Myocardial preservation

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Objective assessment of preservation of myocardium has been stimulated by interest in myocardial infarction and by the hypothesis that infarct size is an important determinant of prognosis and one potentially amenable to favorable modification during the early evolution of ischemic injury. Recently, the importance of myocardial preservation in the setting of cardiac surgery has received increasing attention. In this discussion, the basis for some clinically applicable noninvasive techniques for objectively assessing the extent of myocardial injury will be presented, followed by some results from experimental studies delineating one approach to preserving ischemic myocardium in the setting of cardiac surgery.

As opposed to other criteria, such as electrophysiologic changes or alterations in left ventricular function which may be reversible manifestations of ischemia as well as infarction, biochemical indices of cell death are theoretically suitable for estimating the extent of infarction (or infarct size) in absolute terms.[1]

Assessment of myocardial creatine kinase (CK) depletion and subsequently plasma CK time-activity curves has proven particularly useful. After coronary occlusion in rabbits, myocar-

dial CK depletion is proportional to infarct size estimated morphologically and to regionally decreased blood flow assessed with radioactively-labeled microspheres. In dogs S-T segment elevation, ultrastructural and microscopic evidence of necrosis, and impaired myocardial function correlate with myocardial CK depletion as well. After coronary occlusion, plasma CK curves correlate closely with myocardial CK depletion measured directly in conscious experimental animals.[1–4]

Since marked variation in the CK disappearance rate (k_d) within an individual study could distort enzymatic estimates of infarct size, we have recently assessed k_d in conscious dogs subjected to profound hemodynamic and pharmacologic perturbations simulating those associated with myocardial infarction. Despite marked reduction of cardiac output, acceleration of heart rate, reduction of hepatic or renal perfusion, administration of therapeutic doses of commonly used drugs, or induction of myocardial infarction itself, k_d remained virtually constant.[1,5,6] On the other hand, anesthesia reduces k_d markedly—an effect that must be taken into account to avoid spurious estimates in anesthetized animals.

Enzymatic estimates of infarct size correlate with the frequency of ventricular dysrhythmias, severity of myocardial dysfunction assessed with radionuclides or conventional left ventricular angiography, pulmonary venous congestion, hemodynamic manifestations of impaired ventricular function and compliance, as well as early mortality.[7] Among one series of 60 patients admitted consecutively with plasma CK values increasing at the time of admission, mean infarct size in survivors averaged 22 ± 2.5 CK-g-eq/m^2 (mean ± SE) compared to 66 ± 6.9 in nonsurvivors ($p < 0.001$).[8] Thus, the severity of myocardial damage appears to be a common denominator contributing to electrophysiologic derangements, impaired ventricular function, morbidity and mortality after myocardial infarction.

In recent studies with quantitative assays for MB CK, including a radioimmunoassay developed in our laboratory, the following observations were made: (1) after experimental infarction in dogs, release of MB CK is tantamount to cell death detectable morphologically;[9] (2) in patients with infarction, elevated plasma MB CK occurs consistently averaging 12% to 15% of peak total CK;[10] (3) after noncardiac surgery, MB CK activity is never elevated despite markedly increased total CK; (4) after myocardial infarction in patients given intramuscular injections, total CK curves are distorted, but MB curves are not;[5] and (5) estimates of infarct size based on MB in patients with hemodynamically uncomplicated infarction correlate closely with estimates based on total CK ($r = 0.97$).[5] Since hemodynamic and pharmacologic interventions do not alter k_d substantially, analysis of MB CK curves from hemodynamically complicated patients with infarction permits accurate quantitative assessment of infarct size despite release of noncardiac CK into the circulation.

Enzymatic estimates of infarct size have been used to evaluate potentially therapeutic interventions on evolving myocardial damage. One approach entails predicting infarct size based on projection of plasma CK values by curve-fitting serial early changes.[3,11] When trimethaphan was

administered to hypertensive patients with acute infarction to reduce ventricular afterload and myocardial oxygen consumption, observed infarct size was significantly less than that predicted prior to administration of the drug, suggesting salvage of myocardium that would have otherwise undergone irreversible injury.[12] Furthermore, early mortality was reduced.

In order to evaluate quantitatively evolution of infarction sooner after its onset than possible by projecting plasma-enzyme CK curves, we have recently used physiologic substrates of myocardium labeled with positron-emitting isotopes and computer reconstruction to define the distribution of isotope with cross sections of the heart from apex to base.[13] Distribution of isotope in 1.5-cm thick cross sections of the heart is quantitatively represented in images produced by computer reconstruction from data acquired as a hexagonal array of detectors is rotated around the subject after intravenous administration of ^{11}C-palmitate, a physiologic substrate of myocardium. After ascertaining that ^{11}C-palmitate accumulation was readily demonstrable in normal canine myocardium following intravenous injection and that decreased accumulation accompanied ischemia and was quantitatively related to infarction in vivo,[14, 15] positron emission transaxial tomography was implemented in normal human subjects and patients with myocardial infarction 3 to 12 months previously. Tomograms in normal subjects exhibited homogeneous distribution of ^{11}C-palmitate throughout the left ventricle (*Figs. 1 and 2*). Tomograms from patients with remote infarction exhibited diminished accumulation of ^{11}C-palmitate delineating regions corresponding to the electrocardiographic locus of infarction[16] permitting quantitative, noninvasive estimation of the extent of jeopardized ischemic myocardium undergoing irreversible injury soon after the onset of ischemia and objective evaluation of interventions designed to protect ischemic myocardium.

