Myocardial ischemia: reversible and irreversible changes

E. Carmeliet, M.D., Ph.D.

RECENTLY there has been a growing tendency to remove thrombi, either surgically or medically, from the coronary arterial systems of patients who have had myocardial infarctions. Such interventions are successful or fail depending on the duration of the obstruction, i.e., on whether the ischemic lesion is in the reversible or irreversible stage. It is therefore important to obtain more detailed knowledge of the phenomena determining the reversibility, or lack thereof, of myocardial ischemia.

Reversible phase

Early fall in tension development. During the early stages of myocardial infarction acute pump failure can occur due to deficient contractile machinery or to electrical instability. In the infarcted area a marked decrease in tension occurs within a few seconds of the interruption of the blood supply or hypoxia, preceding any change in electrical activity.1 This decrease in tension may lead to passive extension of the damaged area (aneurysmal bulging) by the active shortening of the surrounding myocardium.2

The following three hypotheses have been proposed as possible mechanisms for the decrease in tension: (1) inhibition of the availability of Ca++ to the myofilaments, either through a decrease in influx through the plasma membrane or a diminution of release of Ca++ from the sarcoplasmic reticulum, (2) decreased myofilament sensitivity to Ca++ secondary to acidosis, e.g., by interaction between H+ and Ca++ at the level of troponin, and (3) insufficient amounts of adenosine triphosphate (ATP), the normal energy source for myocardial contractility.

However, the absence of any clearcut changes in secondary Ca inward current or aequorine signal (which is a direct measurement of intracellular free Ca level) suggests that a decrease in the availability of Ca++ during excitation is not a likely cause of the dramatic decrease in tension.3

The hypothesis that the decrease in myofilament sensitivity is secondary to elevation in proton concentration (acidosis hypothesis)4, although supported by results of skinned cardiac cell experiments,5 is also an unlikely explanation since early and large increases in [H+] levels sufficient to suppress troponin sensitivity to Ca++ have not been convincingly demonstrated.6,7

A similar problem exists with respect to the third hypothesis. Since the rate of ATP consumption per minute in a normal working heart is about five to ten times the concentration of ATP within the myocardium, the finding of a substantial decrease in ATP during ischemia is not surprising. The initial fall in ATP level even precedes the decrease in contractile activity.1 However, this early decrease in ATP is not maintained. Therefore, unless ATP is compartmentalized or its free energy change of hydrolysis is decreased below a critical level, it is not likely that the early decrease in tension is the result of a decline in ATP levels.

Electrophysiologic changes and K+. An upward shift in the ST segment is the first change due to ischemia that is evident on the electrocardiogram. This change results from a decrease in resting potential, a loss of plateau, and a shortening of action potential. The first factor causes an apparent shift and the second a real upward shift in the ST segment.8 An increase in extracellular K+ concentration (Ke+) is responsible for the early depolarization of the ischemic cells. Direct measurements of changes in Ke+ made with K-sensitive electrodes have shown that it may increase by 10 to 15 mM within 10 min of coronary occlusion.9

Inhibition of the Na-K pump has been proposed as the most probable explanation for the rise in Ke+. Contrary to this hypothesis intracellular Na concentration has been shown to remain constant for at least 15 min during metabolic inhibition.10 Also, Ke+ is still actively absorbed during inhibition, as demonstrated by the fall in Ke+ when the rate of stimulation is reduced.11 The increased level of Ke+, therefore, cannot be due to a fall in active K influx, but rather to an increase in unidirectional K efflux secondary to an increase in K

From the Laboratory of Physiology, University of Leuven, Belgium.
Address for correspondence: Dr. E. Carmeliet, Laboratory of Physiology, University of Leuven, Gasthuisberg, 3000 Leuven, Belgium.

Vol. 70, No. 1, July 1984

149
permeability. This conclusion has been verified by results of $^{42}$K$^+$ efflux and voltage clamp experiments in multicellular preparations and in single myocytes. A rise in intracellular Ca secondary to release of Ca from the sarcoplasmic reticulum or mitochondria has been proposed as the underlying mechanism for the increased K$^+$ permeability. It is possible, however, that the link between the increase in K permeability and the metabolic inhibition caused by ischemia is more direct. Measurements of single-channel currents by the patch-clamp technique have shown the existence of a K$^+$ channel in cardiac cells that opens when ATP concentration falls below a critical level of 1 mM. The role of ATP in this process is not to provide energy by its hydrolysis, but to keep this specific K channel closed.

