Editorial

Out of Balance
A Role of Impaired Superoxide Dismutase Activity for Vascular Constrictive Remodeling After Angioplasty

Ralf P. Brandes

Lumen loss by constrictive remodeling is a mechanism-ically still incompletely understood, clinically important problem frequently arising after balloon angioplasty. The arterial trauma, potentially in combination with the destruction of the vascular endothelium, gives rise to a fundamental reorganization of the extracellular matrix. This process is mediated by vascular fibrosis and subsequent condensation of the matrix, ultimately leading to shrinkage of the scar and of the vessel. Several elements contribute to remodeling, including smooth muscle cells and adventitial fibroblasts, resulting in the expression and secretion of matrix proteins such as collagen and of matrix-degrading metalloproteinas (MMPs). Furthermore, cellular proliferation, migration, apoptosis, and vascular spasm are involved in the process.1

See page 2197

Reactive oxygen and nitrogen species play a central role in the regulation of the activity state of vascular cells. Several studies have demonstrated that oxidative as well as nitrosative stress occurs after balloon injury of arteries.2 The pathophysiological role of redox stress for constrictive remodeling, however, is still obscure. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Leite et al3 communicate an elegant study that provides insights into the complicated interplay of reactive oxygen and nitrogen species after balloon angioplasty finally leading to constrictive remodeling. Their observation of an attenuation of vascular superoxide dismutase (SOD) activity after angioplasty in conjunction with the demonstration that delayed systemic application of extracellular SOD (ecSOD) prevents vascular shrinkage after angioplasty is intriguing and could give rise to a reassessment of our current doctrines of angioplasty-induced redox stress.

SOD, as the only enzyme catalyzing the reaction of superoxide anions ($O_2^-$) to hydrogen peroxide ($H_2O_2$) is a central element in the maintenance of the vascular redox balance. If $O_2^-$ is not detoxified by SOD, it rapidly reacts with nitric oxide (NO) to form peroxynitrite ($ONOO^-$). Therefore $O_2^-$ is the main limiting factor for vascular NO bioavailabil-

From the Institut für Kardiovaskuläre Physiologie, Klinikum der J.W. Goethe-Universität, Theodor-Stern-Kai 7, Frankfurt Germany.
Address correspondence to Ralf P. Brandes, MD, Institut für Kardiovaskuläre Physiologie, Klinikum der J.W. Goethe-Universität, Theodor-Stern-Kai 7, D-60596 Frankfurt am Main, Germany. E-mail r.brandes@em.uni-frankfurt.de


Arterioscler Thromb Vase Biol. is available at http://www.atvbaha.org
DOI: 10.1161/01.ATV.0000102552.84528.8f
oxidizing agent than H₂O₂, which activates transcription factors similar to H₂O₂. Indeed, in the setting of inflammation, ONOO⁻ activates NF-κB and mediates E-selectin expression in vitro and in vivo. Alternatively, the inhibitory action of NO on remodeling is more potent than the stimulus elicited by H₂O₂. Indeed, catalase, which decomposes H₂O₂, had no effect on vascular spasms occurring after angioplasty. Finally, H₂O₂ and ONOO⁻ are certainly only two of a multitude of activating factors generated after balloon injury.

The type of vascular remodeling after angioplasty is not necessarily constrictive, and the fate of this process is mainly controlled by NO. To allow outward remodeling, degradation of extracellular matrix is required. NO induces the expression of MMPs, and the NO-mediated outward remodeling in response to endothelial shear stress is mediated by MMP-2 and MMP-9.

An alternative effector to NO could be the group of transforming growth factors (TGF). TGF-β1 has been shown to be involved in remodeling and influences matrix formation and scavenging, and there is a tight link among redox stress, TGF-β1, and matrix generation. In the study by Leite et al., ecSOD application resulted in a reduced collagen accumulation. Indeed, liposomal SOD has previously been shown to reduce the expression of TGF-β1 and collagen in dermal myofibroblasts, and TGF-β1 expression is induced by oxidative stress. Interestingly, TGF-β1 itself activates NADPH oxidases in cultured fibroblasts and inhibits induction of iNOS.

In conclusion, vascular remodeling is influenced by a tight interaction of redox-modulated pathways at several levels of cellular signaling cascades. SOD is the central switch between inward and outward remodeling by determining not only the bioavailability of O₂⁻ but also that of ONOO⁻ and NO.

References

Out of Balance: A Role of Impaired Superoxide Dismutase Activity for Vascular Constrictive Remodeling After Angioplasty
Ralf P. Brandes

Arterioscler Thromb Vasc Biol. 2003;23:2121-2122
doi: 10.1161/01.ATV.0000099269.04527.88

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/23/12/2121

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at: http://atvb.ahajournals.org//subscriptions/