The role of the vascular endothelium for hypertension development is not trivial to define. A quiescent healthy endothelium continuously releases potent vasodilators in response to the flowing blood, which have the potential to lower vascular resistance directly. Endothelial dysfunction is a condition comprising not only attenuated endothelium-dependent vasodilation but also endothelial inflammatory activation. Although it is well accepted that endothelial dysfunction is a predictor of atherosclerosis development and future cardiovascular events, its role for hypertension is less well understood. To assume that attenuated endothelial vasodilator release through an increase in peripheral resistance directly translates into hypertension would be naïve. Not only that metabolic and local nervous factors have a much stronger effect on local vascular tone but also the renal and central control of blood pressure over-rule local vascular factors in their effect on blood pressure. This is easy to understand because the main objective of circulation control is the maintenance of blood pressure so that each organ separately and individually controls its perfusion through local factors. Systemic blood pressure control, however, is usually preserved in conditions associated with endothelial dysfunction, such as hypercholesterolemia and smoking, even if these may eventually result in hypertension development (Figure 1). In patients with heart failure, blood pressure is usually normal, despite the massive increase in peripheral resistance. Under this condition, low cardiac output and systemic hypoxia contribute to peripheral vasoconstriction. The latter is a consequence of increased sympathetic nerve activation and blunted endothelial NO function. Conversely, normalization of endothelial function does not necessarily affect blood pressure. Endothelial-specific deletion of the mineralocorticoid receptor improved endothelial function and attenuated vascular inflammation in aldosterone and deoxycorticosterone acetate (DOCA)/salt-induced vascular dysfunction in mice but did not lower blood pressure. Interestingly, despite the low basal vascular tone of the lung under physiological conditions, sympathetic control of vessel tone becomes important during the development of pulmonary artery hypertension (PAH): In the monocrotaline rat model of PAH, sympathetic activity was increased and ganglion blockade reduced pulmonary pressure, as well as endothelial dysfunction, and increased NO availability.

In addition to peripheral resistance, the endothelium affects other aspects contributing to hypertension development. Vascular stiffness, for example, on one hand, is an expression of systemic aging and correlates with lung stiffness, but on the other, this parameter is also modulated by the endothelium and thus relates to pulse wave velocity and pulse pressure. The endothelium also orchestrates vascular remodeling processes and inflammation; conversely, inflammation induces endothelial dysfunction. For example, tumor necrosis factor α–induced endothelial dysfunction in humans is partly mediated by endothelial nitric oxide synthase (eNOS) mRNA destabilization through miR-155: eNOS is a target of miR-155 and this miR is induced by tumor necrosis factor-α. Thus tumor necrosis factor-α mediates an impairment of endothelium-dependent relaxation of the human mammary artery, an effect prevented by anti–miR-155.

### Endothelial Inflammation and Hypertension

Some evidence indicates that endothelial inflammatory activation promotes hypertension development. With the variable outcome of renal artery denervation, it is important to identify biomarkers predicting the success of the procedure. In a study with 55 patients with hypertension, 9 did not respond to the procedure with an adequate antihypertensive response. These patients had significantly lower plasma levels of soluble fms-like tyrosine kinase-1 (sFLT-1), ICAM-1 and VCAM-1 than responders. This suggests that inflammatory activation predicts responses to the renal artery denervation. Interestingly, in keeping with the concept of hypertension being the consequence of inflammation, studies suggest that inflammatory cells are required for hypertension development. In the DOCA-salt-uninephrectomy model of hypertensive mice, the chemokine receptor CCR2 and its ligands CCL2, 7, 8, and 12 are increased. The CCR2 antagonist INCB3344 prevented vascular macrophage influx and attenuated hypertension development by ∼50%. Similarly, the vascular effects of aldosterone involve inflammatory cells: aldosterone requires the presence of macrophages and slightly decreased the number of anti-inflammatory T regulatory lymphocytes. Adoptive transfer of the latter cells attenuated the negative responses elicited by aldosterone. Similarly, the responses to endothelin and angiotensin II (Ang II) involve myeloid cells, and
depletion of macrophages or congenital lack of macrophages in osteopetrotic mice attenuated hypertension, endothelial dysfunction, and vascular oxidative stress in response to these stimuli.\textsuperscript{13} The inflammation occurring in response to vasoconstrictor agonists, such as Ang II, is mediated by several transcription factors, including nuclear factor κB, activator protein-1, and also signal transducers and activator of transcription. Inhibition of STAT3 with a small-molecule inhibitor prevented the Ang II–induced vascular dysfunction of the murine carotid artery in and ex vivo and reduced the hypertension development in response to Ang II.\textsuperscript{14}

