Protecting the Myocardial Cell During Coronary Revascularization

Sidney Levitsky, MD

Background—Using the ischemic myocardial cell as a paradigm, competitive coronary revascularization technologies will be analyzed for their potential in causing additional myocardial cell damage during the course of therapeutic procedures.

Methods and Results—Percutaneous coronary intervention (PCI) using balloon and/or stent (bare metal or coated) approaches may be associated with myonecrosis related to atherosclerotic debris plugging the downstream coronary microcirculation as well as ischemia/reperfusion injury associated with revascularization of occluded coronary vessels. The placement of distal mechanical devices and filters during the course of PCI has not been successful in ameliorating this problem. Coronary revascularization using coronary artery bypass grafting (CABG) similarly may be associated with myocardial stunning and cell necrosis associated with ischemia/reperfusion injury. Surgically induced myocardial ischemia secondary to aortic cross clamping, results from the attenuation or cessation of coronary blood flow such that oxygen delivery to the myocardium is insufficient to meet basal myocardial requirements to preserve cellular membrane stability and viability. Recovery involves: (1) resumption of normal oxidative metabolism and the restoration of myocardial energy reserves; (2) reversal of ischemia induced cell swelling and loss of membrane ion gradients and the adenine nucleotide pool; (3) repair of damaged cell organelles such as the mitochondria and the sarcoplasmic reticulum. Despite meticulous adherence to presently known principles of surgical myocardial protection using advanced cardioplegic technologies, some patients require inotropic support and/or mechanical assist devices postoperatively, when none was required preoperatively.

Conclusions—Which method of coronary revascularization causes the least amount of myocardial cell injury and is associated with superior long-term outcomes remains an area of increasing controversy. (Circulation. 2006;114[suppl I]:I-339–I-343.)

Key Words: coronary artery bypass graft (CABG) ■ coronary revascularization ■ percutaneous coronary intervention

I am honored to have been chosen as the seventeenth William W.L. Glenn Lecturer. This presentation has very special meaning to me, as I believe that I am the first lecturer to have been a cardiac surgical resident at Yale under Dr Glenn’s supervision. First, a few words about Dr Glenn (Figure 1). Not only was he a creative cardiac surgical pioneer, devising the superior vena cava-right pulmonary artery shunt, popularly known as the Glenn shunt,1 but Dr Glenn also made many other important contributions including the concept of fibrillatory arrest, the radiofrequency pacemaker, and the phrenic nerve pacemaker. Moreover, he was a superb educator and a strong supporter of his residents throughout their academic careers. Finally, Dr Glenn was the first surgeon to be elected President of the American Heart Association.

Although my research interests over the past 45 years have focused on intraoperative protection of the myocardium, I thought for this Lecture, I would focus on how we, as cardiac physicians, protect the vulnerable ischemic myocardial cell undergoing therapeutic coronary revascularization. Since, basically, our job in the patient with myocardial ischemia is not only to increase the coronary blood supply but to act as a “myocardial cell-saver!” Using this paradigm, I will attempt to contrast the competitive coronary revascularization technologies for their potential in causing additional myocardial damage during the course of the therapeutic procedures and the means to avoid this injury. Obviously, a patent coronary artery perfusing a segment of myocardium with numerous areas of myonecrosis serves no useful purpose.

Percutaneous Coronary Intervention-Induced Myonecrosis

Most of the clinical research studies evaluating percutaneous coronary intervention (PCI) have focused on the mechanical techniques and outcomes of opening the stenosed or occluded coronary artery and maintaining vessel patency utilizing...
balloon angioplasty and the insertion of bare metal or coated stents. However, PCI-related injury leading to myonecrosis associated with stent-related side-branch flow impairment/occlusion or associated with atherosclerotic debris plugging the downstream coronary microcirculation as well as ischemia/reperfusion injury associated with revascularization of occluded coronary vessels has not been emphasized.

