Myocardial Protection at a Crossroads
The Need for Translation Into Clinical Therapy

Roberto Bolli, Lance Becker, Garrett Gross, Robert Mentzer, Jr, David Balshaw, David A. Lathrop

Abstract—Over the past 30 years, hundreds of experimental interventions (both pharmacologic and nonpharmacologic) have been reported to protect the ischemic myocardium in experimental animals; however, with the exception of early reperfusion, none has been translated into clinical practice. The National Heart, Lung, and Blood Institute convened a working group to discuss the reasons for the failure to translate potential therapies for protecting the heart from ischemia and reperfusion and to recommend new approaches to accomplish this goal. The Working Group concluded that cardioprotection in the setting of acute myocardial infarction, cardiac surgery, and cardiac arrest is at a crossroads. Present basic research approaches to identify cardioprotective therapies are inefficient and counterproductive. For 3 decades, significant resources have been invested in single-center studies that have often yielded inconclusive results. A new paradigm is needed to obviate many of the difficulties associated with translation of basic science findings. The Working Group urged a new focus on translational research that emphasizes efficacy and clinically relevant outcomes, and recommended the establishment of a system for rigorous preclinical testing of promising cardioprotective agents with clinical trial-like approaches (ie, blinded, randomized, multicenter, and adequately powered studies using standardized methods). A national preclinical research consortium would enable rational translation of important basic science findings into clinical use. The Working Group recommended that the National Institutes of Health proactively intervene to remedy current problems that impede translation of cardioprotective therapies. Their specific recommendations include the establishment of a preclinical consortium and the performance of 2 clinical studies that are likely to demonstrate effectiveness (phase III clinical trials of adenosine in acute myocardial infarction and cardiac surgery). (Circ Res. 2004;95:125-134.)

Key Words: basic science myocardial ischemia reperfusion injury ischemic heart disease cardiac surgery cardioprotection research translation

Ischemic heart disease, as the underlying cause of most cases of acute myocardial infarction (AMI), congestive heart failure, arrhythmias, and sudden cardiac death, is the leading cause of morbidity and mortality in all industrialized nations. In the United States, ischemic heart disease causes nearly 20% of all deaths (~600 000 deaths each year), with many of these deaths occurring before the patient arrives at the hospital.1 An estimated 1.1 million Americans will have a new or recurrent AMI this year, and many survivors will experience lasting morbidity, with progression to heart failure and death. As the population grows older and comorbidities such as obesity and diabetes become more prevalent, the enormous public health burden caused by ischemic heart disease is likely to increase even further. In an effort to improve both short-term and long-term outcomes in these patients, the National Heart, Lung, and Blood Institute (NHLBI) convened an expert Working Group to discuss the reasons for the failure to effectively translate potential therapies for protecting the heart from ischemia and reperfusion and to make recommendations for future approaches that would help to accomplish this task. What follows is a report of this group’s deliberations.

For the purpose of this working group report, “cardioprotection” is defined as the prevention of injury associated with AMI and reperfusion, the primary manifestations of which are myocyte death, arrhythmias, and contractile dysfunction (“stunning”). Myocardial ischemia/reperfusion injury occurs in a wide spectrum of patients, ranging from survivors of out-of-hospital cardiac arrest to AMI victims and patients undergoing cardiac surgery, and represents a major public health burden.

The Mandate: Why Are Protective Strategies Required?

Two critical factors are required to improve the outcome of a patient with an acute ischemic event. First, the patient must survive any arrhythmias. The majority of deaths caused by AMI occur before hospitalization—of >700 000 cardiac
deaths in the United States in 1998, sudden cardiac arrest outside the hospital accounted for >450,000 and was caused primarily by arrhythmias. Although greater access to automatic defibrillators and optimization of cardiopulmonary resuscitation (CPR) protocols offer tremendous potential to save lives, it is remarkable that survival is still dependent on early CPR and rapid defibrillation. Indeed, survival rates from cardiac arrest have shown only marginal improvement over the past 30 years, underscoring the need for novel therapies and resuscitation strategies. This topic was the focus of the National Institute of Health (NIH) and Department of Defense sponsored Post Resuscitation Utilization of Life Saving Strategies (PULS) workshop and is largely outside of the purview of this group.

Second, infarct size needs to be limited, because in patients with AMI who do not die of out-of-hospital arrhythmias, the prognosis is dependent on the amount of myocardium that is lost as a result of ischemia/reperfusion injury. There is no question that timely reperfusion (by thrombolysis or percutaneous transluminal coronary angioplasty [PTCA]) can salvage ischemic myocardium, and has, indeed, become the standard in-hospital treatment for AMI. Although greater benefits can, conceptually, be achieved by continued efforts to implement even earlier restoration of coronary flow, delays in seeking medical attention, together with inherent logistic and temporal limitations in initiating thrombolysis or PTCA, make it unlikely that additional substantive improvements in morbidity and mortality can be achieved by reperfusion therapy without the development of new adjunctive therapies.

