Superoxygen Therapy
A Bayesian Breath of Fresh Air for Myocardial Salvage

Hung Q. Ly, MD, MSc; Kevin E. Kip, PhD; Jean-Francois Tanguay, MD

In North America, every 25 seconds someone will have a coronary event and every minute someone will die of one.¹ ST elevation myocardial infarction (STEMI) is the most dramatic manifestation of coronary artery disease and remains as one of the most important causes of mortality in the industrialized world. Prompt and successful reperfusion therapy (either pharmacologically with use of fibrinolytic therapy or mechanically with primary percutaneous coronary intervention [PCI]) is currently the cornerstone of acute management of STEMI to salvage ischemic myocardium and limit infarct size. Although undoubtedly beneficial, reperfusion of an occluded artery represents “a double-edge sword,”² because restoration of epicardial coronary flow initiates a series of complex biochemical and molecular phenomena, which will ultimately mitigate myocardial healing. Thus, with reperfusion comes reperfusion injury.³

Although the concept of cardioprotection (myocardial salvage) was first suggested by Braunwald,⁴ it was the seminal works of Reimer et al who crystallized the fact that there exists a window of opportunity to act to limit myocardial injury. They postulated that a “wavefront phenomenon” of cardiac necrosis, if left unchecked, would extend the infarct from the subendocardial region to the subepicardial region by using canine models of transiently or permanently occluded coronary arteries.⁵ Thereafter, over the course of 3 decades, mixed and disappointing results have plagued both experimental and clinical attempts to limit the deleterious effects of early reperfusion through either pharmacological (adenosine, calcium channel blockers, Na⁺/H⁺ exchange inhibitors, K⁺ channel openers, and glucose-insulin-potassium infusion) or nonpharmacological (therapeutic hypothermia) means.³,⁶

The reasons for such inconsistent findings in cardioprotection are multifold. First, reperfusion injury encompasses numerous, overlapping mediators of cardiomyocyte death from oxidative stress and Ca²⁺ overload to alterations in cellular pH, as well as an inflammatory process with a central role of neutrophils. Currently, no single therapeutic intervention, even when administered in a timely manner at vessel reperfusion, can quench by itself all these elicited events. Second, the deleterious effect of reperfusion injury is often compounded by the accompanying no-reflow phenomenon.⁷ The ensuing intravascular plugging (caused by leukocytes, platelets, or fibrin), cellular swelling, myocyte contracture, and atherothrombotic embolization do not necessarily respond to interventions used to abate the underlying mediators of reperfusion injury. To that effect, aspiration thrombectomy during primary PCI has been reported to have a positive impact on clinical outcomes.⁸ However, there are currently no data on the combined use of cardioprotective agents (excluding antithrombotic and antiplatelet agents routinely used in this setting) with this mechanical approach to prevent no reflow at the time of reperfusion. Third, studies investigating cardioprotective agents have had a checkered past with regard to translating positive, promising animal findings into clinically meaningful results. As pointed out by the National Heart, Lung and Blood Institute’s Working Group on myocardial protection, translational research in this field will need to highlight efficacy and not just mechanistic understanding, to focus on reproducible interventions performed in a clinically relevant manner, and to use reliable methods to quantify the infarct size.⁹ Finally, highly controlled experimental conditions at the basic/animal research level may not reflect clinical reality where the interplay of numerous factors (such as comorbidities, gender-related differences, or interactions with concomitant medications) confounds interpretation and, ultimately, impacts effectiveness of any given adjuvant therapy.

Bearing these challenges in mind, in this issue of Circulation: Cardiovascular Interventions, Stone et al¹⁰ reported the results of the acute myocardial infarction with hyperoxicemiac therapy (AMIHOT-II) multicenter trial. The investigators showed that, among the high-risk subgroup of patients with STEMI presenting within 6 hours of chest pain onset with a large anterior wall infarction, a 90-minute intracoronary infusion of supersaturated oxygen (SSO₂) is associated with a significant reduction in infarct size after primary PCI relative to standard mechanical reperfusion (pooled study-level infarct size of 25.0% versus 18.5%, P=0.02, respectively). The investigators showed comparable rates of major adverse cardiac events between study groups with the exception of access site-related adverse events being more frequent in the SSO₂ group during the initial phase of the trial. However, the multifactorial etiologies of reperfusion injury notwithstanding, the fact that the significant reduction in infarct size afforded by SSO₂ therapy did not translate into clinical benefit (only a noninferior rate of occurrence of major

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adverse cardiac events), highlights the difficulties encountered by any type of adjuvant therapy when applied concomitantly to early mechanical reperfusion therapy. The requirement in terms of the sample size to achieve statistical power and to demonstrate an incremental clinical advantage above and beyond that garnered by primary PCI would preclude any such study to be realized in the current climate of paucity of trial sponsorship. Another potential explanation may be found in the means used by Stone et al to define success, ie, infarct size (or its reduction). Although the authors made a good case of arguing the use of single-photon emission computed tomography to assess this surrogate end point of efficacy, the use of cardiac MRI with delayed gadolinium enhancement not only would have provided higher spatial resolution with improved sensitivity but also would have collected additional crucial data, such as the extent of myocardial edema and the degree of microvascular obstruction.\(^\text{11,12}\) Such information could have, at least in part, explained the discrepancies between reported proportions of patients with post-PCI thrombolysis in myocardial infarction flow grade 3 and those actually achieving adequate ST-segment resolution (88.4% versus 59.0%, respectively, for patients randomly assigned to SSO\(_2\) therapy). Finally, despite the improved infusion device profile and the subsequent decrease in femoral access site-related complications, one needs to consider whether the current rising trend of radial access site use during primary PCI may limit the routine use of this nonpharmacologic strategy for cardioprotection.\(^\text{13}\)