Traditionally, creatine-phosphokinase–myocardial band (CPK-MB) and electrocardiographic evidence of Q-wave or non-Q-wave myocardial infarction have been used as markers to diagnose post-procedure myonecrosis, which can occur in 16% to 39% of patients and has been documented to be a predictor of poor late outcomes. The concept of “CPK washout” or innocent “infarctlets” as a routine occurrence after PCI has been debunked as a myth and is associated with an increase in late mortality. As a further demonstration of the importance of CPK-MB elevation, the investigators in the PERSUIT (Platelet Glycoprotein 11b/111a in Unstable Angina: Receptor Suppression Using Integrilin Therapy) trial compared the myocardial damage between PCI-induced and spontaneous myocardial infarction and noted “the relative increase in 6-month mortality with each increase in peak CK-MB level was similar for PCI-related myocardial necrosis and spontaneous myocardial necrosis. . . ”

Recent clinical application of magnetic resonance imaging in measuring and reliably quantifying post-procedure irreversible myocardial injury has provided a new tool to document the extent of myocardial tissue loss. In a recent study, the investigators have correlated post-PCI troponin elevations and its relationship to the volume of myocardial tissue destruction using delayed-enhancement magnetic resonance imaging (DE-MRI). The characteristics of the 50 patients included in this study are of note in that a single or double vessel PCI was planned, the mean ejection fraction (EF) was 67±11%, and patients with an EF below 40% were excluded. . . a relatively low risk group of patients. Nevertheless, 28% of the patients had evidence of procedure-related myocardial necrosis resulting in a loss of 5.0±4.8% of total left ventricular mass (Figure 2). Utilizing standard measures of measuring EF, there was no statistically valid adverse effect on global LV function, which raises a question about the validity of this measurement in documenting small but significant changes associated with PCI-induced myonecrosis. There were 2 distinct sites of myocardial cell injury: (1) the previously normal area of the apical myocardium in the majority patients was apparently related to embolization of particulate matter during left anterior descending coronary artery (LAD) balloon inflation and stenting; and (2) the basal or mid-ventricular myocardium adjacent to the inserted stent.

**PCI Myocardial Protection Devices**

In an attempt to ameliorate PCI-induced myonecrosis, mechanical devices, such as the Filter Wire, which uses a polyurethane filter bag contained on a radiopaque loop to trap embolic debris, have been used. In a series of 35 patients, the device entrapped embolic debris in 82% of the cases, although no data are provided to support a decrease in myonecrosis. Furthermore, in patients with ST-segment elevation myocardial infarction (STEMI), thrombectomy and embolic protection devices, investigated in large, multi-center studies, have not demonstrated any clinical benefits.

**CABG-Induced Myonecrosis**

How successful have surgeons been in protecting the ischemic myocardial cell during surgically induced myocardial ischemia secondary to aortic cross-clamping during CABG procedures? Myocardial stunning and myonecrosis associated with ischemia/reperfusion injury results from the attenuation or cessation of coronary blood flow such that oxygen delivery to the myocardium is insufficient to meet basal myocardial requirements to preserve cellular membrane stability and viability. Recovery involves: (1) resumption of normal oxidative metabolism and the restoration of myocardial energy reserves; (2) reversal of ischemia induced cell swelling and loss of membrane ion gradients and the adenine nucleotide pool; and (3) repair of damaged cell organelles such as the mitochondria and the sarcoplasmic reticulum.
Postoperative Myocardial Stunning

Despite meticulous adherence to presently known principles of surgical myocardial protection using advanced cardiopulmonary bypass procedures, some patients require inotropic support and/or mechanical assist devices postoperatively, when none was required preoperatively. There is good clinical evidence to support the concept that all patients undergoing CABG have varying degrees of myocardial stunning, occasionally requiring inotropic support, which after abatement over hours or days after surgery have no objective evidence of myocardial infarction. However, there is a significant downside to the use of inotropic agents. The classic physiological experiment on a Langendorf rat heart preparation teaches us that increasing doses of isoproterenol will cause myonecrosis as the myocardial oxygen consumption exceeds the heart’s capacity to increase coronary blood flow. In addition, there is recent evidence that therapeutic levels of inotropic support in the postischemic heart increases intracellular calcium and subsequent apoptosis resulting in cell death, which is probably accentuated in the post-CABG patient with segments of the heart that have not been adequately revascularized.