Limitation of myocardial ischemia/reperfusion injury is also of paramount importance in the setting of global myocardial ischemia associated with surgical procedures such as coronary artery bypass graft (CABG). Despite the considerable progress that has been made to date, high-risk subsets of patients (ie, repeat CABG, unstable angina, LV dysfunction, diabetes, old age, etc) continue to exhibit postoperative complications, including prolonged contractile dysfunction (stunning), low-output syndrome, perioperative myocardial infarction, and cardiac failure, requiring prolonged intensive care. Thus, in patients experiencing an AMI and in those undergoing CABG surgery, there is a compelling, but still unfulfilled, need to protect the ischemic myocardium.

**Cardioprotection: Genesis of the Concept**

The importance of limiting myocardial ischemia/reperfusion injury has been appreciated for >3 decades. In 1971, Braunwald et al published a landmark study in which they proposed the groundbreaking idea that the extent and severity of tissue damage after coronary occlusion were not predetermined at the onset of ischemia but could be modified by therapeutic manipulations applied during ischemia. This concept produced a major paradigm shift, and as early as 1974, Braunwald and Maroko suggested that it was time to test clinical therapies designed to limit myocardial infarct size. Remarkably, the effort to identify cardioprotective therapies has continued unabated for 3 decades. The number of experimental studies of myocardial protection from ischemia performed since 1971 is enormous (>13,000, according to PubMed) and continues to grow at an exponential rate.

<table>
<thead>
<tr>
<th>Negative Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyaluronidase</td>
</tr>
<tr>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Recombinant superoxide dismutase</td>
</tr>
<tr>
<td>Prostacyclin</td>
</tr>
<tr>
<td>Flusol</td>
</tr>
<tr>
<td>Magnesium</td>
</tr>
<tr>
<td>Poloxamer 188 (RheothRx)</td>
</tr>
<tr>
<td>Trimetazidine</td>
</tr>
<tr>
<td>Eniporide</td>
</tr>
<tr>
<td>Cariporide</td>
</tr>
<tr>
<td>Nitrates</td>
</tr>
<tr>
<td>Magnesium</td>
</tr>
<tr>
<td>Anti–P-selectin</td>
</tr>
<tr>
<td>Antileukocyte interventions</td>
</tr>
<tr>
<td>(anti-CD18 monoclonal antibodies)</td>
</tr>
</tbody>
</table>

**Encouraging Results**

- Adenosine
- Glucose-insulin-potassium

The majority of these studies have been “positive,” ie, they have concluded that the therapy being examined was cardioprotective. As a result, over the past 30 years, several hundred experimental interventions (both pharmacologic and nonpharmacologic) have been claimed to limit myocardial infarct size in experimental animals. Unfortunately, few of these results have been reproducible and, with the exception of timely reperfusion, none has been translated into clinical practice. As the Table shows, in the setting of AMI, numerous attempts have been made to translate experimental results into clinical therapies; however, these interventions were applied late in the ischemic phase or at the time of reperfusion and, with the exceptions of adenosine and glucose-insulin-potassium (GIK), all have yielded disappointing results. It should be noted that none of the interventions clinically tested with negative results had first yielded consistent or reproducible results in experimental animal models.

Thus, 3 decades after its birth, the protection of myocardium in the setting of AMI remains an unfulfilled promise. The chasm between the bewildering number of potentially cardioprotective therapies at the basic science/animal research level and the lack of any cardioprotective therapy at the clinical level threatens the credibility of research in cardioprotection and, if unchecked, will ultimately lead to therapeutic nihilism.

There are, however, a handful of recent studies that provide hope. In patients with AMI, the 2 largest trials of adenosine administered at the time of reperfusion (AMISTAD I and AMISTAD II) have demonstrated a marked reduction in the size of anterior wall infarctions. The beneficial effect in AMISTAD II appeared to be associated with a trend toward improved clinical outcome (ie, reduced incidence of death and/or congestive heart failure [CHF]), although the difference observed was not statistically significant, possibly because the occluded artery was not successfully recanalized in...
many of the patients. Very small open-label clinical studies also suggest that the K ATP channel opener and nitric oxide donor nicorandil may have benefits when administered at the time of reperfusion in patients with AMI. GIK infusion has been found to reduce mortality in acute MI in a meta-analysis of studies performed in the prethrombolytic era and in 2 recent trials of patients undergoing therapeutic recanalization, although in these latter studies mortality was reduced only in subsets of patients, not in the entire study population. In the setting of cardiac arrest, mild hypothermia has recently been demonstrated to improve survival rates; an international recommendation to provide hypothermia to such patients has recently been released. The use of hypothermia has also stimulated a large number of studies in the settings of AMI and stroke.

