JACC Vol. 14, No. 7
December 1989:1814–5

Editorial Comment

No Reflow Revisited*

ROBERT A. KLONER, MD, PHD

Los Angeles, California

The no reflow phenomenon. This term refers to the inability to reperfuse myocardial tissue after removal of a coronary artery occlusion (1). This phenomenon occurs not only in cardiac tissue subjected to ischemia plus reperfusion, but also in brain, skin and kidney (1).

Initial descriptions (1,2) of the no reflow phenomenon in the heart were obtained using experimental preparations in which a coronary artery was occluded for various periods of time; the coronary occlusion was then removed and the vasculature injected with dye. In our initial study (1), anesthetized dogs were subjected to either 40 or 90 min of ischemia followed by reperfusion. Thioflavin S (a fluorescent stain specific for endothelial cells) or carbon black was injected intravenously after 10 to 12 s and 5 or 20 min after removal of the coronary clamp. After a 40 min period of ischemia followed by reflow, the tracers were distributed homogeneously throughout the myocardium. However, after 90 min of ischemia, portions of the subendocardium were not penetrated by these dyes after 10 to 12 s and 5 or 20 min of reflow. In a later study (3) we observed perfusion defects in the subendocardium and portions of the mid-myocardium when thioflavin S dye was injected after 3 h of occlusion and 3 h of reperfusion. Furthermore, the anatomic distribution of no reflow, determined by dye injection, also correlated with a reduction in regional myocardial blood flow as determined by radioactive microspheres (3). In both of these studies the zones of no reflow were confined to areas where the myocardial cells were already dead (as determined by either electron microscopy or tetrazolium staining). Therefore, we thought it unlikely that no reflow was playing a major role in causing myocardial cell death.

A recent study (4) suggests that the no reflow phenomenon may become worse over time. Using a 90 min period of transient coronary occlusion, Ambrosio et al. (4) observed that the area of impaired perfusion assessed by thioflavin S increased in size nearly threefold between 2 min and 3.5 h after reperfusion. Postmortem injection of silicone rubber showed that areas devoid of capillary filling also increased between 2 min to 3.5 h after reperfusion. Whether this progressive reduction in flow after reperfusion contributes to irreversible myocardial cell damage is unknown.

Mechanisms of no reflow. There have been a host of mechanisms proposed to explain the no reflow phenomenon. In our 1974 study (1) electron microscopic evaluation of no reflow areas was obtained to learn more about the mechanisms of no reflow. The most striking feature was damage to the microvasculature, including decreased endothelial pinocytotic vesicles, endothelial gaps, endothelial protrusions or blebs (which often appeared to be occluding the capillaries), fibrin tactoids and rouleaux formation of erythrocytes. On rare occasions swollen myocytes were observed, which appeared to be compressing the capillaries. We doubt that the fibrin tactoids are a major contributor to no reflow because neither streptokinase nor tissue plasminogen activator prevented this phenomenon in a mechanical model of coronary occlusion plus reperfusion (3,5).

Whereas it appears certain that no reflow is due at least in part to microvascular injury, the factors responsible for endothelial cell damage after ischemia and reperfusion are uncertain. In anesthetized dogs subjected to 2 h of transient coronary artery occlusion, we recently observed (6) that no reflow was significantly attenuated by administration of the potent free radical scavenging agents superoxide dismutase and catalase at the time of reperfusion. Furthermore, the enhanced blood flow after reperfusion in dogs treated with these two agents in combination was accompanied by marked preservation of the vascular endothelium (6). These data suggest that no reflow may be a consequence of free radical-mediated microvascular damage.

Accumulation of activated neutrophils in previously ischemic myocardium may contribute to no reflow, both by acting as a source of oxygen radicals (6) and by physically occluding or "plugging" the microvessels (4,5,7). It is clear, however, that neutrophils are not absolutely necessary to induce no reflow. For example, no reflow occurs in isolated perfused heart preparations devoid of neutrophils (8–10). In addition, we (1) observed areas of no reflow within 10 to 12 s of removal of the coronary clamp, which may be too short a time for neutrophils to migrate into the previously ischemic myocardium. Although neutrophils may not mediate acute no reflow, their subsequent migration into the previously ischemic tissue may account for the later worsening of no reflow as described by Ambrosio et al. (4).

The present study. In the study of Carlson et al. (11) in this issue of the Journal, anesthetized dogs were subjected to 2 h of coronary occlusion followed by 4 h of reperfusion.

*Editorials published in *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the Heart Institute of the Hospital of the Good Samaritan and University of Southern California, Section of Cardiology, Los Angeles, California.

Address for reprints: Robert A. Kloner, MD, The Heart Institute, The Hospital of the Good Samaritan, 616 South Witmer Street, Los Angeles, California 90017.

0735-1097/89/$3.50

Bovine neutrophil antiserum was utilized to reduce circulating neutrophil counts by an average of 81%. This reduction in neutrophils did not modify no reflow assessed with the radioactive microsphere technique. Their data thus support the concept that neutrophils are not important in the pathophysiology of no reflow. However, as the authors point out, suppression of neutrophils with antiserum was not complete: the data of Engler et al. (7) suggest that only very few neutrophils may be needed to cause microvascular plugging. Furthermore, the total number of neutrophils within the myocardium may be less important than their state of activation. It is conceivable that had leukopack filters been used to more completely remove neutrophils from the reperfusate, no reflow might have been blunted. Nevertheless, the data of Carlson et al. (11) do support the notion that other factors besides neutrophils contribute to no reflow.

