

## Reducing Myocardial Injury by Minimizing Imbalance between Oxygen Supply and Demand

Eugene Braunwald, M.D.\*

Factors Influencing Infarct Size following Experimental Coronary Artery Occlusion. By P. R. Maroko, J. K. Kjekshus, B. E. Sobel, T. Watanabe, J. W. Covell, J. Ross, Jr., and E. Braunwald. *Circulation* 1971; 43:67-82. Reprinted with permission.

The purpose of this study was to determine whether hemodynamic and pharmacologic factors can influence the extent and severity of myocardial necrosis produced by coronary occlusion. In 48 dogs, 10 to 14 epicardial leads were recorded on the anterior surface of the left ventricle in the distribution and vicinity of the site of occlusion of a branch of the left anterior descending coronary artery. The average S-T segment elevation for each animal was determined at 5-min intervals after occlusion. This elevation was used as an index of the presence and severity of myocardial ischemic injury. Isoproterenol, ouabain, glucagon, bretylium, and tachycardia given prior to a repeated occlusion each increased

the severity and extent of ischemic injury, while propranolol decreased it. Elevation of arterial pressure with methoxamine reduced the occlusion-induced S-T segment elevation, and lowering of the mean arterial pressure by hemorrhage had the opposite effect. In 19 additional experiments, propranolol, isoproterenol, and alterations in arterial pressure produced similar alterations in S-T segment elevation when these interventions were applied as long as 3 hr after ligation. Myocardial creatine phosphokinase (CPK) activity determined 24 hr after coronary artery ligation correlated well with S-T segment elevation at the same sites recorded 15 min after ligation. Moreover, isoproterenol increased and propranolol decreased the area of depression of myocardial CPK activity. We conclude that the hemodynamic status and neurohumoral background at the time of coronary occlusion and for at least 3 hr thereafter can alter the extent and severity of myocardial ischemic injury and myocardial necrosis.

FROM 1955 to 1968, I trained and then led a research program in the intramural program of the National Heart, Lung, and Blood Institute in Bethesda, Maryland, that focused on elucidating the determinants of cardiac oxygen consumption. We found that myocardial tension develop-

ment, contractility, and heart rate were the dominant determinants.<sup>1</sup> In 1967, it was recognized that because pump failure was the most important cause of in-hospital death in patients with acute myocardial infarction (MI) and because pump function was largely dependent on infarct size, the survival of patients with coronary occlusion was dependent importantly on the balance between myocardial oxygen supply and demand.<sup>2</sup> Because myocardial ischemia—and its most extreme form, MI—is caused by an imbalance between oxygen supply and demand (fig. 1),<sup>3</sup> it seemed logical to determine whether ischemic damage of the myocardium could be altered by changing this imbalance. This idea led to the experiments in dogs of the “Factors Influencing Infarct Size . . .” article summarized above. In this article, we concluded:

Of greatest interest, from a clinical point of view, is the finding that the severity and extent of myocardial ischemic injury resulting from coronary occlusion could be radically altered not only by pretreatment of the animal but also by an appropriate intervention as late as 3 h after the coronary occlusion. This suggests that measures designed for reduction of myocardial oxygen demands and im-

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\* Distinguished Hersey Professor of Medicine, Harvard Medical School, and Chairman, Thrombolysis in Myocardial Infarction Study Group, Brigham and Women’s Hospital.

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Address correspondence to Dr. Braunwald: Thrombolysis in Myocardial Infarction Study Group, 350 Longwood Avenue, Boston, Massachusetts 02115. [ebraunwald@partners.org](mailto:ebraunwald@partners.org). This article may be accessed for personal use at no charge through the Journal Web site, [www.anesthesiology.org](http://www.anesthesiology.org).