**Endothelial Reactive Oxygen Species Production and Hypertension**

An important consequence of the inflammation induced by Ang II is increased vascular reactive oxygen species (ROS) formation. It is well established that Ang II induces and activates Nox NADPH oxidases,\textsuperscript{15} but recently additional ROS sources have been established. In small arteries isolated from subcutaneous biopsies of patients with hypertension, a significant portion of ROS is produced by cyclooxygenase 2, which exhibits an increased expression in these patients.\textsuperscript{16} In the mouse aorta, the mitochondrial monoamine oxidase is another mediator of endothelial dysfunction after treatment with Ang II or during inflammation. Mitochondrial monoamine oxidase-A and mitochondrial monoamine oxidase-B are induced in the vessels under these conditions and generate a significant amount of hydrogen peroxide ($\text{H}_2\text{O}_2$) sufficient to attenuate endothelial NO release.\textsuperscript{17} Other mitochondrial ROS sources, such as p66Shc, probably also contribute to hypertension-induced ROS production.\textsuperscript{18} Interestingly, several mechanisms support the signaling pathway from Ang II to Nox induction and oxidative stress. In the kidney, an important role of cytochrome P450 1B1 (Cyp1B1) has been documented. Genetic deletion of the enzymes in mice prevented the Ang II–stimulated increase in 12- and 20-hydroxyeicosatetraenoic acids, ROS formation, Nox activity, and stimulation of ROS-sensitive kinases,\textsuperscript{19} and similar effects were observed in the DOCA and salt hypertension model.\textsuperscript{20} Part of the action of Cyp1B1 seems to be mediated by the metabolism of estrogens, which limit Nox activation and induction.\textsuperscript{21} This aspect is important because renal dysfunction has a much stronger effect on hypertension development than pure endothelial dysfunction in arteries or, for example, the skeletal muscle. Intrarenal vascular resistance in response to Ang II is increased in ApoE\textsuperscript{−/−} mice through a ROS-dependent activation of p38 mitogen-activated protein kinase and subsequent phosphorylation of MLC20. Ang II is produced from Ang I by angiotensin-converting enzyme 1 (ACE1), whereas ACE2 generates Ang-(1-7), which in part antagonizes the responses to Ang II. Indeed, Ang-(1-7) treatment attenuates the effects of Ang II on the kidney of ApoE\textsuperscript{−/−} mice and reduced the basal renal NADPH oxidase and p38 mitogen-activated protein kinase activity. Knockout of Mas, the receptor for Ang-(1-7), or inhibition of p38 mitogen-activated protein kinase blocked the beneficial effects of Ang-(1-7) on the kidney.\textsuperscript{22} Given that Ang-(1-7) is produced by ACE2, it is attractive to speculate that increasing ACE2 results in vascular protection. With the compound 1-[(2-dimethylamino)ethylamino]-4-(hydroxymethyl)-7-[(4-methylphenyl)sulfonyl oxy]-9H-xanthene-9-one (XNT), a small-molecule ACE2 activator has become available. XNT improved endothelial function in spontaneously hypertensive rats and in streptozotocin-diabetic rats through a Mas receptor–dependent effect. Similarly, xanthates attenuated the Ang II–induced ROS production of human aortic endothelial cells.\textsuperscript{23}

