cases in which a 2:1 block of an EAD was present and was associated with electric alternation of the T wave. Note that when a run of VT terminates, an intermittent 2:1 conduction of EAD is present (arrows in the lower trace); this corresponds to T wave alternans on the ECG in the middle trace.

**Early Afterdepolarization Amplitude and Changes in Cycle Length**

The correct definition of EAD amplitude presents a rather complex problem because the latter depends not only on its height, that is, the deviation of the EAD peak from the baseline of the MAP, but also on its width, that is, the changes in the slope of the repolarization. Different methodologies have been proposed\textsuperscript{16,20–22} for the measurement of EAD amplitude, with resulting disparities that may affect a uniform interpretation of studies from different laboratories. For this reason, we have compared the ability of these methodologies to describe the relation between cycle length and EAD amplitude by plotting two to three randomly selected values of these variables, normalized to the MAP amplitude in each experiment in which the EAD occurred.

The computation of the area, either by counting the $1\times1$-mm graticules on the recording paper ($r=0.93$, Figure 5A), by planimetry ($r=0.92$, Figure 5B), or by use of the height of the EAD ($r=0.86$, Figure 5C) allowed good detection of the increase in amplitude related to a reduction in heart rate, whereas the evaluation of the ratio $bc/ac$ was not sufficiently accurate ($r=0.54$, Figure 5D). Based on this analysis, we elected to use the computation of the area by visually counting the $1\times1$-mm graticules on the recording paper and by using high magnification to measure the changes in EAD amplitude induced by changes in cycle length. In three animals, heart rate was modified by atrial pacing and by vagal stimulation as soon as the EAD occurred after reperfusion. Figure 6 shows the base of the MAP recording at three different cycle lengths in one example, and Figure 7 shows the pooled data from the three experiments expressed as the percent difference in EAD area related to changes of cycle length, with an EAD amplitude at a cycle length of 400 msec as a reference. A positive correlation ($r=0.91$) was found between cycle length and EAD amplitude, in good agreement with

**Figure 3.** Scatterplot with regression line showing correlation between the coupling interval of afterdepolarizations in the preceding beat (EAD CI, msec) and that of premature ventricular contractions (PVC CI, msec). Data were obtained from eight trials in six animals. Equation of the regression line, its $r$ value, the number of measurements, and the level of significance are indicated.

**Figure 4.** Simultaneous recordings of blood pressure (BP, mm Hg, top trace), electrocardiograms (ECG, middle trace) and monophasic action potential (MAP, mV, lower trace) a few seconds after reperfusion when arrhythmias develop. Note the presence of early afterdepolarization (EAD) in the lower trace, during the sinus beats that interrupt ventricular tachycardia. When arrhythmias terminate, an intermittent 2:1 conduction of EAD is present (arrows, lower trace), and alternans of the T wave appears on the ECG (arrows, middle trace).
the relation between EAD amplitude and cycle length observed in in vitro studies.\textsuperscript{13,20} This relation was confirmed in the experiments in which simultaneous endocardial and epicardial recordings of MAP, as well as monitoring of ventricular pressure and dP/dt (Figure 8), were performed. These experiments demonstrate that the occurrence of EADs was not related to any significant change in ventricular pressure development; that afterdepolarizations could also be recorded from the epicardial site, with a lower amplitude, compared with the endocardial recording; and that after EAD submerged, changes in dP/dt induced by changes in heart rate and afterload did not induce EAD-like changes in MAP recordings at both sites.

**Discussion**

The present study provides in vivo evidence indicating that afterdepolarizations occur during reperfusion of the ischemic myocardium. This finding further supports the link between triggered activity and reperfusion arrhythmias, as suggested by previous in vitro\textsuperscript{14,15} and in vivo\textsuperscript{12} studies.