Cardioprotective therapies offer potential usefulness in the setting of high-risk CAGB procedures, as well. Administration of adenosine before, during, and after aortic clamping has been reported to reduce the incidence of perioperative infarction and to improve a composite end-point consisting of the need for mechanical or inotropic support, infarction, or death, despite a relatively small patient sample size (84 to 85 patients/group). Likewise, inhibitors of sodium/hydrogen (Na/H) exchange have been shown to protect the ischemic myocardium in cardiac surgery. In the GUARDIAN trial, post hoc analysis indicated that pretreatment with the Na/H exchange inhibitor cariporide resulted in a significant reduction in the primary end-point (death and/or AMI at 36 days after CAGB). Subsequently, the large EXPEDITION trial demonstrated prospectively the ability of the drug to reduce the incidence of perioperative AMI in CAGB surgery. This was the first demonstration that a drug limits myocardial ischemia/reperfusion injury in humans, although the salubrious effects of cariporide were offset by an unexpected increase in the incidence of stroke. Whether the neurologic complications noted in EXPEDITION were related to the higher dose of cariporide used in this trial versus GUARDIAN is unclear. Consistent with preclinical data, the timing of Na/H inhibitor administration appears to be a key factor in clinical cardioprotection. Both in GUARDIAN and in EXPEDITION, the infusion of cariporide was started before the onset of ischemia; in contrast, administration of the Na/H exchange inhibitor eniporide at the time of reperfusion in patients with AMI (ESCAMI trial) failed to show a reduction in infarct size or an improvement in clinical outcome.

In summary, interventions reported to be cardioprotective in experimental models of ischemia/reperfusion have not been demonstrated to improve clinical outcome in patients (AMI or cardiac surgery), although a limited number appear quite promising in initial clinical studies. Cariporide has been shown to be cardioprotective in high-risk CAGB patients, but its neurologic effects preclude its use at the present time.

**Barriers to Translating Experimentally Successful Interventions into Clinical Therapies**

Our failure to translate experimentally effective cardioprotective interventions and new therapies for cardiac arrest into clinical therapies is multifactorial. In general, there exist substantial barriers at the preclinical and at the clinical levels. An underlying theme is a lack of effective communication and coordination between those performing preclinical evaluations, those designing clinical studies, emergency medical service providers, and those developing new tools to enhance these areas. In addition, there is a failure of both the basic and the clinical researcher to carefully consider issues related to the eventual clinical application, such as the impact of comorbidities on the effectiveness of the intervention and the manner in which the therapy will be applied in clinical practice.

**Barriers at the Preclinical Level: Lack of Reproducible Basic Research Findings**

It is clear that the reproducible effectiveness of a potential therapy in preclinical studies is one of the strongest predictors of clinical success. Almost all studies of cardioprotection and cardiac arrest in experimental models have yielded inconsistent and/or unreproducible results. Frequently, the salubrious effects of an intervention cannot be replicated from one laboratory to another, from one model to another, or from one species to another. This lack of reproducibility is perhaps the single major problem with preclinical testing of cardiac arrest and cardioprotective therapies. If the beneficial effects of a treatment cannot be reproduced in the highly controlled experimental setting, it is doubtful that these effects will be reproduced in the much more complex (and less controllable) clinical setting. As already indicated, all of the interventions that have failed to improve outcome in clinical trials of AMI (Table) have yielded conflicting or inconclusive results when implemented in a clinically relevant manner (late into ischemia or just before reperfusion) at the experimental level.

The lack of reproducibility in preclinical studies, in turn, likely results from numerous factors, including: (1) failure to use standardized animal models, research protocols, terminology, and methods of analysis; (2) lack of randomized study design; (3) lack of blinding of investigators; and (4) methodological errors, eg, failure to (a) control basic physiologic parameters, (b) account for differences in group mortality, (c) account for coronary collateral flow (especially in canine models), (d) measure the region at risk, and (e) most importantly, allow a survival time that is sufficiently long to measure a meaningful endpoint (ie, 24-hour neurological scoring for cardiac arrest and measurement of infarct size at 24 hours of reperfusion).

**Use of Animal Models That Do not Adequately Approximate the Clinical Setting**

The increasing emphasis on reductionistic approaches, while both understandable and useful, has led to an increasing use of models that do not adequately approximate actual clinical circumstances (eg, isolated hearts, isolated myocytes, insufficient duration of ischemia). While these models provide important mechanistic information, they do not reflect the complex multifactorial interactions that modulate myocardial ischemia in vivo and that are likely to have a critical impact on clinical effectiveness. Conscious animal models (which might be most relevant to the clinical situation) have virtually
disappeared. Furthermore, the majority of experimental studies utilize healthy, juvenile animals. Comorbid conditions (e.g., diabetes, hypercholesterolemia, hypertension, left ventricular hypertrophy) and other variables (age, nutritional status, or hormonal status) that are prevalent in the clinical setting have seldom been incorporated in experimental studies, although a growing body of literature suggests that such comorbidities have a substantial impact on the effectiveness of many cardioprotective interventions.23,24

Lack of Emphasis on Efficacy
The majority of basic studies focus on understanding molecular and cellular mechanisms of injury and protection rather than establishing the potential clinical efficacy of the interventions tested. Studies that emphasize efficacy over mechanism are typically labeled by reviewers as confirmatory and/or descriptive, and thus are neither funded by federal funding agencies nor published by high-impact journals.

