The Reduction of Infarct Size — An Idea Whose Time (For Testing) Has Come

EARLY IN THIS CENTURY, cardiovascular physiologists began to direct their attention to the study of the control of myocardial oxygen consumption (MVO$_2$). Evans and Matsuoka, in Starling’s laboratory in London,1 and Rohde, in Heidelberg,2 called attention to the importance of intraventricular pressure as a principal determinant of MVO$_2$. Technical developments during subsequent decades allowed a systematic reexamination of this problem in the mid-1950s,3 resulting in more precise elucidation of the role of intraventricular tension, myocardial fiber shortening, contraction frequency, and external cardiac work in regulating the heart’s oxygen needs. Later, the roles of myocardial contractility,4 the basal oxygen needs of the noncontracting heart,5 the costs of electrical depolarization of the myocardium,6 and the effect of shortening against a load7 on MVO$_2$ were defined.8

While of considerable interest to physiologists, an understanding of the determinants of MVO$_2$ has considerable clinical implications as well. After all, myocardial ischemia, the principal consequence of coronary arteriosclerosis, is characterized by an imbalance between myocardial oxygen needs and availability, which results in chest discomfort, as well as in alterations in the electrical, mechanical, and metabolic properties of the heart. Persistent, severe ischemia, of course, results in myocardial necrosis.

Armed with an understanding of the determinants of MVO$_2$, it seemed like a logical step to determine whether altering the relation between myocardial energy supply and demand might actually influence the severity and extent of ischemic injury, as well as the extent of actual myocardial necrosis following coronary occlusion.9,10 Utilizing a technique for epicardial electrocardiography, combined with myocardial enzyme (CPK) determinations,11 histologic, histochemical, and electronmicroscopic12 analysis of cardiac muscle, it soon became clear that following coronary occlusion, interventions which augment MVO$_2$ increase the extent and severity of ischemic injury and ultimately the quantity of necrotic tissue.13 A corollary of this observation was that in the first few hours following coronary occlusion, there is no clear demarcation between normal myocardium and tissue which has been irreversibly injured by ischemia. Indeed, pathologic observations have shown that ischemic tissue damage is spotty in the periphery of the injured zone.14 It now appears that for several hours following coronary occlusion the fate of substantial quantities of myocardium is delicately poised; relatively slight alterations in the balance between energy supply and demand at this time can influence the ultimate viability of large quantities of cardiac muscle.

Initially, we manipulated the balance between myocardial oxygen supply and demand by means of positive inotropic agents and tachycardia, both of which increased oxygen demands and, thereby, increased the extent and severity of ischemic injury.15 In other studies mechanical means were used to alter this balance. For example, raising aortic and thereby coronary perfusion pressure augmented perfusion of the border zone through collateral vessels despite increasing myocardial oxygen needs; that the net balance was affected favorably by raising aortic pressure was not surprising when considered in the light of the observation in the normal dog that when aortic pressure is elevated, coronary blood flow rises proportionately more than does MVO$_2$, so that myocardial oxygenation, as reflected in the coronary venous oxygen tension, rises.16

Since these initial investigations, work in our laboratory, as well as in others, has broadened the number and nature of interventions which can augment or reduce the quantity of infarcted tissue following coronary occlusion$^{17-35}$ (table 1). Substances as diverse as hyaluronidase,15 glucose-insulin-potassium,12 hypertonic mannitol,16 cobra venom factor, an inhibitor of the third component of complement,17 and hydrocortisone18 have been shown to exert beneficial effects. Two findings of great potential clinical interest have emerged from these studies on experimental animals: 1) the quantity of myocardium which can be salvaged by these interventions is substantial, and 2) it is possible to commence the treatment a number of hours following the occlusion and still demonstrate effectiveness.

To date, there has been only a limited number of clinical applications of these efforts designed to reduce myocardial ischemic damage. Freecordial maps have suggested the effectiveness of beta-adrenergic
blockade with propranolol\textsuperscript{19} and practolol,\textsuperscript{20} of hyaluronidase,\textsuperscript{21} of sublingual nitroglycerine,\textsuperscript{22, 23} and of intraaortic balloon counterpulsation\textsuperscript{24} in small numbers of patients. Serum CPK disappearance curves, as developed by Shell and collaborators,\textsuperscript{26} have indicated that lowering arterial pressure in hypertensive patients with acute myocardial infarction may also reduce infarct size.\textsuperscript{26} The aforementioned observations are preliminary, have been carried out on very small numbers of patients thus far, and while they constitute exciting pilot studies, they cannot and do not claim to be formal, clinical trials based on which the routine treatment of acute myocardial infarction can be altered.

The problem of limiting infarct size in patients with occlusive coronary artery disease is of the utmost importance. Acute myocardial infarction constitutes the most common cause of death in this country. In patients with this condition who reach the hospital, death due to arrhythmias has been brought under control, but no real dent has been made on the mortality due to pump failure or on the incidence of postinfarction heart failure, both of which result from reduction of the quantity of the viable contractile mass. These very serious consequences of the atherosclerotic process can obviously be avoided by prevention of the development or actual reversal of the fundamental atherosclerotic process itself. In the very long term this approach is clearly the one of choice, and research into the mechanism of development of atherosclerosis must receive the highest priority. Despite a number of interesting leads, however, the elimination of atherosclerosis still seems far away. Therefore, since millions of individuals now have or are developing serious coronary atherosclerosis, it would appear prudent to pursue a multipronged attack on the problem. We submit that one of these prongs should be the limitation of the extent of myocardial necrosis following coronary occlusion.