**Endothelial Function: A Therapeutic Target for the Treatment of Hypertension?**

Changing the vascular redox environment is an alternative to directly interfering with Ang II signaling in endothelial dysfunction. Ang II–induced vascular dysfunction is endogenously partly blunted by the induction of the copper-containing extracellular superoxide dismutase 3. It turns out that this involves a mechanism in which Ang II induces the copper-low–sensitive transcription factor and copper chaperone Atox1. Deletion of Atox1 prevented the Ang II–mediated SOD3 induction. Ang II simultaneously increased the binding of Atox1 to the copper exporter ATP7A and thereby induced cytosolic copper export, which promoted copper loading of extracellular superoxide dismutase.\textsuperscript{24}
Another approach to restore normal endothelial function is to alter the activity of G-protein–coupled receptor (GPCR) kinases. These enzymes limit GPCR signaling by phosphorylating the activated receptor, which is then internalized. Because GPCRs mediate the harmful signaling of Ang II, thromboxane, endothelin, and other vascular growth factors or vasoactive compounds, they contribute to endothelial dysfunction and vasoconstrictor signaling. Because GPCRs, however, also facilitate endothelial vasodilator release, it was unclear whether GPCR kinases are good antihypertensive drug targets. This was studied by heterozygous deletion of the ubiquitously expressed GPCR kinase 2 in Ang II–induced vascular dysfunction in mice. Heterozygous deletion of GPCR kinase 2 resulted in attenuated Ang II–induced hypertension, remodeling, and endothelial dysfunction. This suggests that at least mild pharmacological inhibition of GPCR kinase 2 could be beneficial.

Improving endothelial function is not a main indication of cardiovascular drugs but a welcome pleiotropic effect. It was, therefore, interesting to note that fenofibrate improves flow-mediated brachial artery dilatation at 2 and 7 days in a placebo-controlled study of 12 and 10 patients in a lipid-independent manner. Probably, fenofibrate-enhanced endothelial NO production as an increased eNOS expression was noted in endothelial cells obtained from patients receiving the drug. Another approach to improve endothelial function is the supplementation of the polyphenol resveratrol, which induces NAD+-dependent histone deacetylases of the sirtuin family and has antioxidant and anti-inflammatory effects. Ex vivo resveratrol induced vascular relaxation and attenuated endothelial dysfunction through a pathway involving AMP-activated kinase–dependent eNOS stimulation and induction of a Nrf2 (nuclear factor erythroid 2-related factor-2)–mediated antioxidant response in the thyroid artery of patients with hypertension.

Although there is little doubt that oxidative stress will ultimately attenuate endothelium-dependent relaxation, there is a phase of compensated stress in which agonist-stimulated endothelium-dependent relaxation is unaltered or even enhanced, despite elevated ROS formation. This was documented long ago in stroke-prone spontaneously hypertensive rats but seems also to be true for obesity: low Ang II salt-sensitive Dahl rats exhibit vascular dysfunction under basal conditions. High-fat diet, however, did not aggravate this state but rather improved vascular function, whereas it induced vascular dysfunction in the control animals. Both effects were sensitive to losartan, illustrating that lack of Ang II and Ang II overactivation in obesity induces vascular dysfunction. Eventually, increased ROS formation will attenuate endothelium-dependent relaxation. This is not only the result of NO scavenging but also the consequence of attenuated NO formation because of direct oxidative modification of eNOS. This effect occurs naturally during aging of mice. Aging per se causes s-glutathionylation of eNOS and protein kinase C, as well as protein tyrosine kinases are activated and place inhibitory phosphorylations on eNOS. Ablation of antioxidant enzymes, such as glutathione peroxidase-1, increased this effect. This obviously brings up the question on the value of antioxidant therapy. Although antioxidant therapy does not improve cardiovascular outcome, there is evidence that in aging antioxidants have an acute positive effect on vascular responses in humans. In a double-blind crossover study, oral supplementation of an antioxidant cocktail of vitamin C, vitamin E, and α-lipoic acid was able to improve endothelium-dependent flow-induced relaxation acutely, without any beneficial effects on vascular function in young health controls (Figure 2).

