Reperfusion Arrhythmias and Sudden Cardiac Death
A Century of Progress Toward an Understanding of the Mechanisms

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The observation that ventricular fibrillation may occur within seconds after restoration of blood flow to myocardium turned ischemic by a period of coronary occlusion (reperfusion) was originally made in the experimental laboratory in the 19th century by Cohnheim and Von Schulthess-Rechberg and later confirmed in the early 20th century by Tennant and Wiggers. In fact, it was found in subsequent laboratory experiments that ventricular fibrillation may occur more frequently after reperfusion than after coronary artery occlusion. It took until the latter part of the 20th century for these early laboratory studies to be translated to clinical medicine. It was noticed that only a minority of those individuals who have been successfully resuscitated from sudden ventricular fibrillation associated with coronary artery disease subsequently developed a myocardial infarction, suggesting that, if indeed myocardial ischemia caused by coronary occlusion was involved, it was transient. Reperfusion must have occurred. This proposed relationship between transient ischemia, reperfusion, and arrhythmias was corroborated by studies in patients with transient coronary artery spasm in whom ventricular arrhythmias, including ventricular fibrillation, occurred within minutes after the beginning of electrocardiographic signs of myocardial ischemia caused by the spasm but also after ST segment changes had returned to normal, when reperfusion had occurred. What is the mechanism responsible for this occurrence of fibrillation? This is a subject that has been pursued in more than a century of experimentation with slow but continued progress. The most recent advance, now in the 21st century, is the article by Cascio et al in this issue of Circulation Research.

The initial information on mechanisms of reperfusion arrhythmias came from experiments on in situ hearts of large animals subjected to periods of coronary artery occlusion followed by release of the occlusion that allowed reperfusion. In these experiments, the incidence of reperfusion-induced ventricular fibrillation increased when occlusion periods were lengthened from 5 minutes to 20 or 30 minutes and decreased when reperfusion was delayed beyond 30 to 60 minutes.

Also, reperfusion-induced fibrillation tended to occur more often when severe arrhythmias developed during occlusion. Both these observations suggested that there was a window of time in which the necessary electrophysiological derangements occurred that caused the reperfusion arrhythmias. What are these alterations in electrophysiology?

At the beginning of the 21st century, when laboratory studies of arrhythmias are taking advantage of cellular biophysical (patch-clamp studies of ion channel function) and molecular approaches (gene alterations of ion channel function), the successful application of the experimental methods used by Cascio et al reminds us that some of the more traditional approaches that originally led to the discovery and clarification of arrhythmogenic mechanisms throughout the 20th century, that is, studies on large tissue preparations and whole hearts, are still important to continue advancing knowledge in this area. Cascio et al have used a preparation of rabbit papillary muscle, perfused through a coronary artery, that was developed in 1987 in the laboratory of André Kléber. The perfused rabbit papillary muscle has the unique advantage of being a preparation that enables coronary artery occlusion and reperfusion to be implemented in a tissue chamber, as it would occur in the in situ heart, while allowing a number of different unique electrophysiological measurements to be made simultaneously rather than individually. This in turn enables elucidation of arrhythmogenic mechanisms and mechanisms for alterations in the ECG. In this study, extracellular electrograms and intracellular potential measurements enabled determination of membrane potentials, longitudinal whole-tissue resistance (rL), extracellular resistance (rE), and intracellular resistance (ri). All of these are important determinants of conduction with the latter being an indicator of cellular coupling via gap junctions. Added to these measurements was continuous registration of changes in extracellular potassium (Ko) that has been shown to fluctuate with coronary occlusion and reperfusion and that is also related to alterations in conduction that cause arrhythmias.

During the period of ischemia in this preparation, Ko increased while Vm decreased, as is known to occur in the in situ heart. There was a simultaneous increase in rE. The increase in rE results from an increase in ri as the microvasculature collapses and an increase in ri that reflects increased gap junctional resistance. Eventually nearly complete cellular uncoupling occurred. During this window of ischemia (20 minutes), prior studies with microelectrode transmembrane recordings in the in situ heart have shown marked depression of transmembrane action potentials, and even inexcitability. Decreased gap junctional conductance (increased ri) has been linked to the conduction disturbances that
result in the reentrant arrhythmias after a coronary artery occlusion in the in situ heart and shows that the behavior of this tissue chamber preparation is the same as in an in situ heart.