Protection of ischemic myocardium in the setting of surgery

Recently, studies performed by Doctors Richard Clark and Philip Henry in our laboratory with nifedipine, an inhibitor of transmembrane calcium flux, demonstrated remarkable protection of ischemic canine myocardium during a 2-hour interval in which dogs were supported on cardiopulmonary bypass. Infusion of the drug at the rate of 5 μg/kg/hr to six dogs, otherwise supported in the identical fashion to seven normal controls infused with saline at the same flow and temperature (20 C), resulted in the maintenance of adequate aortic pressure and cardiac output after 16 minutes of normothermic reperfusion in contrast to the case in the control of dogs—all of whom had profound left ventricular failure unresponsive to large doses of agents with positive inotropic effects. After 2 hours of ischemia, stroke work was depressed by 85% in controls, and only 12% in drug-treated dogs, and ischemic injury detectable by microscopic analysis of the hearts was markedly diminished in animals treated with nifedipine.[17] These results corroborate findings obtained in isolated perfused rabbit hearts in which administration of calcium antagonists precluded intramyocardial accumulation of calcium, contracture

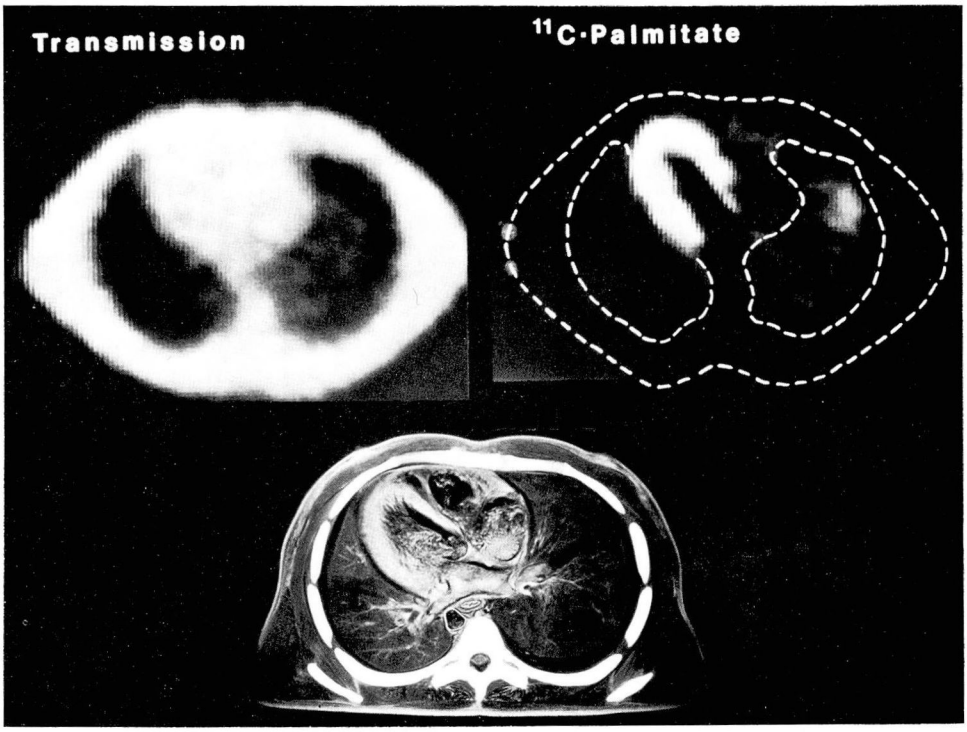

Fig. 1. Emission tomogram (upper right) depicts homogeneous distribution of tracer in a cross section at the same level in a cadaver shown below. The posterior gap in the tomogram represents the nonvisualized mitral valve apparatus and left atrium. For orientation, a transmission x-ray image of the heart in cross section is shown on the left.

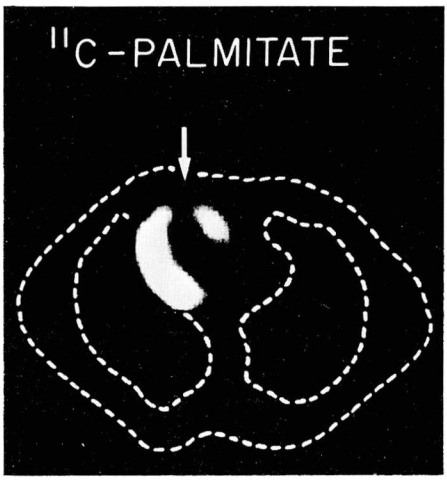

Fig. 2. Tomogram demonstrating decreased anterior distribution of tracer in left ventricular myocardium undergoing infarction in a region corresponding to the electrocardiographic locus of evolving Q waves in the same patient.

of the heart in diastole, and irreversible functional injury induced by hypoperfusion.

Ischemic injury in the setting of cardiovascular surgery appears to be diminished by selected pharmacologic and physiologic tools. Recent progress in noninvasive objective assessment of the distribution and progression of irreversible injury has been striking. Together, these approaches should make effective surgery possible for some subsets of patients now inoperable because of the distribution of coronary artery disease or the rate of evolution of ischemic injury.

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