Late Preconditioning Against Myocardial Stunning

Does Aspirin Close the “Second Window” of Endogenous Cardioprotection?

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“Preconditioning with ischemia” (PC) is the phenomenon whereby one or more episodes of brief ischemia paradoxically renders the myocardium resistant to a later, more sustained ischemic insult (1–3). The cardioprotection afforded by brief, transient ischemia is biphasic; a “first window” of protection is manifest within the initial 5 min to approximately 3 h of the PC stimulus, the hallmark of which is a profound reduction of infarct size, while the “second window” is exhibited approximately 12 to 72 h later and is characterized by both infarct size reduction and an attenuation of posts ischemic contractile dysfunction of viable but “stunned” myocardium (2–4). Although the undoubtedly complex cellular mechanisms contributing to this endogenous, protective response remain incompletely resolved, there is general agreement that the early, “first window” of PC is initiated by stimulation of multiple G-protein–coupled receptors, mediated by kinase activation, and ultimately achieved via the phosphorylation of one or more end effectors (2,3). While the “first” and “second windows” share many common mechanistic features (i.e., proximal triggers and kinase activation) (2–4), the temporal profile of the delayed phase of cardioprotection strongly implicates the potential involvement of nuclear transcription and resultant protein synthesis (4). Indeed, in a series of elegant and comprehensive studies, Bolli, Shinmura, and colleagues (5–7) have demonstrated that the development of the defensive, late PC phenotype is critically dependent upon the coordinated upregulation of two co-mediators: inducible nitric oxide synthase and, most notably, cyclooxygenase (COX)-2. Based on these studies, Bolli et al. (8) have formulated the “COX-2 hypothesis of late PC.”

The quandary: aspirin, COX-2, and cardioprotection. An obvious question, in addition to the issue of mechanisms, is whether ischemic preconditioning is a clinically relevant phenomenon, that is, whether brief bouts of ischemia evoke a protective phenotype in patients at risk of suffering acute coronary events. In this regard, current evidence, although not definitive, favors the concept that, as in the experimental laboratory, brief episodes of antecedent ischemia may confer both an early and delayed phase of endogenous cardioprotection in the human heart (9–11). However, if the conclusions regarding the crucial role of COX-2 in delayed PC derived from experimental models can be extrapolated to the clinical arena, this raises a disturbing possibility: the benefits of delayed PC may, in concept, be compromised in patients using the COX inhibitor acetylsalicylic acid (ASA; aspirin) for relief of fever, pain, and inflammation and, perhaps of greatest concern, in the countless patients prescribed ASA for the prophylactic prevention of acute myocardial infarction and stroke (12–14). Moreover, as the protective role of prostaglandins is not limited to the delayed “second window” of preconditioning—that is, there is experimental evidence implicating the involvement of endogenous prostaglandins in infarct size reduction in some (15) (but not all [16]) models of early, “first window” PC, in the protection afforded by angiotensin-converting enzyme (ACE) inhibitors against posts ischemic myocardial stunning (17,18), and in the reduction of infarct size seen with angiotensin1 receptor blockers (19)—ASA therapy may adversely affect these other cardioprotective modalities. In fact, retrospective analyses of large clinical trials have suggested that the prophylactic use of ASA may deprive the postmyocardial infarction patient, in part, of the benefits provided by ACE inhibitors (20,21). It is not, however, clear from these analyses whether the potential loss of benefit related to antithrombotic, analgesic, or antiinflammatory doses of ASA.

Good news/bad news. In the current issue of the Journal, Shinmura et al. (22) extend their previous work and address the question of ASA therapy and cardioprotection in the conscious rabbit model of late PC against myocardial stunning. Using a multigroup and multidisciplinary study design, the primary end point of late PC against stunning was quantified by measurement of systolic wall thickening; myocardial COX-2 protein levels were determined by Western immunoblotting, COX-2 activity was ascertained by measurement of prostaglandin (PG)E2 and 6-keto-PGF1α synthesis, and in vitro platelet aggregation was assessed using a standard, commercial platelet function analyzer. Shinmura et al. (22) report that a single, low-dose administration of ASA (5 mg/kg), designed to mimic clinical antithrombotic therapy (typical daily dose of 75 to 325 mg) and confirmed by the authors to inhibit in vitro platelet aggregation, attenuated—but did not prevent—the increase in COX-2 activity seen with brief antecedent PC ischemia. Most importantly, however, low-dose ASA, de-
spite its partial inhibition of COX-2 activity, did not block the favorable, delayed PC response (22). Similar "good news" was obtained with three repeated doses of 10 mg/kg ASA designed to simulate analgesic or antipyretic therapy; no reversal of late PC against stunning was observed. In marked contrast, "bad news" was obtained with a high, antirheumatic dose of ASA; a single, 25 mg/kg dose of ASA fully abrogated both the increase in COX-2 activity triggered by the PC stimulus and the delayed, second window of protection (22).

Importance and future directions. This study provides the first experimental insight into the consequences of nonsteroidal anti-inflammatory therapy on the efficacy of the delayed, "second window," of PC, and yields two important observations: 1) late PC against stunning is maintained in the setting of low-dose ASA therapy; but 2) a high dose of ASA may preclude the development of this endogenous, cardioprotective response. As a result, Shinmura et al. (22) urge caution in the administration of high-dose ASA to patients with coronary artery disease.

Despite the rigorous and comprehensive protocol design, there are two caveats that warrant consideration in the interpretation of these data. First, in addition to the care that must always be exercised in the extrapolation of experimental studies to the clinical setting, it must further be acknowledged that the single, low-dose administration of aspirin in this rabbit model does not fully mimic the long-term, daily aspirin therapy prescribed to patients for the primary or secondary prevention of cardiovascular events. Second, although the age of the rabbits was not specified, these studies were presumably conducted in adult animals. The effects of increasing age on the delayed, "second window" of PC are at present unknown; however, concerns have emerged that, in some models, the efficacy of the early, "first window," of protection may wane, or be lost, in senescent cohorts (23–26), while, in other species (i.e., rabbit), recent evidence suggests that the cellular mechanisms responsible for early, "first window," PC may differ in adult versus old animals (27–29). As the aging cohort is, without question, precisely the population in which the incidence of acute ischemic events is greatest and, thus, cardioprotection by any means (including both PC and prophylactic aspirin therapy) is most germane, future studies focusing on delayed PC in old animals, with versus without aspirin therapy, would be of considerable interest and relevance.

In addition to these aforementioned issues, the current study raises several other compelling questions. For example, Shinmura et al. (5) and Guo et al. (6) have previously demonstrated that COX-2 plays a crucial role in the evolution of both late PC against stunning and late PC against infarction; whether aspirin therapy alters the anti-inflammatory component of the delayed, "second window," of protection remains to be determined. Moreover, the widespread clinical use of other nonsteroidal anti-inflammatory agents with greater COX-2 specificity (i.e., ibuprofen, naproxen) and growing popularity of recently developed COX-2-specific inhibitors (celecoxib, rofecoxib) (30) begs the question: do agents that more closely target COX-2 undermine the endogenous, late phase of cardioprotection conferred by brief antecedent ischemia? This concept may, again, be of particular relevance in aging cohorts. Finally, although prospective clinical evaluation of these issues would be daunting, a retrospective analysis of surrogate indexes of delayed, "second window," PC, incorporating use of nonsteroidal anti-inflammatory agents as a covariate, may provide a more feasible approach to explore the clinical implications of the “COX-2 hypothesis of late PC.” All of these concepts would build upon the important observations made by Shinmura et al. (22), and represent fruitful lines of future investigation.

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