Editorial

Cyclooxygenase Inhibition and Adverse Remodeling During Healing After Myocardial Infarction

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For over 2 millennia, physicians have strived to relieve pain, heal, and cause no harm. However, we depend on therapeutic drugs that have side effects and unknown pleiotropic effects. A host of publications and media coverage over the last 2 years alerted us to cardiovascular (CV) risks associated with chronic use of nonselective, nonsteroidal antiinflammatory drugs (NSAIDs) and selective cyclooxygenase (COX)-2 inhibitors (COXIBs). The publicity elicited concern in patients taking these drugs for their valuable antipyretic, analgesic, and antiinflammatory properties and made physicians more vigilant about side effects such as gastrointestinal ulceration, inhibition of platelet aggregation and thrombosis, inhibition of uterine motility, inhibition of prostaglandin (PG)-mediated renal function, and hypersensitivity reactions.

Moreover, randomized clinical trials led to the withdrawal of rofecoxib because of CV concerns. In a trial for the prevention of colorectal adenoma, celecoxib was associated with a dose-related increase in the combined end point of CV death, myocardial infarction (MI), stroke, or heart failure.1 A subsequent publication showed a 2-fold increase in CV risk with celecoxib and a trend to increased blood pressure.2 The Food and Drug Administration reported in April, 2005 that all 3 approved COXIBs (ie, celecoxib, rofecoxib, and valdecoxib) were associated with increased risk of serious adverse CV events compared with placebo, but CV risk was not clearly different when COX-2–selective and –nonselective NSAIDs were compared.3 A large case-control study reported an increased relative risk of MI in the elderly treated with rofecoxib.4 A Danish study concluded that COXIBs in all doses and nonselective NSAIDs in high doses increase mortality in post-MI patients.5 To date, no long-term, randomized, clinical trial of COXIBs or nonselective NSAIDs during and/or after MI healing has been conducted.

CV Risk With NSAIDs and COXIBs in Non-MI Settings

The vascular biology of COX inhibition and CV risk has been reviewed elsewhere.6 Nearly 7 decades after aspirin was marketed for the treatment of pain, fever, and inflammation, it was appreciated that injury and inflammation released PGs and that NSAIDs suppressed their production by inhibiting COX. Evidence indicated that low-dose aspirin causes irreversible inhibition of COX via acetylation and produces beneficial CV effects (ie, prevention of atherothrombotic events, decrease in recurrent MI and stroke) by suppressing platelet thromboxane-A2 (TXA2) synthesis more than endothelial cell prostacyclin (PGI2) synthesis. The discovery of 2 genetically distinct COX isofoms in the early 1990s improved our understanding of the effects of nonselective NSAIDs and led to a targeted approach to therapy. Constitutive COX-1, found in most cells and platelets, protects gastrointestinal mucosa and promotes platelet aggregation, thrombosis, and vasoconstriction. In contrast, inducible COX-2 is stimulated by inflammatory cytokines and other factors in most cells, including cardiomyocytes, and is proinflammatory via PGE2 and antithrombotic and vasodilatory via PGI2 (Figure 1). Adverse effects of nonselective NSAIDs are attributed to loss of gastrointestinal cytoprotection and hemostasis via COX-1, with a 1:3 risk of duodenal and gastric ulceration, and loss of antiinflammatory activity via COX-2. COXIBs were therefore developed to provide analgesic and antiinflammatory benefits without the hemorrhagic risk by disabling COX-2 and conserving COX-1.

Six points about the effects of NSAIDs and COXIBs on vascular complications and atherosclerosis progression merit emphasis (Figure 1). First, vascular homeostasis involves balanced COX-1 and COX-2 activities so that COXIB-induced lowering of PGI2, coupled with unopposed COX-1 activity, leads to continued TXA2 production and increased risk of thrombosis. Second, because both COX-1 and COX-2 are found in atherosclerotic lesions and because COX-2 induced by shear stress in endothelial cells colonizes with PGE synthase-1 and matrix metalloproteinase-1 and -9 in plaque, leading to destabilization, COXIBs might be preventive. In fact, COX-2–derived PGI2 is atheroprotective in female mice.6 Third, although COXIB-induced antiinflammatory effects may be beneficial in atherosclerosis progression, the prothrombotic effect of COXIBs may be harmful during plaque rupture and coronary thrombosis associated with acute coronary syndromes. This harmful effect may explain MI-related deaths in randomized clinical trials. Fourth, both nonselective NSAIDs and COXIBs differ in potency and antiinflammatory activity, and both have a broad range of COX-1/COX-2 selectivity (see Figure 2 in the review by

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Antman et al., which may explain controversies and conflicting findings in experimental reports and randomized clinical trials testing these drugs. Other factors include differences in dose, timing, duration, interactions with background drugs, species, and the targeted disease process. Fifth, nitric oxide plays an important role in the PG-mediated modulation of vascular effects. Nitric oxide augments anti-thrombotic effects by activating PGI2 synthase and suppressing TXA2 synthase. Inflammatory mediators exert an opposite effect by stimulating inducible nitric oxide synthase and generation of superoxide and by leading to the formation of peroxynitrite, which inactivates PGI2 synthase and activates TXA2 synthase.