Failure to Disseminate Negative Results
“Positive” results receive greater priority for publication in high-impact journals than “negative” results. This praxis, caused by the bias of reviewers and editors, distorts the apparent efficacy of potential cardioprotective interventions.

Barriers at the Clinical Level: Presence of Multiple Confounding Variables
Clinical studies are plagued by numerous confounding variables. For example, in the setting of AMI or cardiac arrest it is often difficult to establish the exact duration of ischemia, whether the ischemia was continuous or intermittent, and whether the patient experienced brief bouts of angina resulting in ischemic preconditioning. The size of the region at risk, the presence and magnitude of coronary collateral circulation, the presence of preexisting infarctions, and the level of adrenergic activity are also difficult to quantify. Finally, the concurrent use of medications with possible anti-ischemic properties may vary greatly from patient to patient in otherwise well-designed clinical studies.

Limited Resolution of Methods Available to Measure Infarct Size in Patients
Despite progress in cardiac imaging, the methods available to measure the extent of cell death after AMI have limited spatial resolution. For example, with the possible exception of recent magnetic resonance imaging (MRI) techniques,25-27 it is not possible to reliably distinguish a transmural from a subendocardial infarction. Thus, noninvasive measurements of infarct size as a surrogate for mortality to measure efficacy may miss small infarcts and overestimate the size of nontransmural infarcts.28,29

Inability to Pretreat Patients With AMI or Cardiac Arrest
In patients with AMI and cardiac arrest, pretreatment is virtually impossible because of the unpredictable onset of these events. Therefore, treatments are usually given at the time of, or immediately before, therapeutic reperfusion (by thrombolysis or PTCA) or after return of spontaneous circu-

lation, when significant damage has already occurred. This limitation is a major problem, as many promising therapies found to be effective in preclinical animal studies when administered before ischemia are ineffective when applied during ischemia or on reperfusion.30 In victims of cardiac arrest, an important question is whether therapies delivered after return of spontaneous circulation and a clinically detectable pulse will improve cardiac function.

Premature Clinical Evaluation of Inconsistent and/or Unproven Preclinical Findings
Many of the clinical trials performed to date have been premature and not rationally designed (Table); they tested interventions that were not reproducibly effective in relevant experimental models or failed to take into account the known limitations of otherwise promising approaches. The failure of these trials to identify protective therapies was, therefore, for the most part predictable. Reproducible effectiveness in highly controlled experimental animal models is the best indicator that the intervention will prove effective in the clinical setting, albeit not a guarantee of clinical success.

Difficulty in Translating Reduction in Infarct Size Into Improved Clinical Outcome
Even when a therapy does reproducibly reduce infarct size, this may not necessarily translate into a readily demonstrable clinical benefit (such as reduced mortality or improved functional status). The multiplicity of factors that affect the patient’s clinical condition implies that large sample sizes are necessary to demonstrate that a change in any individual factor will change the outcome. For example, when adenosine was evaluated in the setting of CABG, the reduced incidence of AMI did not translate into a significant reduction in clinical complications, possibly because of the small sample sizes (84 to 85 patients/group).18 Thus, adequately powered clinical trials are necessary to determine whether a reduction in infarct size translates into improved clinical outcome. Infarct size may not impact outcomes such as morbidity and mortality until a threshold infarct size is achieved. Relationships to outcomes may be more subtle, such as tolerance of a second ischemic event. It is important to note that FDA approval requires improvement in morbidity and mortality; secondary end-points such as limitation of infarct size are not sufficient.

Paucity of Sponsors for Clinical Trials
As the morbidity and mortality associated with AMI and CABG decline, it becomes increasingly arduous to document that a new treatment improves the clinical outcome. Demonstration that new therapies are advantageous requires large sample sizes, as exemplified by AMISTAD II,10 by the CABG adenosine trial,18 and EXPEDITION.20 The costs associated with large clinical trials, the disappointing experience of previous clinical studies of cardioprotection, the present difficult economic climate for pharmaceutical companies, and the fact that patents on some of the most promising drugs (e.g., adenosine) will soon expire, all have the potential to lead to a paucity of sponsors for phase III clinical trials in the not-too-distant future.
Gaps in Knowledge That Hinder Translation
As a consequence of the problems detailed, fundamental gaps in knowledge remain that limit the effective translation of cardioprotective therapies from experimental to clinical settings.

Identification of Interventions That Are Reproducibly Effective in Clinically Relevant Settings
Most of the therapies claimed to provide cardioprotection at the preclinical level have yielded contradictory or inconclusive results. With the exception of preconditioning, adenosine, Na+/H+ exchange inhibitors (applied before ischemia), KATP channel openers (applied before ischemia), and hypothermia (in the setting of cardiac arrest), very few, if any, interventions have been reproducibly effective in preclinical studies across a range of species and experimental models. As stated, it is also unknown how effective these therapies will be in models that mimic the clinical setting (diabetes, hypercholesterolemia, hypertension, LV hypertrophy, and/or old age). Thus, in most cases we simply do not know whether an intervention is truly effective at the preclinical level. This problem is particularly conspicuous in the setting of so-called reperfusion injury (ie, injury inflicted by reperfusion rather than by ischemia itself); despite some encouraging results, treatments initiated on reperfusion have not been shown to afford reproducible protection in multiple species and models, yet treatment started at reperfusion is usually the only therapeutic option available in patients presenting with an AMI. In conclusion, there is an urgent need to identify new therapies that are reproducibly effective, particularly when given at, or immediately before, the time of reperfusion.