Clinical implications. What are the clinical implications of the no reflow phenomenon? "No reflow" has now been described in patients after thrombolysis (12). It is our opinion that no reflow is a *secondary* phenomenon that occurs because of microvascular injury within areas of dead myocardial cells. There has been no convincing evidence that reduction of the no reflow phenomenon will limit the extent of myocyte injury. Thus, in the clinical setting, therapy aimed primarily at reducing no reflow is unlikely to reduce infarct size. However, reducing the no reflow phenomenon could conceivably result in certain beneficial effects independent of infarct size reduction. For example, maintaining perfusion into areas of infarcted myocardium could facilitate the removal of necrotic debris and theoretically hasten the healing process. In this regard, it has been shown in experimental studies (13–16) that late coronary reperfusion (too late to reduce myocardial infarct size) may increase scar thickness, reduce myocardial infarct expansion and reduce the severity of ventricular arrhythmias. In addition, maintaining blood flow through necrotic tissue may provide a route by which drugs can gain access to adjacent zones of reversibly injured myocardium.

Conclusions. The no reflow phenomenon is a well recognized consequence of reperfusion after ischemia. It is unlikely that it contributes primarily to irreversible myocardial cell death. No reflow is most likely due to microvascular damage, perhaps mediated by oxygen free radicals. Thrombolytic agents do not prevent no reflow, suggesting that fibrin deposition is not a major mechanism. Whereas neutrophil plugs also have been suggested as a possible cause for no reflow, the present study by Carlson et al. (11) suggests that other factors contribute.

I am grateful to Dr. Robert Jennings, Dr. Charles Ganote, Dr. Keith Reiner, Dr. Karin Przyklenk and Kevin Alker, who have worked with me on the study of no reflow, and to Anne Liwag for excellent typing skills.

References

1. Kloner RA, Ganote CE, Jennings RB. The "no-reflow" phenomenon following temporary coronary occlusion in the dog. J Clin Invest 1974; 54:1496–508.
2. Krug A, Mensil de Rochemont W, Korb G. Blood supply of the myocardium after temporary occlusion. Circ Res 1966;19:57–62.
3. Kloner RA, Alker KJ. The effect of streptokinase on intramyocardial hemorrhage, infarct size, and the no-reflow phenomenon during coronary reperfusion. Circulation 1984;70:513–21.
4. Ambrosio G, Weisman HF, Becker LC. The "no-reflow" phenomenon: a misnomer? Circulation 1986;74(suppl II):II-260.
5. Kloner RA, Alker KJ, Campbell C, Figures G, Eisenhauer A, Hale S. Does tissue-type plasminogen activator have direct beneficial effects on the myocardium independent of its ability to lyse intracoronary thrombi? Circulation 1989;79:1125–36.
6. Przyklenk K, Kloner RA. "Reperfusion injury" by oxygen-derived free radicals? Effect of superoxide dismutase + catalase, given at the time of reperfusion, on myocardial infarct size, contractile function, coronary microvasculature and regional myocardial blood flow. Circ Res 1989; 64:86–96.
7. Engler RL, Schmid-Schonbein GW, Pavelec RS. Leukocyte capillary plugging in myocardial ischemia and reperfusion in the dog. Am J Pathol 1983;111:98–111.
8. Humphrey SM, Gavin JB, Herdson PB. The relationship of ischemic contracture to vascular reperfusion in the isolated rat heart. J Mol Cell Cardiol 1980;12:1397–406.
9. Watts JA, Whipple JP, Hatley AA. A low concentration of nisoldipine reduces ischemic heart injury: enhanced reflow and recovery of contractile function without energy preservation during ischemia. J Mol Cell Cardiol 1987;19:809–17.
10. Elz JS, Nayler WG. Contractile activity and reperfusion-induced calcium gain after ischemia in the isolated rat heart. Lab Invest 1988;58:653–9.
11. Carlson RE, Schott RJ, Buda AJ. Neutrophil depletion fails to modify myocardial no reflow and functional recovery after coronary reperfusion. J Am Coll Cardiol 1989;14:1803–13.
12. Schofer T, Montz R, Mathey DG. Scintigraphic evidence of the "no reflow" phenomenon in human beings after coronary thrombolysis. J Am Coll Cardiol 1985;5:593–8.
13. Hale SL, Kloner RA. Left ventricular topographic alterations in the completely healed rat infarct caused by early and late coronary reperfusion. Am Heart J 1988;116:1508–13.
14. Hochman JS, Choo H. Limitation of myocardial infarct expansion by reperfusion independent of myocardial salvage. Circulation 1987;75:299–306.
15. Arnold JMO, Antman EM, Przyklenk K, et al. Differential effects of reperfusion on incidence of ventricular arrhythmias and recovery of ventricular function at 4 days following coronary occlusion. Am Heart J 1987;113:1055–65.
16. Braunwald E. Myocardial reperfusion, limitation of infarct size, reduction of left ventricular dysfunction, and improved survival: should the paradigm be expanded? Circulation 1989;79:441–4.