**Pregnancy, Endothelial Dysfunction, and Hypertension**

Female sexual hormones delay cardiovascular aging by increasing NO availability and reducing ROS formation. Ovariectomy in rodents is known to induce endothelial dysfunction, which is mediated, in part, by increased ROS formation. Interestingly, under normal conditions, perivascular adventitial fat tissue promotes endothelium-dependent relaxation; this effect is lost after ovariectomy in rats. The protective effects of female sexual hormones and their necessity for the maintenance of pregnancy are well documented, whereas the effect of testosterone on the endothelium is less clear. Testosterone is increased in preeclampsia, in polycystic ovary disease, and in blacks with gestational hypertension. Interestingly, treatment of pregnant rats with testosterone induced gestational hypertension and endothelial dysfunction as a consequence of reduced NO availability. The vascular alterations in preeclampsia are manifold and are partly a consequence of oxidative stress. In the reduced utero-placental perfusion rat model of preeclampsia, vasoconstrictor responses to big endothelin-1 but not endothelin were increased in the mesenteric artery. This was a consequence of...
of an induction of matrix metalloproteinases, which was, in part, a result of increased mesenteric eNOS expression. 35 Also in other vessels, such as the aorta, eNOS expression increases in this model, which was paralleled by an induction of lectin-like oxLDL receptor 1 and an increased sensitivity to oxidized low-density lipoprotein leading to eNOS uncoupling. 36 Collectively, these findings identify the utero-placental reduced perfusion model as a stage of eNOS uncoupling. Preeclampsia has numerous profound effects on the vascular system. Interestingly, it increases the plasma concentrations of the soluble vascular endothelial growth factor receptor sFlt-1, which acts as a scavenger for free vascular endothelial growth factor and thereby limits this important endothelial survival factor. sFlt-1 is produced in the placenta and remarkably parts of the placental tissue in humans are emboled physiologically into the lung during pregnancy. The mobilization rate of this sFlt-1–producing material is increased during eclampsia as revealed from human autopsies. 37 This raises the important question whether latent vascular dysfunction is unmasked by pregnancy. For example, giving preterm birth is associated with an increase rate of hypertension 20 years later. 38 Conversely, problems during pregnancy define the later vascular function of the child: Endothelial dysfunction is increased in children of low birth weight. Growth rate from 0 to 1 month inversely associates with endothelium-dependent vasodilatation of the skin in response to acetylcholine as measured by laser Doppler in a cohort of 104 newborns. 39 Collectively, research in the past 2 years resulted in a refinement of the concepts of interaction of endothelial dysfunction and hypertension. Novel sources of ROS are being identified and elements beyond vascular tone are becoming appreciated, which is particularly true for pregnancy, the immune system and the sympathetic tone.

Sources of Funding
This work was supported by the Goethe-University, Frankfurt and the German Research Foundation, DGF.

Disclosures
None.

References


Keywords: eclampsia ■ endothelium ■ NADPH oxidase ■ nitric oxide ■ oxidative stress ■ pregnancy
Endothelial Dysfunction and Hypertension
Ralf P. Brandes

Hypertension. 2014;64:924-928; originally published online August 25, 2014;
doi: 10.1161/HYPERTENSIONAHA.114.03575

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/64/5/924

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2016/04/10/HYPERTENSIONAHA.114.03575.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension 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 Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/
高血压最新进展

内皮功能障碍与高血压
Endothelial Dysfunction and Hypertension

Ralf P. Brandes

从洪良 审校

明内皮功能障碍在高血压发展中的作用并不是微不足道的。在血流作用下，处于静止状态的健康内皮细胞持续释放强力扩血管物质，后者能够直接降低血管阻力。内皮功能障碍不仅仅包括内皮依赖性血管舒张减弱，还有内皮细胞的炎症活化[1]。尽管人们普遍认为，内皮功能障碍是动脉粥样硬化进展和未来发生心血管事件的预测因子，但是其对高血压的作用，我们还知之甚少。假设内皮舒张功能减弱通过增加周围血管阻力导致高血压，这种想法太过简单。不仅代谢性和局部神经性因素对局部的血管紧张度有极强的影响，并且肾脏和中枢系统的控制可超越局部神经性因素对血压加以控制，这很容易理解，因为循环系统的主要目的是维持血压以便每个器官可以分到独立地通过局部因控制其灌注。然而，体循环血压控制通常在内皮功能障碍的情况下（如高胆固醇血症和吸烟）即使可以维持，但是仍然可能导致高血压的发生（图1）。在心衰患者中，尽管周围阻力显著增加，但血压通常是正常的。在这种情况下，心输出量降低和体循环容量导致外周血管收缩。后者是由交感神经激活增加和内皮一氧化氮（NO）功能减弱所致[2]。相反地，内皮功能恢复正常并不一定影响血压。在抑固醇和醛固酮拮抗剂（deoxycorticosterone acetate，DOCA）/盐诱导血管功能障碍的小鼠，特异性耗竭内皮细胞的盐皮质激素受体能够改善内皮功能，减轻血管炎症反应，但是未能降低小鼠的血压[3]。