Uncertainty Regarding the Magnitude or Even the Existence of Reperfusion Injury
Although the concept of a reperfusion-induced component of lethal tissue injury was proposed many years ago, the quantitative importance of this phenomenon or even its very existence continue to be questioned, based on the persistent inability to identify interventions that reproducibly and consistently limits infarct size when started at the time of reperfusion.31,32 In the setting of cardiac arrest, it has been suggested that the death of nearly 90% of patients who initially regain a pulse (now termed “postresuscitation syndrome”) is actually a form of reperfusion injury,33 but this remains a hypothesis. The uncertainty that surrounds the magnitude and existence of lethal reperfusion injury represents an important gap of knowledge that directly hinders the development of therapies that could be applied to patients with AMI and cardiac arrest.

Reliability of Methods to Measure Infarct Size
The majority of experimental studies have relied on triphenyltetrazolium chloride (TTC) staining to identify viable tissue, often <24 hours after coronary reperfusion. Unfortunately, the ability of TTC staining performed <24 hours after reperfusion (or <24 hours after a permanent coronary occlusion) to provide an accurate measure of the final extent of infarction remains to be demonstrated. As a consequence, it is unclear whether the reduction in TTC negative tissue observed in experimental studies signifies genuine reduction of infarct size or merely a slowing of the rate of progression of the infarct without an effect on its eventual size.

In the clinical setting, 99mTc-sestamibi single photon emission spectroscopy (SPECT) has been the most commonly used tool for measuring infarct size, but this method has the limitations of selective lack of acquisition in the sickest patients, infarct size variation depending on timing of acquisition, and inability to distinguish transmural from subendocardial infarction. Systemic levels of cardiac enzymes have also been used to measure infarct size in patients, and a small number of preclinical studies have used this method, also. This method lacks precision and may provide different patterns depending on the reperfusion status. Novel imaging techniques such as delayed contrast-enhanced MRI37 provide highly quantitative, noninvasive measures of infarct size that allow longitudinal follow-up in individual study subjects and may prove to be more robust than the use of either nuclear medicine approaches or cardiac enzyme levels.

Identification of Suitable Patient Populations
In the setting of cardiac surgery, the fraction of patients who experience postoperative complications related to acute ischemia/reperfusion injury is relatively small. Although such complications can be severe, their relatively low prevalence requires large sample sizes to achieve sufficient statistical power. The uncertainty as to which subgroups of patients will have postoperative complications is an important gap of knowledge that hinders studies of cardioprotection. Data exist from completed studies that should allow for the rational selection of patient subgroups most likely to benefit from such therapies, thereby enabling the design of adequately powered studies with relatively small patient numbers.

Identification of Relevant Models of Sudden Cardiac Death
While experimental models of both AMI and CABG exist, it has been difficult to develop a model that accurately reflects the clinical setting of sudden cardiac death, which is the terminal event for most heart attack victims. This fundamental problem has thus hindered research in the field of cardiac arrest.

Lack of Appropriate Biosensors in the Setting of Ischemia and Cardiac Arrest
Our ability to monitor, in real time, active ischemia in patients is extremely limited. A further challenge is the lack of monitors and sensors for guiding therapies during cardiac arrest, which are for the most part delivered without any knowledge of effect. For example, no monitor is currently available to inform doctors or paramedics whether adequate blood flow is being produced by CPR efforts. Given the lack of such a blood flow or tissue perfusion monitor, it is not surprising that efforts to augment blood flow in the field have been slow, as it is difficult to improve parameters that are not measured or monitored.
Opportunities

Despite the numerous challenges described, opportunities exist for translation of basic findings into clinically effective therapies. The field of cardioprotection is closer to becoming a clinical reality than ever before, and some interventions (eg, adenosine) are on the verge of being proven clinically effective and ready to become part of standard recommended medical practice. Thus, we believe that this is an opportune time to recommend steps to assure translation of promising preclinical experimental findings into clinical practice by capitalizing on the portfolio of opportunities detailed below.

Infarct Size Reduction Is Feasible

That appropriately selected (and administered) therapies can reduce the ultimate size of a myocardial infarct in the experimental setting can no longer be disputed. Thus, limitation of infarct size is feasible.