**NSAIDs and COXIBs in Acute MI**

The hypothesis that COX inhibition might be harmful in acute MI has been tested. In the dog model, the NSAID indomethacin increases infarct size, an effect associated with a mild increase in blood pressure but no change in collateral blood flow. However, in the same model, the NSAID ibuprofen decreased infarct size without altering hemodynamics or collateral blood flow. The hypothesis that prostanoids might be protective during MI also was tested in the dog model; this study showed that PGI2 and PGE1 decrease infarct size and increase collateral blood flow compared with PGE2 and controls and that both PGI2 and PGE1 induce myocardial salvage at low levels of collateral flow. Cardio-protection with PGI2 and PGE1 also has been demonstrated during ischemia-reperfusion in several animal models such as pigs, rats, rabbits, and dogs and is reviewed elsewhere. Although these studies suggested that the protective effects of PGI2 and PGE1 (but not PGE2) and the divergent effects of the NSAIDs might be due to different cellular and metabolic effects, this area has not been well studied. Because COX-2 is pro-inflammatory via PGE2, the cardioprotective effect of increased COX-2 in late ischemic preconditioning on myocardial stunning and MI10 is most likely via PGI2 and PGE1 rather than PGE2 (Figure 2). The net effect of COXIBs in acute MI remains highly controversial.

**NSAIDs and COXIBs During Healing After MI**

Healing after MI is a highly active, dynamic, and time-dependent process that repairs the damaged left ventricular (LV) wall with scar. The process involves acute and chronic inflammation, fibroblast proliferation, collagen deposition, growth, and structural remodeling over several weeks. Suppression of inflammation by COX inhibitors during that interval may impair or delay healing of the infarct zone (IZ), with drastic consequences such as IZ thinning, adverse LV remodeling, aneurysm, and decreased resistance to rupture. Drugs that increase ventricular loading also may cause adverse IZ remodeling during healing after MI. Several studies have suggested that collagen quantity and quality in the infarcted LV play an important role in resisting LV distension and rupture and that drugs that decrease IZ collagen in healing infarcts can augment IZ thinning.

In this issue of *Circulation*, Timmers et al. report the effects of celecoxib on LV remodeling during healing over 6 weeks after posterior MI in a pig model of left circumflex coronary artery occlusion. They document 4 main findings. First, celecoxib increased adverse IZ remodeling, with increased IZ thinning and LV dilation, and LV systolic dysfunction, as evidenced by reduced fractional area contraction on 1-dimensional echocardiography. Second, celecoxib increased LV end-diastolic and end-systolic volumes measured by a conductance catheter. Third, celecoxib decreased LV collagen density assessed by picrosirius red staining. Fourth, celecoxib reduced total mortality (7 of 14 or 50%) compared with controls (0 of 8). Death occurred 3 to 6 weeks after MI; the cause was spontaneous rupture with cardiac tamponade in 3 (43%), heart failure in 2, and sudden death in 2.
Several strengths need emphasis. First, the authors elegantly demonstrate for the first time that celecoxib promotes adverse LV remodeling and rupture during healing after MI. Second, they carefully confirmed COX-2 inhibition in the IZ by showing decreased PGE$_2$ production, excluded COX-1 inhibition by showing no change in TXB$_2$ (metabolite of TXA$_2$), and showed the presence of COXIB in the occluded bed, presumably via collateral vessels. Third, they underscored the use of a "human-like" large animal model and cautioned against direct extrapolation of findings in mice, in which COXIBs appear to be cardioprotective. This conclusion endorses the view that preclinical confirmation in large animals is an important step in translational research. This view is further supported by cumulative evidence indicating that the rate of healing is slower in large than in small animals (Figure 3) and in large than in small MI.12 and that the inflammatory response is different in mice and dogs.18

Several limitations in the Timmers et al study that affect interpretation should be noted. First, there was a disparity in animal numbers between groups (8 controls, 14 treated) despite randomization, and all animals were female. In addition, it is unclear how myocardial tissue was obtained for measuring COX-2 inhibition before MI. Second, only a high dose of celecoxib (400 mg twice daily) was tested. It would have been helpful to know the effect of dose on attenuation of IZ collagen because the effects of NSAIDs and COXIBs on various end points are dose related. For example, indomethacin decreases collagen at high doses but not low doses.19 Third, they relied heavily on the assessment of collagen by picrosirius red staining, which reflects mainly fibrillar collagens. Because collagen quality and quantity are important determinants of remodeling after MI, data on total collagen, types I and III, and cross-linking would have been helpful. In the same context, the authors allude to no decrease in transforming growth factor-β mRNA (fibrogenic cytokine) and protocollagen (index of collagen turnover) but do not show the data. Fourth, the authors studied only left circumflex occlusion with posterior MI, which is considered to be at
lower risk for adverse remodeling, dysfunction, and death. One assumes that the harmful effects of COXIBs may be more severe in anterior MI. Fifth, the evaluation of remodeling relied on 1-dimensional echocardiography at the midpapillary level and did not apply 2-dimensional echocardiography for the temporal assessment of infarct expansion, LV volumes and shape, and LV ejection fraction. Because the MI (and the area of akinesis on 3-dimensional mapping) after LV volumes and shape, and LV ejection fraction. Because the MI (and the area of akinesis on 3-dimensional mapping) after left circumflex occlusion tends to be larger in the basal sections (ie, mitral valve, chordal, and high papillary levels on 2-dimensional echocardiography) and tapers toward the apex, the authors may have missed the area with the most thinning. Sixth, the slightly higher blood pressure in the COXIB group may have contributed to adverse remodeling. Collectively, the findings of the Timmers et al study and emerging evidence endorse the need for more detailed translational and mechanistic clinical studies on the impact of COX-2 inhibition during the subacute phase of MI.

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References

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