有趣的是，尽管在生理条件下，肺的基础血管张力较低，但是在肺动脉高压（pulmonary artery hypertension，PAH）形成过程中，交感神经对血管张力的控制变得重要。在药物合用诱导的PAH大鼠模型中，交感神经兴奋性增加，神经节阻滞不但降低肺动脉压，还改善内皮功能障碍，增加NO生成[4]。

血管内皮细胞不仅影响周围阻力，还影响导致高血压发生的其他方面。例如血管僵硬度，一方面是全身衰老的标志，且与肺硬化（lung stiffness）相关[5]，另一方面血管僵硬度受到内皮细胞的调节，因此与脉搏波传导速度和脉压相关。内皮细胞还调节血管重构过程和炎症反应，反过来，炎症反应还可引起内皮功能障碍。例如，在人体，肿瘤坏死因子-α（TNF-α）和IFN-γ所导致的内皮功能障碍部分是由于miR-155所介导的内皮一氧化氮合酶（endothelial nitric oxidase synthase，eNOS）mRNA失稳定；eNOS是miR-155的作用靶点，而miR-155由肿瘤坏死因子-α诱导产生。因此，肿瘤坏死因子-α诱导的人体胶原血管内皮依赖性舒张障碍，给予Mir-155抗体可避免这一效应[6]。

内皮炎症反应和高血压

有证据表明，内皮细胞炎症活化促进了高血压的发生。由于肾动脉去神经术的不同结局，寻找可预测该操作成功微小的生物标记是非常必要的。在一项有55例高血压患者参与的研究中，9例患者接受肾动脉去神经术治疗后降压反应不足。降压反应不足的患者与反应良好的患者相比血浆可溶性fms样酪氨酸激酶-1（soluble fms-like tyrosine kinase-1，sFLT-1）、细胞间粘附因子-1（ICAM-1）和血管细胞粘附分子-1（VCAM-1）水平显著降低[7]。这提示炎症活化反应能够预测对肾动脉去神经术的反应。有趣的是，与高血压是炎症反应的结果这一概念相一致，研究表明高血压的发生需要炎症细胞的参与。在单侧肾切除的DOCA/盐诱导高血压小鼠模型，趋化因子受体CCR2及其配体CCL2、7、8和12上调。CCR2拮抗剂INCB3344阻止了血管的巨噬细胞聚集，可大约减少50%的高血压发生[8]。同样地，抑制因子对血管的作用也涉及炎症细胞；抑制因子需要巨噬细胞的产生[9]，并且能轻度减少具有抗炎作用的调节性T淋巴细胞的数量。调节性T淋巴细胞的过继性转移可以削弱抑制因子引起的负面效应[10]。同样地，内皮素[11]和血管紧张素II[12]
（angiotensin II, AngⅡ）引起的反应也涉及髓系细胞。去除巨噬细胞或骨硬化病小鼠的先天性巨噬细胞缺乏可以减弱内皮素和血管紧张素Ⅱ刺激所导致的高血压。内皮细胞功能障碍和血管氧化应激。AngⅡ等血管收缩激动剂所导致的炎症反应是由几个转录因子所调节，包括核因子κB、激活蛋白-1和信号转导分子和转录激活因子。无论对于在体内还是离体小鼠颈动脉，采用小分子抑制剂来抑制STAT3的作用均能够预防AngⅡ诱发的血管功能障碍，减少AngⅡ引起的血压升高。