Ten minutes after the onset of cellular uncoupling in the study of Cascio et al., reperfusion was implemented as it would occur in the in situ heart after transient coronary spasm or dissolution of an unstable thrombus obstructing a coronary artery. The rapid decrease in $r_i$ that occurred, representing expansion of the intravascular and interstitial space, and a decline in $K_o$ that accompanied it, are both sensitive indices of successful reperfusion. Intracellular potentials were also restored.

Prior studies in the in situ heart have shown that sudden reperfusion results within seconds in a rapid restoration of action potentials to this ischemic myocardium, although the return of electrical activity is not equally rapid for all cells. During the first 30 seconds of reperfusion, there is a marked inhomogeneity in the action potentials within the ischemic area and at the border. Action potentials of different cells within the ischemic zone often alternate out of phase, some showing relatively high amplitudes and long durations while at the same time others are little more than local responses. Action potential duration of cells close to the ischemic border may be shortened by as much as 60 to 100 msec during reperfusion. Substances that accumulated in the extracellular space of the ischemic compartment such as $K^+$, lactate, and other metabolites, transiently influence electrophysiological characteristics of normal cells close to the ischemic zone as they are washed out of the ischemic compartment. On the other hand, action potential shortening of previously ischemic cells during reperfusion is accompanied by a rapid return of extracellular $K^+$ concentration to normal values, even with an “undershoot,” during which extracellular $K^+$ concentration may reach values that are up to 1 mmol/L lower than preischemic (and control zone) values. This also occurred in the perfused papillary muscle preparation in the experiments of Cascio et al.

It is quite possible that the increased inhomogeneity in action potential duration in and around the previously ischemic zone immediately after abrupt reperfusion is a major factor contributing to the occurrence of fibrillation by enhancing the likelihood for reentry. As suggested by Corr and Witkowski, the fact that the highest incidence of reperfusion-induced ventricular fibrillation occurs after a 20- to 30-minute period of ischemia (a time when some cells show irreversible injury) may be related to maximal heterogeneity when irreversibly and reversibly injured cells are juxtaposed. Studies in which activation has been mapped with simultaneous extracellular recordings have demonstrated the presence of multiple reentrant circuits in the ischemic area during reperfusion-induced fibrillation. The origin of the initial ectopic impulses that induce fibrillation is close to the border and these impulses usually are not caused by reentry.

Perpetuation of tachycardias that lead to fibrillation are also sometimes caused by nonreentrant mechanisms, such as abnormal automaticity or triggered activity that can be linked to elevations in intracellular calcium that occur during ischemia.

What is new and surprising in the study of Cascio et al. is that the ischemia-induced increase in $r_i$ (gap junctional uncoupling) also reversed, although with a slower time course, indicating restoration of cell coupling. The results of previous studies had suggested that once uncoupling had occurred, it was indicative of impending cell death and that restoration with reperfusion did not occur. Therefore, this study clearly shows that cell-to-cell uncoupling during ischemia is not an absolute marker of irreversible cellular injury. Since $r_i$ recovers rapidly and $r_o/r_i$ is decreased during the early period of reperfusion and may be responsible for the characteristic changes in the ST segment (see discussion in Cascio et al.).

The return of cell coupling to preischemic levels was delayed as was a return of normal membrane potentials ($E_M$) with divergence of $E_K$ and $E_M$, suggesting the presence of a persistent inward current. Slowing of conduction existed at this time. Therefore, the study of Cascio et al. shows that at least two factors exist during the early reperfusion period that could contribute to the occurrence of reentrant arrhythmias, persistent membrane depolarization, and gap junctional uncoupling. Later, during reperfusion, further recovery of $E_M$ and $r_i$ is related to restoration of nearly normal conduction.

Therefore, abnormal cellular coupling is becoming a ubiquitous pathophysiological factor in the occurrence of severe arrhythmias, having previously been implicated as having a central role in ventricular tachycardia that accompanies the early period of ischemia before complete uncoupling occurs as well as tachycardia associated with healing and healed infarcts. But how is coupling reestablished in the face of a persistent elevation in factors that had previously been designated as responsible for the uncoupling—increases in $Ca^{2+}$, and lipid metabolites and decrease in pH—since these factors are not quickly restored to normal during reperfusion? Cascio et al. cite as a possibility a study of Beardslie et al. in cell cultures that relates cellular uncoupling during ischemia to dephosphorylation of connexin43 and translocation of connexin43 to intracellular pools. Is there rapid phosphorylation of connexin43 and translocation from intracellular pools to gap junctions during early reperfusion to restore cellular coupling? Important questions continue to arise that must be answered, so the study of mechanisms of reperfusion arrhythmias must go on, despite a century of progress.

References


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