**Arrhythmias.** Ventricular arrhythmias, sometimes of the malignant type, may occur during the first 30 min of myocardial ischemia. Reentry is the most probable underlying phenomenon, but other phenomena may also play a role in the genesis of these arrhythmias. Most of these have already been noted in the analysis of the changes in contractility and in electrophysiologic studies. The increases in K$^+$ and membrane depolarization, for instance, are thought to be responsible for inactivation of Na$^+$ channels, which results in a decrease in action potential amplitude and suppression of rate of depolarization and conduction velocity. The cell uncoupling that occurs secondary to acidosis and an increase in intracellular Ca$^{2+}$ can also reduce conduction velocity. The fact that “cardiac cells communicate in life, but fail to give a message of their decay” was recognized by Engelmann in 1875. Another factor that may be related to the genesis of reentry arrhythmias is the destabilization of the cell membrane that results from interaction with increased amounts of free fatty acids and lysophosphatidylcholine. Since both species of compounds act as amphiphiles, they may cause membrane expansion, displacement of Ca$^{2+}$, and destruction of the lipid anulus surrounding transport or channel proteins. In vitro these substances have been shown to shift the voltage dependence of Na and Ca current to cause depolarization, and to induce non-specific changes in membrane permeability. Whether the concentrations of these substances rise high enough in vivo during early ischemia remains an open question.

**Irreversible phase**

When the period of ischemia extends beyond 30 min, certain ischemic lesions become irreversible. The shift from reversibility to irreversibility is related to a critical decrease in concentrations of high-energy phosphate compounds and/or in free energy change of ATP hydrolysis. The decrease in high-energy phosphate levels inhibits the Na pump, which results in Ca$^{2+}$ overload. In this situation not only does reperfusion not result in recovery, but it may aggravate the situation by activating positive feedback mechanisms. With respect to this problem the following should be mentioned (1) the no-reflow phenomenon and changes in osmotic pressure, (2) the waste of oxidative energy on Ca absorption instead of ATP synthesis in mitochondria, and (3) the peroxidation of lipids and the formation of radicals, which causes membrane breakdown.

Upon reperfusion, cells often swell due to increased osmotic pressure generated during ischemia by accumulation of lactic acid and phosphate. The resulting increase in extravascular resistance eventually occludes the nutritive vessels. The importance of this phenomenon has recently been demonstrated by the finding that much better recovery of electrical and biochemical functions occurs when the osmotic pressure of the reperfusing solution is increased to levels above normal to avoid cell swelling.

Dangers secondary to reperfusion of ischemic tissue may also result from altered Ca$^{2+}$ homeostasis. During ischemia the concentration of free Ca$^{2+}$ may increase secondary to release of Ca$^{2+}$ from the sarcoplasmic reticulum and mitochondria. Upon reoxygenation, the reenergization of the mitochondria in the presence of high concentrations of Ca$^{2+}$ and adenosine diphosphate will not restore ATP formation; instead, all energy provided will be spent by the mitochondria for the absorption of Ca. This process results in severe depletion of ATP and formation of rigor mortis (stone heart).

The third factor that plays an important role in the irreversible phase of myocardial infarction is excessive membrane leakage. During ischemia membrane permeability increases, in part because of the rise in intracellular Ca$^{2+}$ and interaction of phosphatides and fatty acids with the membrane constituents. Upon reperfusion the reavailability of oxygen together with large amounts of xanthine, a degradation product of ATP, results in the formation of superoxide and hydroxyl radicals. Thus, the peroxidation of membrane lipids and fatty acids would further enhance membrane leakage.

Fairly good and reliable information is now available on the processes that occur during the different phases of myocardial ischemia. The underlying mechanisms for ischemia-induced changes, especially...
those of the irreversible phase, are less well understood. This kind of information is important in predicting whether recovery of normal contractile and electrical activity may be expected after removal of an obstructing thrombus. Future research should therefore be aimed at delineating and solving problems related to reperfusion.

References


16. de Mello WC: Effect of 2,4-dinitrophenol on intercellular communication in mammalian Purkinje fibers. Pflugers Arch 380: 267, 1979


Myocardial ischemia: reversible and irreversible changes.
E Carmeliet

_Circulation_. 1984;70:149-151
doi: 10.1161/01.CIR.70.1.149

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1984 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/70/1/149.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/