A rather novel feature of the AMIHOT-II data analysis was the use of a Bayesian approach. This particular approach may be unfamiliar to some readers of this journal, but is espoused by a minority, yet vocal, cadre of statisticians and methodologists,\(^\text{14}\) including those with interest in large trials of cardiovascular practice.\(^\text{15}\) Moreover, the Food and Drug Administration Modernization Act of 1997 mandates consideration of the “least burdensome” means of demonstrating effectiveness or substantial equivalence (ie, of a device), and when applied correctly, the Bayesian approach may be less burdensome than the conventional frequentist approach.\(^\text{16}\)

In brief, the Bayesian approach calculates “probabilities” for decision making, such as a recommended treatment regimen. This analysis makes use of prior information (ie, what is known before a new study or trial commences), known as a prior probability, and is augmented with data collected from a new study. This results in calculation of a posterior probability. In contrast, the conventional frequentist approach may use prior information in designing a clinical trial, but the analysis is based solely on data from the current trial. The key attributes that distinguish the conventional frequentist approach from the Bayesian approach are shown in the Table. Particularly notable is that the Bayesian approach estimates the posterior probability that the research hypothesis is true (eg, a 90-minute infusion of SSO\(_2\) in the infarct artery is superior to the standard of care without intracoronary infusion). In contrast, the probability value that is calculated from the frequentist approach is typically based on the null hypothesis, that is, how unlikely are the observed between-group differences (eg, infarct size at 14 days) assuming that there is truly no difference?

Conceptually, formal use of prior information in a Bayesian analysis (eg, the AMIHOT-I data) may seem nearly identical to conduct of a traditional meta-analysis, such as simply merging summary results from AMIHOT-I and AMIHOT-II. However, in the Bayesian hierarchical modeling conducted by Stone et al, the amount of evidence “borrowed” from AMIHOT-I was based on the similarity of results between AMIHOT-I and AMIHOT-II. In contrast, in a traditional random effects meta-analysis, an individual study with disparate results from the other studies included would tend to carry more weight than less weight in the analysis.\(^\text{17}\)

As described by Stone et al, a particular strength of the Bayesian approach was borrowing of evidence from AMIHOT-I and hence the ability to conduct AMIHOT-II with a smaller sample size than would be required as a stand-alone trial. Although a reduced sample size will typically result in cost and time savings, there is an equally, if not more important benefit. Specifically, AMIHOT-I enrolled subjects with anterior or large inferior STEMI that occurred within 24 hours after symptom onset; in AMIHOT-II, inclusion was further restricted to anterior STEMI within 6 hours of symptom onset. Thus, the recruitment pool of eligible subjects was substantially smaller for AMIHOT-II, which puts a premium on approaches that reduce the required sample size.

There are important issues related to the use of Bayesian analyses. First, it is often not clear what sources of prior information should be included in specifying the prior probability, and different choices can produce substantially different results (posterior probabilities). Conceptually, this is somewhat analogous to deciding which studies (based on their similarity) need to be included in a meta-analysis. However, some Bayesian analyses use “expert opinion” in lieu of, or in addition to, empirical evidence in specifying the prior probability. This adds in a degree of subjectivity. As a general rule, investigators should be prepared to clinically and statistically justify choices of prior information and, as appropriate, perform sensitivity analyses to check robustness of models and priors.\(^\text{16}\) In the AMIHOT-II analysis, specification of the prior probability (based on AMIHOT-I) was both straightforward and well justified. Second, Bayesian analyses are computationally complex, have limited software

### Table. Primary Differences Between the Frequentist and Bayesian Approaches (as Reported by Diamond et al.\(^\text{15}\))

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<thead>
<tr>
<th>Attribute</th>
<th>Frequentist</th>
<th>Bayesian</th>
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<tbody>
<tr>
<td>Prior information</td>
<td>Excluded</td>
<td>Included</td>
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<tr>
<td>Subjective influences</td>
<td>Implicit</td>
<td>Explicit</td>
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<td>Consistent</td>
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<td>Randomization</td>
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<td>Incidental</td>
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<td>Sample size</td>
<td>Prespecified</td>
<td>Unrestricted</td>
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<td>(\alpha) and (\beta) errors</td>
<td>Prespecified</td>
<td>Unnecessary</td>
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<tr>
<td>Stopping rules</td>
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<td>Unnecessary</td>
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<tr>
<td>Test hypothesis</td>
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<tr>
<td>Clinical interpretation</td>
<td>Misleading</td>
<td>Straightforward</td>
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currently available, and require considerable statistical expertise. Regarding the latter, Stone et al are to be commended on their hierarchical Bayesian approach, which reduced the likelihood of making a type I error (ie, erroneously concluding efficacy of infusion of SSO₂ in the infarct artery), and their explicit modeling of efficacy within a superiority framework and safety within a noninferiority framework. Other clinical trial investigators would be well served to consider similar analytic approaches.

In light of the clinical and statistical issues noted above, Stone et al should be applauded for conducting their trial because their findings extend the field of cardioprotection and, along with recent clinical data, add to the body of evidence validating the concept of reperfusion injury in humans and the potential to contain it in a clinically significant manner. Moreover, new molecular targets (reperfusion injury salvage kinase pathway, mitochondrial permeability transition pore) or novel strategies (such as cardiac cell therapy) offer further opportunities to limit infarct size after reperfusion therapy.

Although research into novel cardioprotective therapeutic approaches is laudable, resources and effort should also be focused on reducing delays and optimizing timely intervention after symptom onset in the setting of a STEMI. In our quest to quench the fire of reperfusion injury, one should not forget that prompt restoration of flow to an acutely occluded coronary artery remains the best and most reliable strategy to salvage ischemic myocardium.

References


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