Overview of Physiology, Vascular Biology, and Mechanisms of Hypertension

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ABSTRACT

BACKGROUND: Our understanding of the process leading to hypertension is allowing us to adopt principles of therapy that may be more beneficial for patients.

OBJECTIVE: To review the physiology, vascular biology, and mechanisms of hypertension.

SUMMARY: Hypertension, particularly in high-risk patients, is a result of loss of balance and the absence of the ability to vasodilate normally. The interaction between the endothelial cell and the smooth muscle cell is very important in this process. The endothelium is a group of cells that produce compounds that are important in regulating vascular homeostasis by elaborating factors such as angiotensin II, nitric oxide (NO), endothelin, and prostaglandins. Specifically, NO is found in endothelial cells responsible for smooth muscle relaxation. Gaseous NO diffuses across the endothelial cell and into the underlying smooth muscle cell, where it stimulates the pathway of guanylate cyclase to produce vasorelaxation.

Normal endothelium maintains vascular tone and blood viscosity, prevents abnormal blood clotting and bleeding, limits inflammation of the vascular, and suppresses smooth muscle cell proliferation. Abnormal endothelium causes increased inflammation and hypertrophy of the smooth muscle cells, promotes thrombosis and vasoconstriction, and creates a situation ripe for establishment and rapid growth of atherosclerotic plaques. Endothelial dysfunction also predicts poor outcome in patients with non–insulin-dependent diabetes mellitus and may worsen insulin resistance, increase vascular reactivity, and encourage macrovascular disease.

CONCLUSION: Understanding endothelial vasculature will be imperative as researchers develop newer compounds that may enhance NO formation within the vasculature.

KEYWORDS: Hypertension, Endothelium, Endothelial dysfunction, Nitric oxide, Nitric oxide synthases

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Our understanding of the process that leads to hypertension is allowing us to adopt principles of therapy that may be more beneficial for patients. When I was in medical school, we learned that the endothelium was a single cell lining that had a negligible role in the production of compounds affecting cardiovascular function—and that was wrong. Over the years, we have learned that the endothelium is a single layer of cells that surround the arteriole lumen. Underneath the endothelium are the smooth muscle cells. The interaction between the endothelial cell and the smooth muscle cell is very important. Underlying the endothelium and muscle is the third layer, the adventitia. The endothelium is a huge, living organ that has more cells than the liver, which is the largest organ in the body.

Our increased understanding of the endothelium's role began with the 1980 publication of Furchgott and Zawadzki's article with the obscure title, "The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine."

The first sentence in the abstract states, "Despite its very potent vasodilating action in vivo, acetylcholine does not always produce relaxation of isolated preparations of blood vessels in vitro." Furchgott and Zawadzki had observed that application of acetylcholine in vivo led to arterial vasodilatation. But in biological preparations of smooth muscle, the opposite occurred—vasoconstriction. They hypothesized that the endothelial cell had an important role in smooth muscle relaxation. In the absence of endothelial cells (the in vitro experiment), no vasodilatation occurred. Vasoconstriction did. This finding represented a considerable advance for medicine because the causative compound called endothelial-derived relaxing factor (EDRF) had yet to be identified and, in fact, remained unidentified for years. This work was eventually acknowledged with the Nobel Prize in physiology or Medicine in 1998.

Acknowledging Medical Breakthroughs

The 1998 Nobel Prize in physiology or medicine was jointly awarded to Robert Furchgott, Louis Ignarro, and Ferid Murad “for their discoveries concerning nitric oxide as a signalling molecule in the cardiovascular system.” Thus, EDRF was identified as nitric oxide (NO). The exact mechanism, shown in the figure, involves the endothelial cell and smooth muscle. Furchgott and Ignarro demonstrated that applying acetylcholine affects a muscarine receptor in the endothelial surface. It stimulates the enzyme NO synthetase to use L-arginine as a donor source for NO. Gaseous NO diffuses across the endothelial cell and into the underlying smooth muscle cell, where it stimulates the pathway of guanylate cyclase to produce vasorelaxation.