Abundant experimental evidence indicates that this is now possible. Pilot studies support its clinical feasibility, and a careful, rigorously conducted prospective trial is likely to provide useful results and would now be timely. If such a clinical trial demonstrated success in reducing infarct size, it would represent the extension of a chain whose earliest links were represented by the investigations of Evans and Matsuoka,\textsuperscript{1} and Rohde\textsuperscript{2} which, at the time they were carried out, must have seemed of little, if any, clinical relevance.

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\textbf{Table 1}

\textbf{Interventions That Modify Myocardial Injury Following Coronary Occlusion}

<table>
<thead>
<tr>
<th>I. Interventions That Reduce Myocardial Injury</th>
</tr>
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<tbody>
<tr>
<td>A. By decreasing myocardial oxygen demand</td>
</tr>
<tr>
<td>1. propranolol\textsuperscript{16, 11, 19, 27-29}</td>
</tr>
<tr>
<td>2. practolol\textsuperscript{20, 23}</td>
</tr>
<tr>
<td>3. cardiac glycoside in the failing heart\textsuperscript{11, 12}</td>
</tr>
<tr>
<td>4. counterpulsation</td>
</tr>
<tr>
<td>a. intraaortic balloon treatment\textsuperscript{24, 27, 34}</td>
</tr>
<tr>
<td>b. external counterpulsation\textsuperscript{28}</td>
</tr>
<tr>
<td>5. nitroglycerin\textsuperscript{29, 30, 34-38}</td>
</tr>
<tr>
<td>6. by decreasing afterload in hypertensive individuals — Arfonad\textsuperscript{26}</td>
</tr>
<tr>
<td>7. by inhibition of lipolysis — beta-pyridyl-carbinal\textsuperscript{27}</td>
</tr>
<tr>
<td>B. By increasing myocardial oxygen supply</td>
</tr>
<tr>
<td>1. directly</td>
</tr>
<tr>
<td>a. coronary artery reperfusion\textsuperscript{40-44}</td>
</tr>
<tr>
<td>b. elevating arterial pO\textsubscript{2}\textsuperscript{45}</td>
</tr>
<tr>
<td>c. thrombolytic agents\textsuperscript{46}</td>
</tr>
<tr>
<td>2. through collateral vessels</td>
</tr>
<tr>
<td>a. elevation of coronary perfusion pressure by methoxamine, neseynephrine, or norepinephrine\textsuperscript{41, 11, 18, 34, 47}</td>
</tr>
<tr>
<td>b. intraaortic balloon counterpulsation\textsuperscript{24, 31, 34}</td>
</tr>
<tr>
<td>c. external counterpulsation\textsuperscript{35}</td>
</tr>
<tr>
<td>3. by increasing plasma osmolality</td>
</tr>
<tr>
<td>a. mannitol\textsuperscript{14, 48}</td>
</tr>
<tr>
<td>b. hypertonic glucose\textsuperscript{12}</td>
</tr>
<tr>
<td>C. By augmenting anaerobic metabolism (presumed)</td>
</tr>
<tr>
<td>1. glucose-insulin-potassium\textsuperscript{12, 49}</td>
</tr>
<tr>
<td>2. hypertonic glucose\textsuperscript{47}</td>
</tr>
<tr>
<td>D. By enhancing transport to the ischemic zone of substrate utilized in energy production (presumed) — hyaluronidase\textsuperscript{15, 21}</td>
</tr>
<tr>
<td>E. By protecting against autolytic and heterolytic processes (presumed)</td>
</tr>
<tr>
<td>1. hydrocortisone\textsuperscript{10, 48}</td>
</tr>
<tr>
<td>2. cobra venom factor\textsuperscript{17}</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Interventions That Increase Myocardial Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. By increasing myocardial oxygen requirements</td>
</tr>
<tr>
<td>1. isoproterenol\textsuperscript{10, 11, 19, 30-37}</td>
</tr>
<tr>
<td>2. glucagon\textsuperscript{11, 31}</td>
</tr>
<tr>
<td>3. ouabain\textsuperscript{11}</td>
</tr>
<tr>
<td>4. bretylium tosylate\textsuperscript{11}</td>
</tr>
<tr>
<td>5. tachycaardia\textsuperscript{17, 47-48}</td>
</tr>
<tr>
<td>B. By decreasing myocardial oxygen supply</td>
</tr>
<tr>
<td>1. directly</td>
</tr>
<tr>
<td>a. hypoxemia\textsuperscript{13}</td>
</tr>
<tr>
<td>b. anemia\textsuperscript{14}</td>
</tr>
<tr>
<td>2. through collateral vessels — reducing coronary perfusion pressure (hemorrhage)\textsuperscript{11, 11, 20, 47}</td>
</tr>
</tbody>
</table>
| C. By decreasing substrate availability — hypogly-

*UIt denotes intervention which has received some clinical application.

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