**内皮活性氧簇生成和高血压**

由AngⅡ诱导的炎症产生一个主要结局是血管活性氧（ROS）的形成增加。众所周知，AngⅡ可诱导和活化Nox NADPH氧化酶[13]，但最近发现了其他来源的ROS。在高血压患者皮下分离出小动脉活组织检查中，ROS在很大一部分是由活氧酶2产生，活氧酶2在此类患者中呈现升高趋势[16]。在小鼠主动脉中，线粒体单胺氧化酶在经过AngⅡ处理后或炎症反应中也可介导内皮功能障碍。线粒体单胺氧化酶A和B在这些条件下在血管中产生，可生成大量过氧化氢（H₂O₂），进而减少内皮NO释放[27]。其他线粒体ROS来源，如p66Shc也可导致ROS诱导性高血压[17]。有趣的是，有几种机制支持从AngⅡ产生的信号转导诱导Nox产生及氧化应激。在肾脏中，细胞色素P450 1B1（Cyp1B1）的重要作用已经被证明。小鼠中这种酶的基因敲除可阻断AngⅡ引起的12,24-羟基二十碳四烯酸的增加、ROS的形成、Nox活性及ROS敏感酶的激活[18]。在DOCA高盐高血压模型中也产生了相同效果[20]。Cyp1B1的部分性能可由雌激素的新陈代谢诱发，可限制Nox的激活和诱导[21]。这方面的研究表明，因为肾功能不全相比纯粹的动脉或如骨骼肌中内皮功能不全对于高血压的影响更大。AngⅡ引起ApoE－小鼠肾脏内血流量增加的作用是通过p38促分裂原活化蛋白的依赖于ROS活化作用及随后的MLC20的磷酸化。AngⅠ通过血管紧张素转化酶（ACEI）产生AngⅠ，与此同时，ACE2产生Ang-(1-7)，有部分拮抗AngⅡ的作用。事实上，应用Ang-(1-7)可减弱AngⅡ对ApoE－小鼠肾脏的作用，降低基础肾小管NADPH氧化酶及p38促分裂原活化蛋白激酶的活性。敲除Mas，即Ang-(1-7)受体或抑制p38促分裂原活化蛋白激酶，可阻断Ang-(1-7)对肾脏带来的益处[22]。考虑到Ang-(1-7)是ACE2的产物，那么推测ACE2增加具有保护血管作用是值得关注的。利用1-(2-二甲基氨基)乙胺基]-4(羟甲基)-7-(4-甲基苯磺酰氧)-9H-氧杂环-9-酮(XNT)的结合，这种小分子ACE2活化剂变得可实现。XNT可通过Mas受体依赖作用改善自发性高血压和糖尿病引起刺激性小鼠的内皮功能。同样，黄原酸盐可减少人体巨大动脉内皮细胞中AngⅡ诱导的ROS的产生[23]。

**内皮功能：高血压的靶点？**

改变血管氧化还原环境是另一个直接干预内皮功能障碍中AngⅡ信号转导的机制。AngⅡ引起的血管功能障碍在体内可以被含铜的细胞外超氧化物歧化酶3（SOD3）的诱导所改善。目前发现，这一效应涉及下述机制，即AngⅡ诱导低敏感性的转录因子和铜伴侣分子Atox1的生成。耗竭Atox1能够预防AngⅡ介导的SOD3诱导作用。AngⅡ同时增加Atox1与铜转运体ATP7A的结合，从而促进细胞质内的铜向外转运，这能够增加细胞外超氧化物歧化酶的铜负荷[24]。
恢复正常内皮功能的另一个方法是改变G蛋白偶联蛋白受体（G-protein-coupled receptor, GPCR）激活的活性。此类激活通过使内皮化的受体磷酸化，使受体内化而抑制GPCR信号传导。由于GPCR介导了Ang II、血栓烷、内皮素和其他血管生长素和血管活性物质的有害信号转导，因此导致内皮功能障碍和缩血管信号的转导，不过，由于GPCR同时促进内皮舒张因子的释放，因此还不明确GPRC是否为理想的降压药物作用靶点。对此，通过小鼠广泛表达的GPCR激活-2的杂合缺失对Ang II诱导的血管功能障碍的作用进行了研究。GPCR激活-2的杂合缺失减弱了Ang II所诱发的高血压、血管重构和内皮功能障碍。这提示，通过给予药物至少轻度抑制GPRC激活-2是有效的[23]。