**Protocol Characteristics**

Before discussing the relevance of the data in the present study and comparing our results with those obtained in other studies in vitro and in vivo, some characteristics of the study protocol need to be addressed. As both incidence and severity of reperfusion arrhythmias are directly dependent on the duration of the ischemic period,\textsuperscript{4} we selected a 10-minute interval of ischemia, a duration likely to result in a relatively low incidence of VF but with sufficient episodes of VTs to allow a meaningful analysis. Indeed, in three series\textsuperscript{23–25} of previous experiments with the feline model of occlusion-reperfusion, we had observed a relatively high incidence of VF (62%, 47%, and 62%, respectively) with 20 minutes of coronary artery occlusion, whereas the incidence of VF was clearly reduced to 13% with a 10-minute occlusion.\textsuperscript{24} The latter result was very similar to the incidence observed in the present study (17%). The main reason for our care in reducing the likelihood of VF stems from the need to closely monitor MAP modifications after reperfusion, an impossible task if VF is present. The EAD area was used to estimate its amplitude because the height or width may offer an insufficient estimate of afterdepolarization. When computation of EAD area was com-

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5}
\caption{Scatterplots with accompanying regression lines showing comparison of EAD amplitude variation in response to changes in cycle length (msec) by the different techniques described in Figure 1. Panel A: EAD amplitude measured as area (mm\textsuperscript{2}), obtained by counting the 1\times1-mm graticules on the recording paper; panel B: EAD amplitude measured as area (mm\textsuperscript{2}), obtained by planimetry; panel C: EAD amplitude measured as EAD height (h); and panel D: EAD amplitude measured as ratio bc/ac. Signal gain was set at 1 mm/mV, and values were adjusted to a monophasic action potential (MAP) amplitude of 20 mV to account for interanimal variations in MAP amplitude.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6}
\caption{Traces showing examples of the effect of changes in cycle length (CL, msec) on early afterdepolarization (EAD) amplitude (mV). To facilitate visual comparison, only the base of the monophasic action potential (MAP) curve is depicted. Panel b: MAP recording during sinus rhythm (cycle length, 320 msec). In panel a, EAD amplitude is reduced by atrial pacing at a CL of 190 msec. In panel c, EAD amplitude increases when CL is prolonged to 690 msec by vagal stimulation.}
\end{figure}
pared with other criteria proposed in the literature, it appeared that while the measure of height is a good approximation of amplitude, the measure of the deviation from the slope of phase 3 is not a suitable parameter for evaluation of EAD amplitude, at least for MAP recording in vivo. The measurement of EAD area both by manual counting the 1 x 1-mm graticules on the recording paper and by planimetry gave almost identical results; therefore, these techniques seem the most accurate for calculating EAD amplitude, a major point when modifications in EAD amplitude are critical for data interpretation. Thus, we used manual calculation of EAD area to assess the relation between EAD amplitude and changes in cycle length.

Finally, the catheter for MAP recording was positioned in the lower portion of the intraventricular septum near the apex. Although positioning of the electrode was reproducible, its relation with the ischemic area could still be variable due to interanimal variability in the coronary distribution. Also, the degree to which the electrode catheter tip makes contact with the endocardial surface may have an important effect on the amplitude of the signal. Despite these limitations, the consistent reduction in MAP amplitude during ischemia indicates that the recording site was within the area undergoing ischemic alterations. Indeed, Franz et al13 have recently characterized MAP changes during ischemia in the intact heart and have shown that the major change occurring during ischemia in the endocardial recording was a reduction in MAP amplitude with a lowering of the plateau that was totally reversible on reperfusion.

Reperfusion and Afterdepolarizations

Two in vitro studies have shown occurrence of afterdepolarizations during reperfusion. Ferrier et al13 showed that, after reoxygenation of myocardial tissue previously exposed to hypoxia, delayed afterdepolarizations developed in Purkinje fibers, with a mean onset time of 5.3 ± 0.6 minutes after reperfusion. In a recent report, Molina Viamonte and Rosen14 showed, for the first time, development of EADs in vitro during reoxygenation in Purkinje fibers. EADs were present in 11% of cases during reoxygenation in normal medium, but the incidence of EADs increased to 40% when free radical generators were added, and the incidence further increased to 50% during superfusion with a free radical generator plus norepinephrine.

In the present study after reperfusion, modifications of phase 3 of the MAP developed in approximately 50% of cases. These modifications were not related to the rapid changes in pressure development within the ventricle (Figure 8).