Preconditioning

Preconditioning is one of the most powerful cardioprotective interventions identified to date.\textsuperscript{34,35} It is also, by far, the most reproducible.\textsuperscript{34,35} It consistently limits infarct size in every animal model and in every species examined, and there is considerable evidence that it is effective in protecting human myocardium, as well. Many of the molecular and biochemical pathways responsible for the salubrious actions of preconditioning have been elucidated, providing potential targets for the development of novel cardioprotective strategies. However, despite its demonstrated efficacy and reproducibility in experimental settings, the power of preconditioning has not yet been harnessed for therapeutic purposes. Thus, preconditioning represents a major opportunity for cardioprotection. This is particularly true for the delayed (or late) phase of preconditioning, which affords relatively long-lasting protection (30- to 40-times longer than the early phase) and can be elicited by pharmacologic or genetic stimuli.\textsuperscript{34} The ability of various classes of clinically relevant drugs (eg, NO donors, adenosine receptor agonists, \delta-opioid receptor agonists, inhaled anesthetics) to reproduce the salutary effects of the late phase of ischemic preconditioning provides specific opportunities for translation.\textsuperscript{34,36}

Feasibility of Prophylactic Cardioprotection

In AMI, current therapies initiated at the onset of reperfusion have limited efficacy, and pretreatment is not feasible in the majority of patients. Therefore, the most practical strategy for limiting infarct size and improving clinical outcome may be to induce a chronically protected cardiac phenotype by triggering late (sustained) preconditioning with pharmacologic agents or gene therapy (prophylactic cardioprotection). Preclinical studies suggest that it is possible to induce a chronically protected cardiac phenotype by emulating the phenomenon of delayed preconditioning with pharmacologic or genetic approaches. For example, a study in rabbits\textsuperscript{37} has shown that intermittent (every 48 hours) administration of adenosine A\textsubscript{1} receptor agonists can maintain the heart in a chronically protected state for at least 12 days. Furthermore, gene transfer of the heat shock protein HSP70, inducible NO synthase (iNOS), heme oxygenase-1 (HO-1), or extracellular superoxide dismutase (Ec-SOD) (all of which are upregulated during delayed preconditioning) has been shown to confer protection against ischemia/reperfusion injury\textsuperscript{38–42} and, at least in the case of HO-1 and iNOS, this protection is long-lasting (for a period of 8 weeks after gene transfer).\textsuperscript{40,42} The feasibility of inducing a sustained or chronic state of cardioprotection represents a major opportunity. This prophylactic cardioprotection could be the most effective approach to AMI, because it would be operative at the very onset of ischemia, thereby limiting both the ischemia-induced and the reperfusion-induced components of injury.

Progress in Unraveling the Mechanism of Ischemia/Reperfusion Injury and Protection

Over the past 30 years, enormous progress has been made in our understanding of the basic biochemical and molecular mechanisms that underlie the development of lethal ischemia/reperfusion injury and the protective actions of therapeutic interventions. The aggregate knowledge derived from these basic insights provides a formidable opportunity to develop effective cardioprotective therapies.

Encouraging Clinical Data

The encouraging results of recent clinical trials of adenosine in AMI\textsuperscript{9,10,43} and CABG\textsuperscript{18} suggest that there is an opportunity to convincingly demonstrate that adenosine improves the outcome in these settings if adequately powered clinical studies are performed. The outcome of recent studies of GIK is also promising.\textsuperscript{13,15} Similarly, the results of the GUARDIAN and EXPEDITION trials indicate that administration of Na+/H\textsuperscript{+} exchange inhibitors before aortic clamping alleviates the myocardial ischemia/reperfusion injury associated with CABG surgery,\textsuperscript{19,20} although the neurologic complications observed with the high dose of cariporide used in EXPEDI-TION resulted in an unfavorable risk/benefit profile.\textsuperscript{20} Studies of hypothermia after cardiac arrest suggest that cooling is an important therapy to improve recovery of neurologically intact survivors.\textsuperscript{44,45} The window of opportunity to apply cooling to victims of cardiac arrest remains unknown, but new technology will allow faster and more controlled cooling than currently possible. These encouraging clinical data represent an opportunity for rapid translation into clinical application. Importantly, EXPEDITION has clearly demonstrated the feasibility of pharmacologic cardioprotection in humans.\textsuperscript{20}

Availability of Sophisticated New Technologies

The problems inherent in measuring infarct size in patients could be alleviated by the use of emerging MRI technologies that afford higher resolution and the ability to quantify infarct size in the clinical setting.\textsuperscript{28,46–48} MRI also enables measurement of function in conjunction with assessment of cell death\textsuperscript{26,49} to serially evaluate the response to treatments. In addition, the advent of gene array technologies and proteomic analyses may aid in the identification of high-risk patient populations who are most likely to benefit from cardioprotective therapies.
Reciprocal Feedback Between Preclinical and Clinical Studies

An opportunity exists for fostering improved communication and interaction between preclinical and clinical investigators so that preclinical data may be better used as a foundation to design rational clinical trials and, conversely, the results of clinical trials may be better-used to improve the preclinical evaluation of promising cardioprotective interventions.

Enhanced Collaboration Among Investigators, Government, and Industry

There is currently a high level of interest in cardioprotection in the scientific community, within the pharmaceutical industry, and at the NIH. Enhanced collaboration among these groups would likely result in more expeditious evaluation of cardioprotective interventions and translation of basic research into clinical therapies.

