Putting the vasoactive effects of COX-2-derived prostanoids into clinical perspective

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This editorial refers to ‘Selective cyclooxygenase-2 inhibition directly increases human vascular reactivity to norepinephrine during acute inflammation’ by Foudi et al., pp. 269–277, this issue.

Ever since the recognition that the selective inhibitor of cyclooxygenase (COX)-2, rofecoxib, increases the risk for adverse cardiovascular events, enormous attention has been given to the mechanisms underlying these adverse vascular effects of the coxibs. Many recent studies that have investigated the biological consequences of COX-2 inhibition in the vasculature have focussed either on the prothrombotic side effects of decreased endothelial prostacyclin production during selective COX-2 blockade or on detrimental effects of such an intervention on atherosclerosis. Although such studies have greatly broadened our understanding of the pathophysiological roles of COX-2-mediated prostanooid production in vascular biology, the important vasodilatory functions of COX-2-derived prostanoids have been somewhat eclipsed by them.

Foudi et al. presents data that address the topic of detrimental vascular effects of COX-2 inhibition from this different, yet important, point of view. They show in isolated human internal mammary arteries (IMA) that under conditions of acute septic inflammation, which is induced by simultaneous administration of interleukin-1β (IL-1β) and lipopolysaccharide (LPS), COX-2 is upregulated and produces prostacyclin and prostaglandin E2 (PGE2) rather than thromboxane A2 (TxA2). COX-2 expression is shown to be enhanced not only in the intima, but also in the smooth muscle cell-containing media of the vasculature. When vasoconstriction is induced by norepinephrine in the IMA preparations, COX-2 inhibition leads to potentiated vasoconstriction during inflammation. By rubbing the endothelium off their arteries, they show that this potentiated vasoconstriction to norepinephrine is due to a loss of smooth muscle cell-derived prostanoids because the constriction-potentiating effect of COX-2 inhibition is similar, no matter whether the endothelium is present or not.

The interesting experimental approach with human material used by the authors here not only brings attention to the recently underrated role of prostacyclin for vasodilation, but—more importantly—it also commemorates the role of smooth muscle cells as important sources of vasoactive prostanoids. Arterial smooth muscle cells, especially in inflammation, have been known for a long time to be a relevant prostanoid source. They have been described to exhibit cytokine-inducible COX-2 expression, mainly in the pulmonary arterial system. In aortic tissue, smooth muscle-derived, COX-2-dependent prostacyclin has been shown to be the main prostanoid produced after stimulation with angiotensin II and also under inflammatory conditions. In spite of the obvious potential for a role of these prostanoids in vasomotor function, a role for COX-2-derived smooth muscle cell prostanoids in many of these observations has been seen in its contribution to atherosclerosis development, as COX-2 inhibition in experimental studies was shown to result in down-regulation of adhesion molecules, such as ICAM or VCAM, that play a role in atherosclerosis. In addition, in vivo, macrophage-derived COX-2 products have been shown to enhance atherosclerosis. Clinical studies were undertaken to undermine the beneficial potential for COX-2 inhibition in the treatment of stable coronary disease; however, in the aftermath of the rofecoxib scandal, these studies were later abandoned, thus highlighting the incessant change in paradigm with respect to the role of COX-2 in vascular disease.

Considering this enormous amount of seemingly contradictory information about the vascular effects of COX-2 inhibition, an attempt must be made to put the study by Foudi et al. into a clinical perspective. How can their findings translate into a disease situation? As discussed by the authors, the experimental demonstration of a vasoconstriction of human arterioles caused by selective COX-2 inhibition that is independent of TxA2 gives reason to argue for a role in atherosclerosis. Indeed, in addition to the prothrombotic effects of Coxibs that seem well established nowadays, this vasoconstriction due to diminished release of vasodilator prostanoids is likely an important factor in detrimental COX-2 inhibitor effects. In keeping with this, non-steroidal anti-inflammatory drugs, including selective

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COX-2 inhibitors, have many times been shown to deteriorate hypertension.1,2 It is also tempting to take a closer look at the exact experimental conditions that Foudi et al. use in their study and try to translate them into a real-world clinical surrounding, where endotoxin, cytokines, and norepinephrine may be encountered together. Clearly, the use of LPS and IL-1β represents a type of inflammation as it may occur in bacterial sepsis. LPS released from bacterial membranes causes monocytes to release cytokines, among them several interleukins such as IL-1β, and both certainly have a role in septic shock. Of note, in patients suffering from septic shock, norepinephrine is the drug of choice in order to prevent life- and organ function-threatening hypotension. On the basis of the study of Foudi et al. one can speculate not only how selective COX-2 inhibition may contribute to adverse cardiovascular effects by conveying vasoconstriction in atherosclerotic disease, but also how this exact treatment could even be beneficial in fighting severe hypotension in a patient suffering from septic shock, because then simultaneous COX-2 inhibition could enhance the vasocostrictive effects of norepinephrine. Such consideration may seem odd at first glance, but coxibs have not been investigated clinically under these circumstances. It is certainly unclear, whether the vasoconstriction observed by Foudi et al. in IMA preparations ex vivo would also occur in vivo. Experimental studies that have approached similar situations, such as by testing whether COX-2 inhibition prevents hypotension and organ dysfunction, have not given evidence for an increase in blood pressure due to COX-2 inhibitors.3 However, norepinephrine was not used in conjunction with COX-2 inhibitors.15 This demonstrates that it is still unclear whether COX-2 inhibition, in general, exerts negative effects in diseases other than atherosclerosis. Of note, Gitlin and Loftin6 also report that inhibition of COX-2 in an animal model exerts detrimental effects by increasing atherosclerosis in ApoE−/− mice.6 Although the majority of researchers come to the conclusion that COX-2 inhibition exerts deleterious vascular effects, one lesson that should be learned from the past decades of research on vascular effects of coxibs is that one cannot always attribute beneficial vascular effects to prostanooids formed by COX-2.

In summary, the study by Foudi et al. once again demonstrates the high degree of complexity of prostanoid function in the vascular system and the enormous dependence of the effects of COX-2 inhibition on the specific pathophysiological background that is investigated. Although not interpreted this way by the authors themselves, looking at the data from different pathophysiological perspectives—as such the situation of a patient in septic shock mentioned above—allows one to speculate about the direction into which the effects of vascular COX-2 inhibition would actually drive a specific patient—it could be detrimental, but there may also be beneficial aspects.

References