Editorial

Personal reflections on efforts to reduce ischemic myocardial damage

Eugene Braunwald*  
Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA  
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1. Background

In the second half of the 19th Century, physiologists observed that ligation of a major coronary artery in the dog was immediately fatal. During that era, pathologists occasionally encountered thrombosis of such vessels and acute myocardial infarction (AMI) at autopsy, and considered this combination of findings to be quite uncommon and uniformly fatal. At the dawn of the twentieth century, Krehl, a Viennese physician, challenged these beliefs and reported that coronary thrombosis was actually compatible with survival [1]. In 1910, Obrastov and Strazheske [2], two Russian physicians, and in 1912, Herrick, a Chicago physician [3], described the clinical features of AMI, related them to the pathologic findings and distinguished AMI from angina pectoris. Herrick also adapted the then new technique of electrocardiography to the premorbid diagnosis of AMI, considered at the time to be a very uncommon condition.

By the middle of the 20th Century, during my clinical training in internal medicine and cardiology at New York University, New York's Mount Sinai Hospital, and Johns Hopkins, it was clear that rather than being a curiosity, AMI was, in fact, the most common cause of death in the United States and western Europe. Arrhythmias and pump failure were the two major reasons for both the very high early (approximately 30% in 30 days) and late (approximately 50% in 1 year) mortality in patients who reached the hospital. The development of the coronary care unit in the early 1960s with continuous electrocardiographic monitoring and prompt external defibrillation by a trained team eliminated almost all early arrhythmic deaths in patients treated in such units, thereby reducing the early mortality by half [4], leaving pump failure associated with large infarction as a major challenge in cardiology.

2. Early research

In 1951, as a medical student at New York University and Bellevue Hospital, I was introduced to cardiovascular research in the hemodynamic laboratory of Ludwig Eichna, a pioneer in the study of human heart failure. I participated in some of the earliest measurement of cardiac output in patients with cardiogenic shock secondary to AMI. During a postdoctoral fellowship in the Nobel Prize winning laboratory of Professors Andre Cournand and Dickinson Richards in 1954–55, on the Columbia University Service of Bellevue Hospital, we studied patients with chronic congestive heart failure, many of whom had previously suffered a MI. Therefore, by the time that I began my second postdoctoral fellowship with Stanley Sarnoff in the newly created Laboratory of Cardiovascular Physiology in the intramural research program of the then National Heart Institute (now the National Heart, Lung and Blood Institute) in 1955, I was aware that myocardial ischemic injury plays a central role in both acute and chronic heart failure and that ischemic heart failure was a major problem in cardiology. Since myocardial ischemia was, by definition, secondary to an imbalance between myocardial oxygen supply and demand, I welcomed the opportunity to investigate the hemodynamic determinants of one side of this balance, i.e. $O_2$ demand, as reflected in myocardial $O_2$ consumption ($MVO_2$). Over the course of the next two years we identified myocardial tension development and heart rate as two important determinants of both $MVO_2$ [5] and coronary blood flow [6]. In the early 1960s, and now working in my own laboratory at NIH in collaboration with Ross, Sonnenblick, and Covell,
it became clear that tension development and heart rate could not be the only important determinants of MVO₂, since stimulation of the cardiac adrenergic nerves or the administration of sympathomimetic amines increased MVO₂ without altering, indeed while often reducing, the product of developed tension and heart rate. We identified myocardial contractility, as expressed by the maximum velocity of myocardial shortening of unloaded muscle, i.e. \( V_{\text{max}} \), as the third major determinant of MVO₂ [7]. It was our distinct honor to publish the first paper in the first volume of *Cardiovascular Research* on the relation between two of the three determinants of MVO₂, i.e. heart rate and contractility [8].

Simultaneously, in another section of the laboratory, we were studying cardiovascular control by the carotid sinuses and learned that stimulation of the carotid sinus nerves causes reflex venodilatation, thereby reducing ventricular preload [9] and we confirmed earlier observations that such stimulation also reflexly lowers heart rate, ventricular wall tension and myocardial contractility. Thus, stimulation of the carotid sinus nerves reflexly reduces all of the determinants of MVO₂ that we had previously elucidated. Dr Samuel Levine, one of the fathers of American cardiology and an eminent cardiologist at the Harvard Medical School and the former Peter Bent Brigham (now Brigham and Women’s) Hospital, had many years earlier described a clinical maneuver to distinguish angina pectoris from non-anginal chest pain. When external massage of the neck in the region of the bifurcation of the carotid artery relieved ongoing chest pain it was very likely to have been angina pectoris; when it failed it usually was not.