Although we cannot positively dismiss the possibility that these modifications of phase 3 of the MAP reflected a dishomogeneity in APD among adjacent cells,26 which has been shown to occur with rapid and dishomogeneous changes in extracellular concentration of K+,27 the time course of their development and the increase in their amplitude when heart rate was reduced (Figure 6) are consistent with the possibility that they represent high-potential EADs. Indeed, these EADs appear very similar to those induced (S.G. Priori, M. Mantica, C. Napolitano, and P.J. Schwartz, unpublished observations) by cesium infusion in the same animal species.

The mechanisms by which EADs can be elicited by reperfusion can only be inferred. It seems likely that enhancement of a Ca2+ inward current by catecholamines could play a major role, as suggested for EADs induced by Bay K 8644.28 The
increase in α-receptors during ischemia\textsuperscript{29} and the remarkable antiarrhythmic effect of α-adrenergic antagonists against reperfusion arrhythmias\textsuperscript{30} suggest an important role of α-adrenergic effects. In agreement with this concept, Ben David and Zipes\textsuperscript{31} recently reported that α-adrenergic stimulation enhances cesium-induced EADs in vivo.

The dependence of EADs on catecholamine release may also explain the present observation that EADs can actually occur at a faster heart rate than those originally proposed by Damiano and Rosen.\textsuperscript{20} Cranefield and Aronson\textsuperscript{32} proposed that EADs can occur at heart rates of 100–120 beats/min, and they reported a communication by Hoffmann that their rate “would be expected to be considerably speeded by the addition of catecholamines.” Recently, Priori and Corr\textsuperscript{33} demonstrated the occurrence of adrenergic-induced EADs in isolated ventricular myocytes at frequencies between 60 and 200 beats/min.

**Early Afterdepolarizations and Reperfusion Arrhythmias**

The concept of a possible involvement of triggered activity in reperfusion arrhythmias in vivo was first suggested by several studies showing protection from reperfusion arrhythmias with Ca\textsuperscript{2+} channel blockers.\textsuperscript{10,23} More recently, Pogwizd and Corr\textsuperscript{12} have suggested that automaticity at the endocardial level is more likely than reentry to be responsible for the development of VT after reperfusion of the ischemic myocardium. These authors proposed that either enhanced automaticity or triggered activity might have been responsible for the development of VT. Also, EADs, by prolonging the refractory period in specific ventricular regions, may lead to dispersion of refractory periods and facilitate reentrant arrhythmias.\textsuperscript{10,32}

In our study, the time course of EADs paralleled the development of reperfusion arrhythmias, and their coupling correlated with the coupling of reperfusion-induced PVCs (Figure 3). However, afterdepolarizations were not recorded in all the animals with reperfusion arrhythmias. While this may be taken as presumptive evidence against a direct relation between EADs and reperfusion arrhythmias, there are, on speculative grounds, at least two reasons for not excluding on this basis alone the possibility that EADs may be related to arrhythmia development. The “field of view” of the electrode is 1 cm wide and allows detection of EADs present in only a limited portion of the myocardium.\textsuperscript{34} Also, in 30% of the cases of VT studied by Pogwizd and Corr,\textsuperscript{12} a reentrant circuit was responsible for arrhythmia development; accordingly, one cannot expect to find evidence for triggered activity in all instances of reperfusion arrhythmias.

A collateral observation of this study was that, after reperfusion, an alternating morphology of the T wave associated with 2:1 block of the EAD was recorded in two cases by the intracavitary ECG.
(Figure 4). This raises the possibility that an intermittent block of an afterdepolarization may represent one of the mechanisms for T wave alternans. Such a possibility has also been suggested recently by El Sherif et al., who observed a similar phenomenon when EADs were induced in vivo with anthopleurin A.

Alternation of the T wave has been very frequently observed in patients affected by the idiopathic long QT syndrome. Since afterdepolarizations have been suggested as a mechanism for arrhythmias in the long QT syndrome, the possibility that an abnormality in their conduction may be responsible for a very characteristic ECG aspect of this unusual disease is intriguing.

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References


**KEY WORDS** • monophasic action potentials • ventricular fibrillation • early afterdepolarizations
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