Clinical Studies

In a study comparing PCI and CABG outcomes from the Cleveland Clinic, there was a greater incidence of CPK-MB leak from CABG patients than PCI patients. However, when the criterion for significant myocardial injury was arbitrarily changed to 10-times normal, there was no difference and the CABG patients had a significant, but small, increase in 3-year cumulative survival. In the Arterial Revascularization Therapies Study (ARTS), there was a direct relationship between CPK-MB elevation and long-term outcomes. At 1 year, the worst adverse outcomes as defined by the incidence of MACCE (death, myocardial infarction, repeat revascularization, as well as combined major cardiac and cerebrovascular events) occurred in patients with CPK-MB levels greater than 5-times normal. In a more recent study using troponin levels and DE-MRI, the Oxford group noted a 36% overall incidence of myonecrosis and a 2% loss of LV mass. However, these investigators used cold crystalloid cardioplegia, which in North America is considered suboptimal compared with blood cardioplegia.

Intraoperative Myocardial Protection

Biology of Ischemia/Reperfusion

The surgical perception of myocardial cell injury occurring after ischemia/reperfusion involves 2 major hypotheses: increases in intra-cellular calcium and/or the accumulation of reactive oxygen species (ROS) causing the sarcolemmal peroxidation of the cellular phospholipid layer, leading to the loss of cellular integrity and facilitating calcium entry. After the aortic cross-clamp is removed, the myocardial cell may function normally, be stunned, or become dysfunctional from either necrosis or apoptosis (Figure 3).

Calcium Transport

Ischemia leads to the induction of metabolic acidosis and the activation of the sodium–proton exchanger, resulting in the transport of hydrogen ions to the extracellular space and the movement of sodium into the cytosol (Figure 4). As the sodium–calcium exchanger is activated, sodium is transported to extracellular space and calcium is taken up into the cytosol, increasing cytosolic calcium ([Ca$^{2+}$]). Accumulation of cytosolic calcium is augmented by ischemia-induced depolarization of the membrane potential, which allows for the opening of the l-type calcium channels and further calcium entry into the myocyte. Celluar and [Ca$^{2+}$]-dependent phospholipases and proteases are, in turn, activated inducing membrane injury and the further entry of calcium into the cell. In trying to understand the clinical observation that neonates had less postoperative stunning compared with both newborns and adult patients, we measured intracellular calcium and demonstrated that at the extremes of life, there is an increased accumulation of intracellular calcium after ischemia/reperfusion. Later studies demonstrated that the neonate’s resistance to the effects of ischemia/reperfusion is related to the developmental differences in calcium transport and sequestration. The increase in [Ca$^{2+}$], could be decreased, using a simple cardioplegia solution, consisting of potassium to achieve rapid diastolic arrest and magnesium to inhibit calcium entry into the cell. In addition, calcium accumulation occurred in increased concentrations not only in the cytosol but also in the nucleus resulting in DNA fragmentation, which appeared to be worse in the senescent heart, and inhibited the production of reparative proteins during the reperfusion period.

Basic Principles and Technical Details

Historically, the concept of “elective cardiac arrest” was introduced in 1955, by rapidly injecting into the aortic root, after aortic cross-clamping, a 2.5% potassium citrate solution in warm blood to arrest the heart. Thereafter, a variety of approaches evolved including normothermic ischemic arrest, intermittent aortic cross-clamping, fibrillatory arrest, continuous coronary perfusion, topical hypothermia, and, finally, the introduction of cardioplegia. Similarly, the basic principles of myocardial protection have evolved, which include: rapid cardiac arrest, since the myocardial oxygen stores are depleted within 6 seconds as oxidative metabolism...
switches from aerobic to anaerobic metabolism, hypothermia to decrease myocardial oxygen consumption and prevent the depletion of high-energy phosphate moieties, avoidance of myocardial edema, and a question whether it is necessary to add metabolic substrates to the “cardioplegic soup” As far as the ingredients are concerned, most European groups use crystalloid cardioplegia, while most US surgeons use blood cardioplegia to provide additional substrate oxygen. Most surgeons use a combination of antegrade and retrograde delivery systems. Although there have been proponents of all or some of these methodologies, and despite numerous reports in the literature, there have been no definitive prospective studies that narrow the techniques enough to allow universal adaptation of one particular methodology.