3. The reduction of ischemia by carotid nerve stimulation

I did not put these various pieces together until early in 1967 when I served as a Visiting Professor at the University of Rochester, NY. There I met a young Assistant Professor of Surgery, Seymour Schwartz, who later served for many years as the Chair of the Department at Rochester. Schwartz showed me how he controlled blood pressure in dogs with renal hypertension by continuously stimulating both carotid sinus nerves with a modified cardiac pacemaker implanted into the chest wall. On the flight back to Washington it occurred to me that patient-activated electrical stimulation of the carotid sinus nerves might relieve intractable angina. In collaboration with my late first wife, Nina Starr Braunwald, who was a cardiac surgeon at the Institute, as well as with Glick, Epstein and Wechsler, we set about to implant radiofrequency pacemakers which stimulated the carotid sinus nerves. It took just 10 weeks from the development of the idea to its clinical execution and we were gratified that severe angina could be readily relieved [10]. Nina and I continued this work at the University of California, San Diego in 1968 after we moved there to help start a new medical school. Indeed, we were preparing to conduct a large Phase III trial on this approach, when Favolaro and Effler described a new operation—coronary artery bypass grafting—which was very successful in restoring the balance between myocardial O₂ supply and demand by directly increasing supply. This operation immediately made our more indirect approach obsolete. However, our efforts had not been a waste of time since they had provided us with a unique opportunity to study reflex control of the circulation in conscious humans [11]. Much more important, however, had been an observation on one of our patients with an implanted carotid sinus nerve stimulator who had returned to the hospital because of an AMI. Contrary to our instructions, he maintained the stimulator in the active mode despite severe and prolonged chest pain. I turned the stimulator off but after I left the coronary care unit he had the good sense to turn it on again until I returned to turn it off once more. Later, inspection of his electrocardiogram showed that his precordial ST segments rose each time I turned the stimulator off and they became isoelectric when he reactivated it.

Before considering the interpretation of this observation, it is useful to place it into context. Simply put, it was widely assumed in the 1960s that myocardium perfused by a vessel which became acutely occluded was irreversibly injured. However, two important early papers had suggested that perhaps some opportunity existed for salvaging infarcting myocardium. In the first of these, Tennant and Wiggers in 1935 temporarily occluded a major coronary artery and observed that dyskinetic contraction of the ischemic myocardium commenced within seconds. When the duration of ischemia was brief, i.e. less than 20 min, normal myocardial contraction returned after reperfusion, but when it was longer, dyskinesis continued [12]. In 1941, Blumgart et al. [13] reported pathologic observations, also in the dog, that extensive infarction occurred when coronary occlusion was maintained for 40 min or longer, while occlusions of 5–20 min did not result in infarction. With occlusions of intermediate duration, the extent of necrosis depended on the time to reperfusion.

In 1967, I speculated that techniques which augment O₂ delivery to the infarcting myocardium while reducing its O₂ needs might be beneficial in patients with acute MI [14]. Thus, the observation in 1968 that ST segment elevations were reduced in our patient undergoing an AMI when his myocardial O₂ demands were lowered by carotid sinus nerve stimulation, supported the suggestion that myocardial ischemic injury was not necessarily irreversible in this situation.

4. Early efforts to reduce ischemic damage

Working with Maroko, a talented post-doctoral fellow, as well as with Ross, Sobel and Covell who had accom-
panied me from Bethesda to La Jolla, and with Libby, a promising medical student, we obtained evidence to support this hypothesis. We employed epicardial ST segment elevation as an indicator of ischemic injury in the open-chest anesthetized dog and extended the Tennant and Wiggers observations by finding that ST segment elevations rapidly became isoelectric when reperfusion was carried out within 20 min following coronary artery occlusion [15–17]. However, our new finding was that the extent and severity of ischemic injury—which correlated closely with the size of the evolving MI—could be expanded by increasing myocardial O₂ demands (e.g. by beta-adrenergic stimulation) or by reducing further the O₂ delivery to the border of the ischemic zone (e.g. by lowering arterial pressure). More importantly, ischemic injury produced by coronary occlusion could be reduced by lowering myocardial O₂ demands by beta-adrenergic blockade (Fig. 1), increasing O₂ supply by reperfusion [17–19] (Fig. 2) or by simultaneously increasing myocardial O₂ supply and reducing O₂ demands with intra-aortic balloon counterpulsation.