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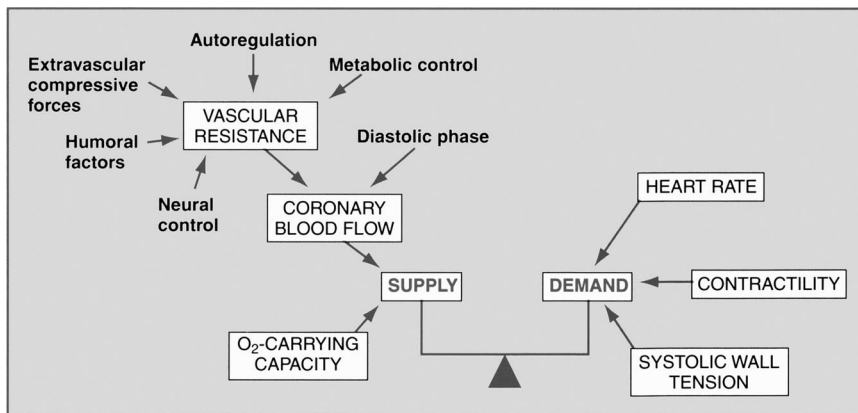


Fig. 1. Factors influencing myocardial oxygen supply and demand. From Ardehali and Ports<sup>3</sup>; reproduced with permission.

provement of coronary perfusion, when effected promptly after a patient has been brought to a hospital, might potentially reduce the ultimate size of the infarction.<sup>4</sup>

During the decade that followed, and building on the pioneering work of Eugene Chazov, M.D., Professor of Cardiology and Director of the Myasnikov Heart Institute in Moscow,<sup>5</sup> and Peter Rentrop, M.D., Assistant Professor of Medicine at the University of Gottingen, Germany,<sup>6</sup> and their collaborators, the intracoronary infusion of streptokinase in patients was used increasingly in the treatment of acute MI. Our own efforts were devoted to the demonstration, using imaging after the intracoronary infusion of <sup>201</sup>thallium, that timely administration of intracoronary fibrinolytic therapy could protect severely ischemic myocardium from ischemic cell death.<sup>7</sup> We then showed that early and sustained reperfusion with intravenous fibrinolytic agents improved survival of patients with evolving MI. This led to our proposal of the “open artery theory.”<sup>8</sup> In accord with this theory, the preferred treatment of evolving MI is immediate revascularization.

More recently, our group has demonstrated that the addition of the thienopyridine clopidogrel to aspirin improves coronary patency and clinical outcome in acute MI patients treated with both direct and indirect plasminogen activators.<sup>9</sup> Also, we have obtained evidence that the low-molecular-weight heparin, enoxaparin, with its balanced anti-Xa and -IIa activities, reduces the composite endpoint of death and recurrent MI in patients receiving fibrinolytic therapy.<sup>10</sup>

In the mid-1980s, as the benefits of early coronary revascularization in the treatment of acute MI became more widely appreciated, we began to direct our attention to improving the fate of patients who had survived an acute MI but who were still at risk of subsequent death and heart failure. With Marc Pfeffer, M.D., Ph.D., and Janice Pfeffer, Ph.D., Assistant Professors of Medicine at Harvard Medical School and the Brigham and Women’s Hospital, we demonstrated the deleterious long-term consequences of ventricular remodeling that follows experimental MI in rats and showed that this remodeling could be markedly re-

duced by angiotensin-converting enzyme inhibition.<sup>11</sup> These findings were then applied to patients in the Survival and Ventricular Enlargement trial, which showed that angiotensin-converting enzyme inhibition reduced long-term mortality in infarct patients with impaired left ventricular function.<sup>12</sup> This (then) novel therapeutic approach was subsequently confirmed in many trials and has been widely adopted worldwide.

Most recently, our group demonstrated in the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT)-Thrombolysis in Myocardial Infarction 22 trial that reducing low-density lipoprotein cholesterol with a  $\beta$ -hydroxy- $\beta$ -methylglutaryl-coenzyme A reductase inhibitor (statin) to very low levels (average = 65 mg/dl) in patients after acute MI and other acute coronary syndromes significantly improved clinical outcome compared with less vigorous reduction of low-density lipoprotein cholesterol.<sup>13</sup> Based in large part on this trial, the US guidelines for management of these patients have been modified, and a lower target for low-density lipoprotein cholesterol (70 mg/dl) is now recommended.

