EDITORIAL

Salvage of Myocardium in Acute Ischemia

CLINICIANS have long been concerned that some of the therapeutic measures employed in patients with heart failure caused by myocardial infarction may exert paradoxical effects by causing direct damage to the myocardium. Administration of agents that enhance the inotropic state of the myocardium may increase oxygen demand, and since oxygen supply is critically limited, further ischemic damage to cardiac muscle may result.

It is entirely proper that clinicians concern themselves with the possibility that salvage of ischemic myocardium may have a place in the therapy of myocardial infarction. In this issue of Circulation, Maroko and his colleagues have attempted to define factors that may influence the extent of the ischemic process, using as an experimental model dogs with temporary or permanent coronary ligation. Severity of ischemia is assessed from two measurements: (1) height and extent of S-T segment elevation measured from epicardial electrodes within minutes after temporary ligation, and (2) depletion of creatine phosphokinase from the ischemic area 24 hr after permanent ligation. The authors found that inotropic interventions (isoproterenol, glucagon, ouabain, bretylium, and rapid pacing) increased the severity and extent of S-T segment elevation within minutes after ligation, and that, conversely, a cardiac depressant (propranolol) did the opposite. Also, lowering blood pressure by hemorrhage increased ischemia, and raising it with methoxamine decreased ischemia. The results with isoproterenol and propranolol were supported by measurements of levels of myocardial creatine phosphokinase after 24 hr, which showed relatively greater and lesser degrees of depletion than predicted from control experiments.

The crucial question these studies seek to answer is whether or not there is indeed a significant border zone of myocardial ischemia around an area of infarction where there are myocardial cells, which, though inadequately oxygenated, are viable and may be salvaged. That such a border zone exists in experimental canine infarction has been suggested by histochemical studies. Similarly, the finding of islands of morphologically intact cells around or within areas of infarction in human hearts at autopsy suggests the presence of zones of marginal ischemia. Yet it is also clear that the central area of an infarct in experimental coronary ligation receives very little blood, and that the presence of an infarct large enough to cause heart failure must require a large avascular area. It seems unlikely that drugs exert any direct effect, either beneficial or deleterious, upon the central necrotic area.

The criteria of severity and extent of S-T elevation as a measure of ischemia also require evaluation. Presence of S-T elevation indicates transmural injury. As the authors have shown, and as is also true in certain patients with angina, S-T elevation does not necessarily signify permanent cell damage. Furthermore, since in experimental canine infarction from coronary ligation there is usually relative subepicardial sparing, the absolute quantity of myocardial tissue at stake when there is subepicardial spread of ischemia is uncertain.

In the experiments using depletion of creatine phosphokinase as a label for degree of injury, the authors are properly concerned with “washout” of the enzyme from the damaged area. If no blood perfuses an area, no enzymes can be “washed out,” and so it is possible that high residual levels of enzymes may indicate relatively severe ischemia.

Despite these methodological problems, it does seem clear from this report that a zone of borderline ischemia does exist around an area...
of infarction caused by coronary ligation in dogs, and that its size can be modified by pharmacological interventions and changes in blood pressure. Certain questions remain unanswered, some theoretical and some of clinical importance:

(1) How much tissue mass is really at stake?
Is the "zone of borderline ischemia" really a significant fraction of the total infarct, or is it a thin layer of subepicardial cells? Some recent experimental studies have shown that inotropic stimuli such as rapid pacing may actually improve cardiac failure caused by infarction without evidence of residual damage when pacing is stopped, suggesting that the "border zone" may be of little functional importance or possibly that, in the presence of failure, reduction in ventricular volume by inotropic stimuli may reduce wall tension sufficiently to lower myocardial oxygen requirements.4

(2) Are results in the dog really applicable to clinical myocardial infarction? Extent of collaterals already present and speed of new collateral formation around areas of ischemia are of key importance in determining extent of necrosis and extent of the "border zone" of injury. As the authors note, in the normal canine heart collaterals are more abundant than in the normal human heart; however, in patients with chronic coronary disease, extensive collateral formation may be present. These variations in abundance of collaterals in coronary patients make it difficult for us to know precisely how pertinent findings in canine infarction may be to man.

(3) Is it realistic for us to believe that salvage of borderline areas of ischemia is a therapeutic possibility in man, using drugs and other interventions as in the present experimental study? The animals studied had small areas of ischemia, and presumably were not in failure. This is also true of many patients with small infarcts, or with preinfarction angina. Perhaps in this group of patients, cautious trials of propranolol are warranted, and use of inotropic drugs or interventions should be proscribed. However, in patients with severe heart failure, pulmonary edema, or cardiogenic shock, propranolol is clearly contraindicated, and may worsen failure. The drug may increase myocardial oxygen requirements by causing further ventricular dilatation and increases in wall stress. Particularly in the cardiogenic shock syndrome, the hand of the clinician is often forced, and he must administer drugs which will maintain arterial pressure, either by systemic vasoconstriction or inotropic mechanisms, in order to preserve adequate coronary perfusion pressure. The conclusion is, paradoxically, that "salvage of myocardium" is least feasible therapeutically in patients in whom it is most desirable, i.e., those with extensive myocardial damage.

(4) Do the findings of the present study imply that the compensatory physiologic reactions in cases of severe cardiac damage are inherently inappropriate? Ventricular dilatation, sinus tachycardia, and enhanced endogenous sympathetic tone are all present in advanced cardiac failure, and each of these increases myocardial oxygen requirement. For the reasons stated above, the clinician cannot usually afford to block these reactions, even though they may possibly cause extension of the infarct.5

From all these considerations, it appears that there truly may exist a theoretical basis, clearly demonstrable under certain conditions, for attempting to salvage areas of ischemic but viable myocardium by pharmacologic means. Presently available information would suggest, however, that application of this technique is limited to milder forms of ischemia, in which advanced cardiac decompensation is absent.

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Circulation. 1971;43:11-13
doi: 10.1161/01.CIR.43.1.11

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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:
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