After moving to Harvard and the Brigham in 1972, Maroko and I were joined by Muller and Kloner and our efforts were extended in two directions. We sought methods more precise than epicardial ST segment mapping to assess the effect of interventions on ischemic injury. We employed pathological techniques to measure the area at risk, i.e. the portion of the myocardium perfused by the occluded artery, and assessed the fraction that became necrotic. Simultaneously, we assessed ischemic injury in patients with evolving AMI using a 35-lead precordial electrode system [20].

While we were aware from the aforementioned studies by Tennant and Wiggers in the 1930s [12], of Blumgart et al. in the 1940s [13], and of course our own group’s observations in the early 1970s [17–19] and of the elegant work of Reimer and Jennings [21] in the late 1970s that timely reperfusion could limit damage during evolving MI, it remained for others to develop techniques for myocardial reperfusion in patients.

5. Clinical myocardial reperfusion

In 1933, Tillett and Garner showed that hemolytic streptococci could liquify clotted human plasma [22]. The fibrinolytic substance produced by the streptococcus, named streptokinase, was purified and administered to patients with various thrombotic disorders. Indeed, Tillett was chair of the department of Medicine when I attended the New York University School of Medicine and I recall observing some of the earliest administrations of streptoki-
nase to patients at Bellevue Hospital in 1950. At the time, streptokinase had not yet been well purified and frequently caused severe febrile reactions. In 1976, Chazov et al. [23] reported the successful lysis of coronary thrombi in patients with AMI with intracoronary streptokinase. Two years later, Rentrop et al. [24] achieved patency of acutely occluded coronary arteries by disrupting coronary thrombi with a guide wire passed through a catheter. These two seminal papers were the forerunners of modern reperfusion therapy of AMI, i.e., thrombolysis and primary percutaneous coronary intervention (PCI).

In 1981, we utilized myocardial thallium-201 imaging to demonstrate that early opening of the infarct-related artery indeed salvages substantial quantities of myocardium in patients with ST segment elevation MI (STEMI) [25]. In 1984, the National Heart, Lung and Blood Institute invited me to chair the first Thrombolysis in Myocardial Infarction (TIMI) trial. In this multicenter trial, we compared intravenous streptokinase with the then new thrombolytic agent, tissue plasminogen activator (t-PA), and learned that: (1) t-PA was superior to streptokinase in opening totally occluded coronary arteries [26,27]; and (2) that one year survival was greater in STEMI patients in whom the infarct related artery was open (irrespective of how that opening was achieved) than in those in whom it remained occluded [28]. Subsequently, in a much larger trial, the GUSTO investigators demonstrated that t-PA treatment was associated with a lower mortality than treatment with streptokinase [29].

6. The TIMI trials

I have had the privilege of chairing the TIMI Study Group since its inception. As many as 800 hospitals in 32 countries on five continents have been involved in 20 completed trials; ten additional trials are ongoing or in the late planning stages. McCabe, Antman and Cannon are three of the many talented collaborators in these trials. Among the observations made on patients with STEMI, the TIMI Study Group has: (1) developed and championed the ‘open infarct-artery’ theory, which holds that early reperfusion of the infarct-related artery results in myocardial salvage which preserves ventricular function, which in turn improves survival [30,31]; however, while the benefits of reperfusion diminish with time from the onset of symptoms [32], even late revascularization may be beneficial [30]; (2) demonstrated reductions in death and recurrent infarction with beta-blockers in STEMI patients who received early t-PA [33]; (3) developed a system for describing epicardial coronary flow on angiography (the TIMI Flow Grade) [26], a system that has been universally adopted, and M. Gibson, a member of the group described quantitative angiographic assessments for measuring both epicardial and myocardial blood flow in patients with STEMI [34,35]. Taken together, these techniques have allowed comparisons of the state of myocardial perfusion between patients, treatment arms, and even laboratories; (4) showed the ability of the surface electrocardiogram to predict survival and coronary patency in STEMI patients [36]; (5) characterized the efficacy and safety of TNK–tPA, which is likely to become the most widely used thrombolytic [37]; (6) reported that thrombolytic therapy can be safely administered in the ambulance, thereby reducing further the time between the onset of symptoms and reperfusion [38]; and (7) showed that platelet inhibition with a glycoprotein IIb/IIIa inhibitor can enhance early myocardial reperfusion with t-PA [39].