## Concluding Comments

Looking back on our research on MI, now spanning more than half a century, I am struck by the value of using a wide spectrum of techniques to attack important problems in medicine. My colleagues and I have, at various times, studied isolated hearts, intact animals, individual patients, and, most recently, large groups of patients in “mega” trials. It is important, I believe, in research not to become the slave of any particular technique, but to use whatever approach is required to solve the problem at hand. In my case, the “problem” has been the excessive morbidity and mortality after acute MI.

My work has been relevant to several medical specialties, including anesthesiology. As the population ages, so does the prevalence of ischemic heart disease in patients undergoing surgery (cardiac and noncardiac). Therefore, the need for anesthesiologists to maintain a favorable balance between myocardial oxygen supply and demand

is of growing importance. Anesthesiologists can do relatively little to improve myocardial oxygen supply but can certainly influence oxygen demand, and its three principal determinants—tension development (afterload), contractility, and heart rate.<sup>1</sup>

An increasing fraction of patients are coming to operation while receiving drugs that we found to be useful in our studies— $\beta$  blockers<sup>2</sup> and angiotensin-converting enzyme inhibitors.<sup>12</sup> Although enormously beneficial in preventing the maladaptive consequences of neurohormonal stimulation, these agents also reduce the patients' normal responses to hypovolemia and other hypotensive stimuli. Here again, anesthesiologists play a critical role in anticipating and minimizing hemodynamic instability. Finally, an increasing number of patients are also coming to the operating room on an urgent basis while taking antiplatelet agents, especially aspirin and clopidogrel, that are of value in the management of acute coronary syndromes.<sup>9</sup> These patients are at risk of serious intraoperative and early postoperative hemorrhage. Anesthesiologists must be prepared to anticipate and deal with this excess risk as well.

## References

1. Braunwald E: 13th Bowditch Lecture: The determinants of myocardial oxygen consumption. *Physiologist* 1969; 12:65-93
2. Braunwald E, Covell JW, Maroko PR, Ross J Jr: Effects of drugs and of counterpulsation on myocardial oxygen consumption. *Circulation* 1969; 40 (suppl IV):220-8
3. Ardehali A, Ports TA: Myocardial oxygen supply and demand. *Chest* 1990; 98:699-705
4. Maroko PR, Kjekshus JK, Sobel BE, Watanabe T, Covell JA, Ross J Jr, Braunwald E: Factors influencing infarct size following experimental coronary artery occlusion. *Circulation* 1971; 43:67-82
5. Chazov EI, Mazaev AV, Sargin KE, Sadovskaia GV, Ruda MI: Intracoronary administration of fibrinolysin in acute infarction [in Russian]. *Terapeuticheski Arkhiv* 1976; 8:48
6. Rentrop P, Blanke H, Karsch KR, Kaiser H, Kostering H, Leitz K: Selective intracoronary thrombolysis in acute myocardial infarction and unstable angina pectoris. *Circulation* 1981; 63:307-17
7. 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
8. Kim CB, Braunwald E: Potential benefits of late reperfusion of infarcted myocardium: The open artery hypothesis. *Circulation* 1993; 88:2426-36
9. Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, Claeys M, Cools F, Hill KA, Skene AM, McCabe CH, Braunwald E: Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005; 352:1179-89
10. Antman EM, Morrow DA, McCabe CH, Murphy SA, Ruda M, Sadowski Z, Budaj A, Lopez-Sendon JL, Guneri S, Jiang F, White HD, Fox KAA, Braunwald E, for the ExTRACT-TIMI 25 Investigators: Enoxaparin *versus* unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med* 2006; 354:1477-88
11. Pfeffer JM, Pfeffer MA, Braunwald E: Influence of chronic captopril therapy on the infarcted left ventricle of the rat. *Circ Res* 1985; 57:84-95
12. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, Klein M, Lamas GA, Packer M, Rouleau J, Rouleau JL, Rutherford J, Wertheimer JH, Hawkins CM, on behalf of the SAVE Investigators: Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: Results of the Survival and Ventricular Enlargement Trial. *N Engl J Med* 1992; 327:669-77
13. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM: Intensive *versus* moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; 350:1495-504