Recommendations

Many of the barriers and gaps detailed can be remedied by appropriately designed studies. We believe that the enormous amount of work performed over the past 30 years can be brought to fruition if the aforementioned problems are addressed at both the preclinical and the clinical levels in a manner that fosters improved interactions among investigators working in these areas.

Specific Recommendation 1: Establish a Preclinical Research Consortium

We believe that a key reason for the failure to successfully translate basic research findings into clinical practice has been the inappropriate interpretation of discordant, preliminary, and often nonreproducible preclinical findings and the premature application of such findings to the design of clinical studies. Therefore, our primary recommendation is the establishment of a consortium of basic and clinical investigators who would join forces to provide rigorous preclinical evaluation of promising cardioprotective interventions.

As conceived by us, this preclinical consortium should serve as a “filter” between investigator-initiated mechanistic studies and clinical efficacy trials of potential cardioprotective therapies. By testing both existing and promising new interventions (including combinations of potential therapies) in a standardized and rigorous manner, this consortium will address the lack of reproducibility that has plagued the field of cardioprotection for the past 30 years and will prevent premature or inappropriately designed translational clinical studies. The consortium should test promising interventions in a number of relevant animal models (including large mammals and conscious preparations) and in multiple laboratories using standardized, clinically relevant protocols, with the long-range goal of identifying those therapies that have the highest probability of clinical success. All studies will be randomized and blinded to the extent possible and all data analyzed by an independent, blinded, centralized core facility using uniform statistical methods.

In addition to basic scientists, such a consortium will include clinical investigators, statisticians, and bioengineers to provide input into the design of the studies and the interpretation of the results. Clinical investigators will also perform initial phase I human subjects-based studies on safety and dosing, using end-points, such as ST-segment elevation during PTCA, exercise tolerance, etc, that indicate protection from ischemia but do not require large sample sizes. Inclusion of experts in a number of different disciplines will foster communication and interaction between experimental and clinical investigators. Improving such communication will increase the clinical relevance of experimental studies and prevent premature extrapolation of inconsistent or preliminary preclinical findings to the clinical arena.

The goal of the consortium is not to create new ideas but to validate promising basic science findings. Therefore, the work of the consortium will not in any way supplant the necessary independent, investigator-initiated, hypothesis-driven basic science studies. The consortium is intended as a bridge between mechanistic studies and the clinical arena. The primary purpose is to determine whether an intervention shown to be promising in investigator-initiated, independently supported basic science studies is reproducibly effective when examined in multiple relevant models by multiple laboratories using standardized research protocols and optimal biostatistical analyses. Thus, the preclinical consortium will operate in a manner similar to a clinical trial network, using the same standards of statistical rigor throughout each laboratory.

Clinical trials of an experimental therapy should be performed only if the therapy proves to be reproducibly effective in multiple animal models using this rigorous study design. In keeping with our belief that the full potential of cardioprotective treatments will be realized only through the induction of a chronically protected phenotype in patients at high risk for an acute event, a major focus of the consortium should be the evaluation of strategies aimed at inducing prophylactic cardioprotection.

The consortium will apply a more cost-effective approach to research that is becoming progressively more costly. Instead of evaluating a therapy several times in single-center studies under differing sets of conditions and with noncomparable designs (an approach that over the past 30 years has almost always resulted in contradictory, and thus inconclusive, data), this system will evaluate a therapy in multiple experimental laboratories using an agreed-on standard protocol, modern design elements, and optimal methods, and thus will provide more conclusive results. The findings will be more likely to be published even if they are negative, thereby preventing inappropriate clinical trials (which would be predictably negative) and avoiding the attendant large expenses. Because of the rigorous preclinical evaluation (with sharing of negative as well as positive results), the consortium will provide a sound ethical basis for human subject testing with a high probability of clinical benefit. The risks inherent in this consortium will be low because even negative results will be important, because they will obviate further preclinical or clinical studies of the therapy at hand.
Specific Recommendation 2: Phase III Clinical Trial of Adenosine in AMI

Adenosine is one of the few agents that has been well validated at the preclinical level and has also shown promising results in initial clinical evaluations. Phase I and II clinical trials of adenosine (and related compounds) in AMI have yielded encouraging results, demonstrating that intravenous infusion of adenosine in conjunction with reperfusion therapy (thrombolysis or PTCA) reduces infarct size in patients with an anterior wall infarction.\textsuperscript{9,10,14,41} In the largest of these trials (AMISTAD II), there was a trend toward an improvement in the clinical outcome (death and/or heart failure at 6 months after the AMI) which, however, did not reach statistical significance, possibly because of the fact that many patients were not successfully reperfused.\textsuperscript{10} Based on these facts, it appears that among all of the potentially cardioprotective interventions that have been tested thus far, adenosine is one of the closest to being proven clinically effective. The next step is a phase III trial that is rationally designed, ie, a study that has adequate power and in which patients are effectively reperfused with optimal fibrinolysis or primary PTCA (because adenosine would not be expected to be cardioprotective in the absence of reperfusion), are treated <6 hours from the onset of pain, and receive an effective dose of adenosine. A trial of adenosine that incorporates newer imaging technologies such as MRI to noninvasively measure infarct size would also provide a paradigm for future investigations of cardioprotection.

