In the current issue of Hypertension, Virdis et al report an elegant series of experiments on isolated small arteries harvested from normotensive and essential hypertensive humans. They conclude that, in the blood vessels of their hypertensive subjects, cyclooxygenase-2 (COX2) represents a major source of reactive oxygen species (ROS), in particular superoxide anions, which in turn reduces the bioavailability of NO, thus curtailing endothelium-dependent relaxations to acetylcholine. They feel that these observations provide the major explanation for the endothelial dysfunction characteristic of human essential hypertension. The data reported are convincing, despite the small size of the studied populations, which indirectly reinforces the importance of the mechanism revealed. As such, these findings seem to provide the finishing touch to a translational picture drafted more than a quarter of a century ago in the aorta of the essential spontaneously hypertensive rat (SHR) and thereafter outlined in the human forearm.

One can always find imperfections in any study (except one’s own!). A common temptation is to use only 1 dose of a pharmacological agent and to believe in its selectivity. For example, in the study by Virdis et al, only a minor role for NAD(P)H oxidase (by most believed to be the main generator of superoxide anions in the vascular wall) is inferred from the modest effect of single concentrations of apocynin and diphenylene iodinium, presented as selective inhibitors of this enzyme. However, the latter agent interferes with several other flavoenzyme oxidoreductases, and the former is regarded (at least in Frankfurt) as a nonselective antioxidant that should yield effects comparable with those of ascorbic acid. Similarly, the lovers of the role of thromboxane-prostanoid (TP) receptor activation in COX-mediated endothelial dysfunction could argue that it is swept under the carpet of the e-supplemental information with one concentration of a single TP antagonist, without providing data that in the studied preparations under the experimental conditions tested TP antagonism actually is achieved…

It is not surprising that vascular COX produces free radicals during stimulation with acetylcholine. Thus, when viewing the data presented by Virdis et al, one can only bow to the logical conclusion reached that in the human arteries studied COX plays a major role in producing ROS, curtailing the relaxations to acetylcholine solely by reducing the bioavailability of endothelium-derived NO. In a sense, this conclusion is most pleasing because it provides direct human relevance to the old observation that superoxide anions scavenge endothelium-derived relaxing factor. But, if the overproduction of superoxide anions undermines the action of NO in the vascular smooth muscle, why do they not blunt the response to an exogenous NO donor? One could also regret that the production of prostaglandins (in particular prostacyclin), which remains the major function of COX, was not measured, although this can be done in small arteries. If the release/production of prostaglandins is not increased, are we dealing with an uncoupling of the enzyme, as envisaged for endothelial NO synthase? If it is augmented, why do the prostanoids not contribute to vascular tone as suggested by the lack of effect of COX inhibition beyond that of ascorbic acid or that of the TP receptor antagonist (if effective)? Have the smooth muscle cells of the small arteries of hypertensive patients, in the process of accelerated aging on chronic exposure to the increased arterial blood pressure, lost the responsiveness of both their TP and IP (prostaglandin I₂) receptors? The latter would be consistent with data in the SHR and in other aging animals, but the former certainly not, on the contrary.

Virdis et al conclude that most of the increased presence of COX in the small arteries of their hypertensive patients is located in the media. In the rat also, chronic exposure to high arterial blood pressure, diabetes mellitus, and oxidative stress can cause upregulation of COX in vascular smooth muscle. Again, being utterly critical when looking at the immunostaining images provided, one could argue that the integrity of the endothelial cell layer in the arteries from their hypertensive patients is not as well preserved as in the preparations of their nornotensive subjects and thus that the suggestion of a decreased endothelial expression of COX can be questioned. Nevertheless, giving them the benefit of the doubt, if the problem with the chronic exposure to high blood pressure is mainly the abundance in the media of COX generating ROS, the unavoidable conclusion is that the release of NO is just fine (as suggested by the normal responses to acetylcholine in the presence of either ascorbic acid or apocynin plus the COX-2 inhibitor) in the small arteries of the hypertensive patients; again, a similar conclusion had been reached in the SHR aorta when NO was called EDRF
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(endothelium-derived relaxing factor). In addition, Virdis et al report that substantial relaxations to acetylcholine remain in the presence of L-NAME (Nω-nitro-L-arginine methyl ester) (with or without COX inhibitors), although they do not comment further on the mechanism underlying them. In the absence of sympathetic nerve activity under their in vitro experimental conditions (which they amusingly term clinical setting), these L-NAME–resistant relaxations to acetylcholine can reasonably be attributed to endothelium-dependent hyperpolarization. They are remarkably similar in preparations of normotensive and essential hypertensive subjects. Hence, is the endothelium of the latter truly dysfunctional or is it trying very hard to cope with the abnormal events in the media?

At first sight, the situation in the hypertensive humans, with medial COX-2–generating superoxide anions that scavenge endothelium-derived NO, seems to differ fundamentally from that in the SHR, the most commonly used animal model of essential hypertension. Indeed, in the latter endothelial COX-1 can be upregulated and seems to play a dominant role in endothelium-dependent responses by generating vasoconstrictor prostaglandins but also ROS. However, does it really matter whether COX-1 or COX-2 are upregulated and whether the upregulation is in the endothelium or the media? Indeed, the consequences seem to be the same, and the common result is abnormal endothelium-dependent relaxation to acetylcholine, an accepted biomarker of increased risk for vascular disease (Figure). Is the important question not why do we see upregulation of COX (whether COX-1 or COX-2) in the vascular wall (whether intima or media) of chronically hypertensive mammals? What feedback loop is dysregulated to the extent that such excessive production of ROS and vasoconstrictor prostanoids is permitted? If one takes the simple-minded approach that production of prostanoids is the primary role of COX, this implies that any regulatory feedback loop must involve the end products of the enzyme. Then, one can only speculate, in the absence of overt signs of local inflammation, that the COX overexpression after chronic exposure to high blood pressure results from an imbalance in prostanoid receptor responsiveness/sensitivity in either endothelial (SHR) or vascular smooth muscle (essential hypertensive human) cells preventing end product feedback inhibition.

The unequivocal message given by the tissues studied by Virdis et al is that, at least in small arteries of subcutaneous fat of hypertensive subjects, COX-2, a usual suspect in pathology, is indeed the major culprit in causing abnormal endothelium-dependent relaxations to acetylcholine. Their findings throw a new light on the vascular, possibly beneficial effects of COX-2 inhibition. Whether or not, after the rofecoxib tsunami, their enthusiasm will be sufficient to reactivate interest in the pharmaceutical industry is another matter…

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Disclosures

None.

References


One or Two, Does it Matter as Long as the Arterial Wall Is Coxygenated?
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