虽然改善内皮功能并非心血管药物的主要适应证，但是一种受欢迎的多效性作用。因此，有必要的是，一项安慰剂对照研究观察到，在用药的第2天和第7天，非诺贝特能够分别改善12例和10例患者的血流介导动脉舒张，该作用独立于降脂作用。非诺贝特可能增加内皮细胞的NO生成，因为它在使用该药物患者的内皮细胞观察到了eNOS表达上调[20]。另一个改变内皮功能的方法是补充多酚类白藜芦醇，该物质能够诱导sirtuin家族的NAD+依赖型脱乙酰基酶类的生成，同时具有抗氧化和抗炎效应。在高血压患者甲羟戊酸盐的离体实验中，白藜芦醇可通过包含AMP活化激酶依赖的eNOS刺激和诱导核因子红细胞2-相关因子-2（Nrf2）介导的抗氧化反应通路，引起血管舒张，改善内皮功能障碍[27]。

尽管氧化应激毫无疑问会最终减少内皮依赖性血管舒张，但是存在一个代偿性的应激阶段，此时尽管ROS生成增加，但是激动剂刺激时的内皮依赖性血管舒张保持正常，或者甚至得到增强。在较早开展的易患性中自发性高血压大鼠研究中对此已有记载[24]，另外似乎肥胖研究也得出同样的结果：即在基础条件下，低Ang II盐敏感性的Dahl大鼠表现出血管功能障碍，但是，高脂饮食并不加重血管功能障碍，反而能够改善血管功能，不过在对照动物则诱发血管功能障碍。上述两个效应均对氯尿苷敏感，提示Ang II缺乏和肥胖时的Ang II过度激活诱发了血管功能障碍[25]。最后，ROS生成增加会减弱内皮依赖性血管舒张。这并不是由于NO被清除，而是由于eNOS直接氧化修饰所导致的NO生成减少。这一效应在小鼠衰老的过程中自然发生。衰老本身即可引起eNOS和蛋白激酶C的-谷胱甘肽化，同时激活蛋白激酶A磷酸激酶，抑制eNOS磷酸化。去除抗氧化酶类（例如谷胱甘肽过氧化酶-1）能够增强上述效应[26]。这显然带来了关于抗氧化治疗价值的问题。尽管抗氧化治疗不能改善心血管转归，但有证据显示在人体衰老过程中，抗氧化剂往往短期的有益效应。在一项双盲交叉研究中，口服补充抗氧化剂鸡尾酒（维生素C，维生素E和α-硫辛酸）在年轻的健康对照组能够短期改善内皮依赖性血管介导的血管舒张，但对血管功能无有益效应[23]（图2）。

妊娠、内皮功能障碍和高血压

女性性激素通过增加NO生成和减少ROS生成而延缓心血管系统的老化。已知切除啮齿类动物的卵巢会诱发内皮功能障碍，该作用部分由ROS生成增加所介导[32]。有趣的是，在正常情况下，血管周围的动脉外膜脂肪组织促进内皮依赖性血管舒张对大鼠切除卵巢后该效应消失[33]。女性性激素的保护作用及其维持妊娠的作用已经相当明确，但是睾酮对内皮的作用还不清楚。先兆子痫、多囊卵巢综合征和黑人妊娠高血压人群的睾酮水平升高。有趣的是，对妊娠大鼠给予睾酮能够诱发妊娠高血压和内皮功能障碍，其原因可能为NO生成减少[34]。先兆子痫时的血管变化是多方面的，部分是由于氧化应激。在子宫-胎盘灌注减少的先兆子痫大鼠模型中，肠系膜动脉对大内皮素-1和血管紧张素的血管收缩反应增强。这是由于诱导了基质金属蛋白酶所致，该酶的诱导