The available preclinical and clinical data strongly suggest that such a trial is likely to conclusively demonstrate that adenosine improves clinical outcome in AMI. Such a finding would be the first demonstration in a large trial that any intervention (other than reperfusion) intended to limit infarct size in humans produces a tangible clinical benefit. Proof of effective cardioprotection in patients treated with adenosine would stimulate further investigations of other cardioprotective agents that are associated with fewer untoward effects (eg, adenosine A\textsubscript{1} receptor agonists, adenosine A\textsubscript{3} receptor agonists, adenosine-modulating drugs such as AMP579, etc) or have synergistic effects with adenosine. We believe that translational efforts in the field of cardioprotection need to be galvanized by the demonstration that a drug limits infarct size and improves clinical outcome.

Specific Recommendation 3: Phase III Clinical Trial of Adenosine in Cardiac Surgery

In addition to the existing data indicating a likely beneficial effect of adenosine in patients with AMI, a significant literature exists suggesting that these benefits may also exist in the setting of cardiac surgery. Many of the considerations pertaining to a clinical trial of adenosine in cardiac surgery are similar to those enunciated for the trial of adenosine in AMI and, therefore, will not be repeated. The results of the trial of adenosine in CABG were promising, demonstrating that administration of adenosine before, during, and after aortic clamping limited the incidence of perioperative AMI and reduced the composite end-point of use of high-dose inotropic agents, intra-aortic balloon counter pulsation, myocardial infarction, or death.\textsuperscript{18} These results were obtained despite a relatively small sample size (84 to 85 patients/group). Based on this encouraging experience, it appears that a rationally designed phase III trial of adenosine in cardiac surgery would likely demonstrate that this drug limits the incidence of perioperative complications and improves clinical outcome (ie, reduces the incidence of death or AMI).

Conclusions

The field of cardioprotection in AMI, cardiac surgery, and cardiac arrest is at a crossroads. The process that has been used thus far to identify cardioprotective therapies at the basic research level is often inefficient, wasteful, and ultimately counterproductive. For 3 decades, pharmaceutical companies and federal funding agencies have invested significant resources in single-center experimental studies of cardioprotection, which have often been inconclusive and have failed to be translated to the clinical arena. The opportunity exists for a new paradigm that can obviate many of the un reproducible, conflicting, contradictory, and unconfirmed results of single-center studies. We believe the time has come to focus on translational research that addresses clinically relevant outcomes in addition to mechanisms of action. Our recommended approach is to establish a system for rigorous preclinical testing of promising cardioprotective agents with methods analogous to those used in clinical trials (ie, blinded, randomized, multicenter, and adequately-powered studies using standardized methods). In addition, continued efforts are justified in pursuing the interventions that have been identified as promising in preclinical studies and, in some cases, in phase I and II clinical trials. A preclinical research consortium would advance our ability to rationally and progressively translate important findings from the basic science laboratory into eventual clinical use. In addition, this consortium would increase opportunities for productive collaborations with industrial partners.

We believe that the investment in cardioprotection made by the pharmaceutical industry and the federal government during the past 3 decades can and should be developed into clinically effective therapies. We, therefore, recommend that the NIH proactively intervene to remedy the problems that have impeded the translation of cardioprotective interventions. Our recommendations include a short-term, low-risk project (preclinical consortium) and 2 medium-term, clinical studies with a high likelihood of demonstrating effectiveness (phase III clinical trials of adenosine in AMI and cardiac surgery). Among these recommendations, we assign the highest priority to the preclinical consortium, because such an entity would serve as a source of potentially useful therapies to be tested in subsequent clinical trials. With these initiatives, the NIH could catalyze the translation of cardioprotection into clinical reality.

Acknowledgments

We thank Ms. Mary Hinely for her assistance in organizing the meeting. Working Group Roster: Chair, Roberto Bolli, MD (University of Louisville); Session Moderators: Lance Becker, MD (University of Chicago); Garrett Gross, PhD (Medical College of Wisconsin); Robert Mentzer, Jr, MD (University of Kentucky); Participants: Christopher Granger, MD (Duke University); Dara
References


22. Kratich RJ, MD, VMD, PhD (Johns Hopkins University); Rakesh Kukreja, PhD (Virginia Commonwealth University); Robert Myerburg, MD (University of Miami); Karin Przyklenk, PhD (University of Massachusetts); Jakob Vinten-Johansen, PhD (Emory University); Richard Weisfel, MD (Toronto General Hospital); James WEISS (UCLA); Prof. Sir Magdi Yacoub (Harefield Hospital); Hasan, MD; David A. Lathrop, PhD.

23. Boll et al Cardioprotection at a Crossroads 133


Myocardial Protection at a Crossroads: The Need for Translation Into Clinical Therapy
Roberto Bolli, Lance Becker, Garrett Gross, Robert Mentzer, Jr, David Balshaw and David A. Lathrop

Circ Res. 2004;95:125-134
doi: 10.1161/01.RES.0000137171.97172.d7

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/95/2/125

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/