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EDITORIAL COMMENT

New Observations Regarding Post-Ischemia/Reperfusion Myocardial Swelling*

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In the 1960s and 1970s, the laboratory of Dr. Robert Jennings performed many experimental studies exploring the effect of reperfusion on myocardial pathology using an anesthetized canine model of mechanical proximal circumflex coronary artery occlusion followed by reperfusion (1–3). They observed reversible ischemic injury with coronary artery occlusions shorter than 20 min and followed by reperfusion; the myocardial cells recovered and did not die (3). When ischemia was prolonged to 20 to 40 min before institution of reperfusion, subendocardial myocardial cells underwent necrosis (3). However, midmyocardial and subepicardial cells were salvaged. As the duration of coronary occlusion was extended from 40 min to 3 h and then 6 h, necrosis extended within the ischemic risk zone from the subendocardium to the subepicardium, which they called the "wave front phenomenon of ischemic cell death" (4). This observation, confirmed by other laboratories (5), helped pave the way for the current established therapy for acute ST-segment elevation myocardial infarction—early and complete reperfusion of the culprit coronary artery.

Biochemical and ultrastructural features of myocardium subjected to ischemia and reperfusion have been described (1,2). At the end of 40 min of ischemia in the subendocardium of the anesthetized canine model, myocytes display a characteristic ultrastructural feature of irreversibly injured cells: the presence of amorphous dense bodies within the mitochondria (2). Additional common features included: intermyofibrillar edema, mild subsarcolemmal edema, loss of glycogen granules, mitochondrial edema, nuclear chromatin clumping and margination, and wide I bands. Upon reperfusion, ultrastructural abnormalities in this region worsened markedly. Myocytes exhibited evidence of extensive swelling. The sarcolemmal membrane appeared lifted off of the myofilaments with edema fluid below it (so-called sarcolemmal blebbing or blistering) and also demonstrated breaks or gaps. Large fluid-filled vacuoles appeared within the cytoplasm and thick contraction bands appeared. Mitochondria showed additional swelling and separation of the cristae; a second type of dense body, doughnut-shaped, with dark black particles (thought to represent calcium phosphate precipitates), appeared within mitochondria. Endothelial cells showed loss of pinocytotic vesicles, diffuse and focal swelling, and clumping of the nuclear chromatin. These ultrastructural findings were corroborated by studies showing the association of reperfusion with a marked increase in tissue water, and an increase in myocardial sodium and calcium (1). The increased tissue swelling occurred very rapidly—within seconds to minutes of release of the epicardial coronary artery clamp. The theory is that some cells within the most ischemic subendocardium of the left ventricle (where collateral flow is lowest in the canine model) are irreversibly injured at the end of the period of ischemia. When reperfusion occurs, these cells are exposed to a sudden influx of fluids and electrolytes. Because these cells have sarcolemmal membrane defects resulting in impaired volume control, fluids, sodium, and calcium overwhelm them, leading to "explosive cell swelling" (6) within seconds to minutes of reperfusion. Reversibly injured cells located in the midmyocardium and subendocardium of this model may also demonstrate some degree of swelling with ischemia/reperfusion, but considerably less than in

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cells that die; reversibly injured cells eventually recover structure and function and are salvaged by reperfusion (3).

Following this acute phase of cellular edema, there is likely resorption of fluid from dead cells that degenerate and extrusion of fluid from those cells that have survived the ischemic insult. Inflammatory cells, including neutrophils and macrophages, enter the debris area of necrotic cells and begin to "clean up the mess." This begins within days of the insult and continues for several weeks as fibroblasts and collagen begin building a scar to replace the fragile necrotic tissue (7).

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In this issue of the *Journal*, Fernández-Jiménez et al. (8) describe their in-depth study of the time course of edema in a porcine model of 40 min of coronary artery occlusion followed by reperfusion using cardiac magnetic resonance imaging and direct measurements of water content. They make the important, original observation of a rapid, marked increase in tissue water at 2 h of reperfusion; at 24 h the edema is largely resolved, but water content increases at days 4 and 7 after reperfusion. Hence, myocardial edema followed a bimodal pattern. The first wave, observed in the early hours of reperfusion, very likely represents, in part, the explosive cell swelling described earlier. However, examination of their cardiac magnetic resonance images and transmurality assessments suggests a degree of transmural edema of the left ventricle. This may be because the pig model has almost no collateral flow compared with the dog model; thus, a shorter duration of ischemia may cause irreversible injury across the wall of the ventricle in the pig model, whereas 40 min of ischemia followed by reperfusion in the canine model causes a subendocardial infarction. These images may also represent transient edema of salvaged tissue. The second wave of edema that begins on day 4 may be due to the post-necrotic inflammatory reaction in which mononuclear cells (e.g., macrophages and fibroblasts) enter the necrotic area to break down and phagocytize debris and begin repair.

The authors are to be congratulated on defining the time course of myocardial edema over 7 days of reperfusion and making the important observation that the edema is not static, but fluctuates—with an early, dramatic increase in the first few hours, resolution at 24 h, and then a second wave at 4 to 7 days. One important and practical aspect of this study is that it suggests that researchers testing adjunctive therapies to reduce myocardial infarction size should be careful about assuming that the zone of edema observed on cardiac magnetic resonance imaging captures a reliable area at risk or ischemic risk zone (9) present before the infarction. The zone of edema fluctuates over time and may be influenced by therapy. Any therapy that reduces ischemic necrosis may reduce the zone of edema in the early hours of reperfusion, thus falsely reducing the size of the ischemic risk zone. Measurement of the zone of edema at 24 h, when the early edema has resolved, will also falsely lower the risk zone. Anti-inflammatory agents have the potential to reduce the zone of edema that occurs at 4 to 7 days.

Several questions remain. How much time after reperfusion is needed to resolve the edema? Presumably, once the scar is fully formed, the edema should fully and permanently dissipate. The authors studied 1 duration of ischemia (40 min); would these time courses be similar with earlier or later reperfusion? What happens to edema within the infarct, within the zone of microvascular occlusion (no-reflow), within salvaged tissue in the risk zone, in the noninfarcted border zone beyond the risk zone, and in the noninfarcted remote zone? Sampling tissue from various regions of the risk zone would be useful.

In summary, the fine paper by Fernández-Jiménez et al. (8) adds to our knowledge of the pathophysiology of reperfusion phenomenon in the setting of ST-segment elevation myocardial infarction and shows real-time assessment of water content using a noninvasive imaging technique. These investigators have made the important observation that real-time imaging detects a true bimodal pattern of tissue edema over the first 7 days of reperfusion.

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