Microplegia or Whole Blood Cardioplegia
This technique avoids hemodilution associated with administering large volumes of the classically diluted ratio of 1:4 blood cardioplegia, uses minimal amounts of potassium and magnesium to arrest the heart and deter the influx of calcium, eliminates concerns about buffering, and avoids myocardial edema. In a retrospective study, we compared microplegia with whole blood and the standard 4:1 blood cardioplegia in a series of patients with severe multivessel disease and low ejection fraction below 30% and prolonged cross-clamp times. While there was no difference between the patient groups, there was a significant decrease in inotropic support favoring the microplegia group. (Figure 5)

Comparison of PCI and CABG
Now let us go back to our original question, which is which method of coronary revascularization salvages the greatest number of ischemic myocardial cells and, in turn, results in superior long-term outcomes. Using the same metric by the same investigators comparing the DE-MRI technologies, there is evidence that PCI appears to injure a greater number of myocardial cells during the procedure because, in my mind, of limitations in myocardial protection associated with PCI, as compared with CABG (Figure 2). Obviously these uncontrolled studies to address the hypothesis are provocative and by no means conclusively answer the question posed in this lecture. Nevertheless, this hypothesis may partially explain the 4-year outcome studies using the New York cardiac registry in 59,314 patients, which demonstrated a survival benefit for CABG. An editorial commenting on the study attributes the differences to CABG’s ability to bypass numerous “culprit lesions,” compared with PCI. My own thinking is related to the high incidence of repeat revascularization procedures in the PCI group (27.3% versus 4.6% in the CABG group; $P<0.001$), with each repeated PCI associated

| TRADITIONAL BLOOD CARDIOPLEGIA (4:1) VS. MICROPLEGIA: CABG WITH POOR LV FUNCTION |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Age                            | 67.4            | 65.6            | NS              |
| EF                             | 27.7            | 30.0            | NS              |
| Distal Anast.                  | 4.5             | 4.5             | NS              |
| CFR (min)                      | 174             | 166             | NS              |
| S Clamp (min)                  | 122             | 120             | NS              |
| Intubation (hrs)               | 22.4            | 15.5            | NS              |
| Isotropic Use                  | Yes             | No              | Yes             | No              |
| Dobutamine                     | 11/12           | 2/16            | 0.01            |
| Amiodarone                     | 17/6            | 4/14            | 0.001           |

Figure 5. Comparison of 4:1 cardioplegia to microplegia.
with an additive superimposed myocardial injury, may be responsible for the differences in outcome. However, a preliminary review by the investigators does not support this hypothesis “. . . due to a variety of factors that counterbalance the dangers of multiple PCIs. . . “.24

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Conclusion

In closing, I understand that I have ventured into a stormy scientific sea, full of conflicting hypotheses and great difficulties in interpreting retrospective and prospective randomized trials. And, in addition, I have added to the confusion by advancing an untested hypothesis in an attempt to explain long-term outcomes. Perhaps a recent editorial, of which I

... is likely that most patients undergoing coronary arteriography are not told the entire story when a decision is made about undergoing a percutaneous intervention nor is there an appropriate setting for alternative viewpoints to be expressed by cardiac surgeons. . . our patients deserve to hear the full, unbiased story. . . about coronary revascularization.” points the way in assisting clinicians to manage the patient with the vulnerable ischemic myocardial cell.

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Disclosures

None.

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