More NO-No More ROS

Combined Selective Mineralocorticoid Receptor Blockade and Angiotensin-Converting Enzyme Inhibition for Vascular Protection

Johann Bauersachs, Daniela Fraccarollo

Angiotensin-converting enzyme (ACE) inhibitors significantly reduce cardiovascular events in patients with established or at high risk for coronary artery disease; however, the favorable effect appears to be modest.1 Although early after initiation of therapy ACE inhibition reduces plasma levels of both angiotensin II and aldosterone, during prolonged ACE inhibition aldosterone levels may increase, the so-called aldosterone escape. Aldosterone levels independently predict cardiovascular risk,2 and direct detrimental effects of aldosterone on the vascular wall have been described:3 mineralocorticoid receptor (MR) activation stimulates the formation of reactive oxygen species (ROS) in endothelial cells and limits NO generation and bioavailability.4 Angiotensin II–mediated ROS formation in the vascular wall may be mediated in part by MR activation,5 and aldosterone potentiates angiotensin II–induced signaling processes in vascular smooth muscle cells.6 During inflammatory conditions, aldosterone and cortisol may act as agonists at the MR, thus leading to detrimental effects of MR activation, even in the absence of elevated concentrations of aldosterone.7

MR blockade reduces ROS formation and improves left ventricular remodeling, as well as endothelial function, when added to ACE inhibition in heart failure.8 Although eplerenone attenuated atherosclerosis in cholesterol-fed monkeys,9 it was unclear whether adding eplerenone to an ACE inhibitor would be more useful for preventing atherosclerosis progression than monotherapy with an ACE inhibitor.

In the present issue of Hypertension, Imanishi et al10 show the additional impact of eplerenone and ACE inhibition on atherosclerotic changes in genetically hyperlipidemic rabbits and dissected several potential underlying mechanisms. ACE inhibition and MR blockade displayed sustained vascular protection by complementary and additive effects on the balance between NO and ROS in the vascular wall (Table and Figure).

With regard to the attenuation of reduced nicotinamide-adenine dinucleotide oxidase activity and ROS formation, ACE inhibition alone was somewhat more effective than eplerenone; however, the combination led to an additive reduction. The larger decrease in ROS formation by enalapril, as compared with eplerenone monotherapy, may also relate to the more effective prevention of tetrahydrobiopterin oxidation and subsequent endothelial NO synthase (eNOS) uncoupling by ACE inhibition. eNOS uncoupling, a condition that leads to eNOS-mediated superoxide anion production instead of NO, possibly resulting from a mismatch between eNOS and its cofactor tetrahydrobiopterin, is increasingly recognized as an important mechanism underlying endothelial dysfunction.4 The unique bradykinin-mediated stimulation of eNOS protein expression by ACE inhibitors,8,11 together with the effective attenuation of ROS formation, may explain the greater effect of enalapril compared with eplerenone monotherapy on basal and stimulated NO bioavailability in the rabbit vasculature observed by Imanishi et al.10

In sharp contrast to enalapril, eplerenone markedly increased eNOS phosphorylation at Ser1177 (Table), an effect that may be mediated by the prevention of MR-driven activation of protein phosphatase 2A.4 Site-specific dephosphorylation of eNOS at Ser1177 represents an important mechanism modulating eNOS enzyme activity and NO bioavailability in the vasculature by aldosterone. Improvement of endothelial dysfunction by normalization of reduced eNOS phosphorylation at Ser1177 in response to selective MR blockade in vivo has recently also been observed early after experimental myocardial infarction.12

Taken together, Imanishi et al10 have demonstrated a marked additive reduction of the plaque area in genetically hyperlipidemic rabbits by long-term selective MR blockade.

Table. Effects of Chronic Treatment With The Selective Mineralocorticoid Receptor Blocker Eplerenone, the ACE Inhibitor Enalapril, or the Combination of Both on Various Parameters Related to Vascular NO/Superoxide Balance and Plaque Area in Genetically Hyperlipidemic Rabbits as Observed by Imanishi et al10

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Eplerenone</th>
<th>Enalapril</th>
<th>Eplerenone Plus Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>eNOS expression</td>
<td>↓↑</td>
<td>↑↑↑</td>
<td>↑↑↑↑</td>
</tr>
<tr>
<td>eNOS Ser 1177 phosphorylation</td>
<td>↑↑↑</td>
<td>(↑)</td>
<td>↑↑↑↑</td>
</tr>
<tr>
<td>BH4 levels</td>
<td>↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑↑</td>
</tr>
<tr>
<td>NO release</td>
<td>↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑↑</td>
</tr>
<tr>
<td>NADPH oxidase activity</td>
<td>↓↓</td>
<td>↓↓↓</td>
<td>↓↓↓↓</td>
</tr>
<tr>
<td>Superoxide formation</td>
<td>↓↓</td>
<td>↓↓↓</td>
<td>↓↓↓↓</td>
</tr>
<tr>
<td>Plaque area</td>
<td>↓↓</td>
<td>↓↓↓</td>
<td>↓↓↓↓</td>
</tr>
</tbody>
</table>

BH4 indicates tetrahydrobiopterin; NADPH, reduced nicotinamide-adenine dinucleotide phosphate.
added to ACE inhibition. These observations are remarkable, because this experimental evidence may stimulate clinical trials using MR blockade to retard atherosclerosis progression in patients with atherosclerotic disease who are at high risk for cardiovascular events even when treated with ACE inhibitors.1

Disclosures
J.B. received research grant support and honoraria from Pfizer related to eplerenone. D.F. received research grant support from Pfizer related to eplerenone.

References
More NO-No More ROS: Combined Selective Mineralocorticoid Receptor Blockade and Angiotensin-Converting Enzyme Inhibition for Vascular Protection
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Hypertension. 2008;51:624-625; originally published online January 28, 2008;
doi: 10.1161/HYPERTENSIONAHA.107.106625

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