The combination of early reperfusion, combined with aspirin and anticoagulant therapy, has reduced the early mortality of STEMI by one-third, from about 15 to 10%. However, there clearly is still room for additional progress. We are now studying a carefully blended combination of therapies that has been termed ‘facilitated PCI.’ In the ADVANCE MI trial (TIMI-26) we are testing the efficacy and safety of a reduced dose of TNK–tPA, eptifibatide, a platelet glycoprotein IIb/IIIa inhibitor, aspirin, and low molecular weight heparin as a ‘holding maneuver,’ and then transporting the patient to a facility where immediate PCI can be carried out. It is likely that some combination of pharmacologic management and PCI will become the standard of care for reducing myocardial ischemic injury in STEMI.

The TIMI Study Group has also focused attention on unstable angina–non ST segment elevation MI (UA/NSTEMI), very common ischemic conditions that are closely related to STEMI, and also usually caused by a coronary thrombus. Unlike STEMI, the thrombus in UA/NSTEMI usually causes a subtotal coronary occlusion. We have learned that: (1) surprisingly, the outcome in patients with UA/NSTEMI is not improved by thrombolytic therapy [40]; (2) low molecular weight heparin, with its anti-coagulation factor Xa (as well as anti-IIa) activity, is superior to unfractionated heparin [41]; (3) an invasive therapeutic approach with early mechanical revascularization is superior to a conservative approach [42]; (4) the management of patients with UA/NSTEMI can be facilitated by risk stratification, which can be accomplished by a combination of clinical assessment [43], measurement of serum troponin [44], C-reactive protein [45], and brain natriuretic peptide [46] and even more effectively by a combination of these three biomarkers [47]. Both ischemic damage and death in UA/NSTEMI have been declining in the last ten years.

7. Stunning and hibernation

In 1978, Heyndrickx et al. [48], working in Vatner’s laboratory, noted in the conscious dog that after a brief (15–30 min) period of severe ischemia followed by reperfusion, not long enough to cause myocardial necrosis,
the myocardial dysfunction in the ischemic region persisted for hours following reperfusion. We termed this condition myocardial stunning [49] and were able to identify its presence in many clinical situations, such as post surgical cardiac ischemia, exercise induced ischemia, unstable angina and following thrombolytic reperfusion of evolving AMI [50]. We also proposed that chronic stunning, i.e. persistent moderate ischemia—not sufficiently severe to cause myocardial necrosis—could cause prolonged contractile impairment of viable myocardium. This condition, which was aptly named 'myocardial hibernation' [51,52] has emerged as an important cause of ischemic heart failure which can be reversed by revascularization. Hibernating myocardium can be detected by a variety of imaging techniques, and observational studies suggest that surgical revascularization prolongs survival in these patients. I am now chairmaning an NIH-supported randomized controlled trial that is testing this hypothesis.

8. ACE inhibitors and statins

In the 1980s, working with Marc Pfeffer and the late Janice Pfeffer, we observed late remodeling of the left ventricle in rats with MI [53]. There is not only stretching of the infarcted tissue, but also expansion and hypertrophy of the remaining viable myocardium [54]. In 1980, we were fortunate to obtain small quantities of captopril, the first angiotensin-converting enzyme inhibitor, and found that its administration could greatly reduce this remodeling [55]. After confirming this observation in patients with MI [56], we conducted a large multicenter trial, the SAVE trial, which demonstrated improved survival in patients randomized to the ACE inhibitor [57] (Fig. 3). This observation, also, has been amply confirmed in a number of clinical trials involving more than one hundred thousand patients. ACE inhibition is now standard therapy and appears to be very helpful in reducing the myocardial consequences of ischemic injury for the majority of patients recovering from AMI.

With the progressive reductions in mortality from AMI, we are focusing attention on prevention of recurrent MI and improving survival of post-MI patients using HmG-CoA reductase inhibitors. We have reported in the CARE trial that post-MI patients with average levels of LDL-cholesterol show an improved outcome with statin therapy [58], not only by lipid lowering, but perhaps also by the statin’s anti-inflammatory actions reflected in its ability to reduce C-reactive protein [59]. Currently, we are examining in the A to Z (TIMI 21) [60] and in the PROVE IT (TIMI 22) trials [61], whether commencement of statin therapy within days of an acute coronary event improves clinical outcomes further.

9. Conclusions

I have been especially fortunate in my professional life in several respects. I have had outstanding mentors who taught me to focus on significant clinical–scientific problems and to use a variety of approaches and techniques to address them, rather than to become a slave of a single technique. I have selected for investigation an important problem—ischemic impairment of myocardial function, its treatment and prevention. I have worked in great institutions, including New York University, NIH, Johns Hopkins, University of California, Harvard Medical School and the Brigham Hospital—all of which have been very supportive of my efforts. I have been most fortunate of all to have had the opportunity to work closely with several generations of extraordinarily talented colleagues and trainees.

References