For years, physicians knew that NO—in a form that we use as nitroglycerin tablets sublingually—could help patients with angina or with chest pain due to ischemia. In actuality, giving NO sublingually bypasses the need for endothelial cell action and causes direct smooth muscle cell vasodilatation and symptom relief.
How does this apply to the endothelium? The endothelium is not a static cell but a group of cells that produce compounds that are important in regulating vascular homeostasis by elaborating factors such as angiotensin II, NO, endothelin, and prostaglandins. The net effect is maintenance of normal vascular tone. The endothelium also maintains normal blood viscosity, prevents abnormal blood clotting, and prevents abnormal bleeding in terms of a balance between plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator. It limits inflammation of the vasculature and it can suppress smooth muscle cell proliferation. These are functions of the normal endothelium. The opposite occurs in the presence of abnormal endothelium.

An abnormal endothelium creates a phenotype that presents in patients with coronary artery disease, diabetics, and high-risk patients. Abnormally functioning endothelial cells cause decreased NO formation and a decrease in vasodilatation, as well as decreased angiotensin I and prostaglandin formation. The net effect is increased inflammation and hypertrophy of the smooth muscle cells. An abnormal endothelium promotes thrombosis and vasoconstriction and creates a situation ripe for establishment and rapid growth of atherosclerotic plaques. The normal endothelium maintains vascular health by providing a balance between vasodilatation and vasoconstriction. Hypertension—particularly in high-risk patients—is a result of loss of balance and the absence of the ability to vasodilate normally.

**Antihypertensives and Vasodilatation**

Panza et al. designed a study to determine whether using antihypertensive treatment in 15 controls and in 15 patients with essential hypertension restores impaired endothelium-dependent vasodilation. They examined vascular responses to acetylcholine and sodium nitroprusside administered into the brachial artery in each patient: after withdrawal of medications, when the patients were hypertensive, and during the medical treatment that reduced BP to normal limits. Forearm blood flow response, a test of endothelial-dependent vasodilatation, was measured. In normotensive controls, acetylcholine-induced forearm blood flow increased with relatively modest reductions in vascular resistance. In the hypertensive patients, blood flow and vascular resistance responses to acetylcholine were significantly reduced. Responses to sodium nitroprusside, a direct vasodilator, were similar between groups. They concluded that clinically effective antihypertensive therapy does not restore the impaired endothelium-dependent vascular relaxation of patients with essential hypertension. Altered endothelial dysfunction is either primary or irreversible once the hypertensive process is established.

The importance of this finding was underscored by a study conducted by Murakami et al. Following 150 patients for 24 months, the researchers established lower, middle and upper tertiles of coronary blood flow increases in response to acetylcholine at the onset of the study. Patients who fell in the reduced endothelial function (lower) tertile experienced cardiac events at a higher rate than other tertiles. Fourteen percent experienced cardiac death, myocardial infarction, the need for revascularization, or worsening angina during the 24-month follow-up period. Two percent and 0% of patients in the middle and upper tertiles, respectively, experienced cardiac events. These findings are not only physiologically but prognostically important.

It remained to be determined whether NO-mediated vasodilation is abnormal in patients with non–insulin-dependent diabetes mellitus, which might explain the high prevalence of vascular disease in diabetes. Williams et al. looked at 21 patients with non–insulin-dependent diabetes mellitus and 23 matched healthy control subjects, again measuring vascular reactivity in the forearm resistance vessels. All study subjects were free of hypertension or hypercholesterolemia. The researchers pretreated subjects with aspirin to inhibit endogenous vasoactive prostanoid production, then administered methacholine chloride (an endogenous NO donor at 0.3 to 10 mcg/min) and sodium nitroprusside (an exogenous NO donor at 0.3 to 10 mcg/min). Although basal forearm blood flow in diabetic and nondiabetic subjects was comparable, forearm blood flow responses to methacholine chloride and nitroprusside were attenuated in diabetic subjects. The blunted response to exogenous as well as endogenous NO suggests either an increased NO inactivation or a decreased vascular smooth muscle reactivity. Again, endothelial dysfunction predicted poor outcome.

Using these findings, one can predict the interaction between insulin and the NO system. Again, acetylcholine using L-arginine
Overview of Physiology, Vascular Biology, and Mechanisms of Hypertension

as a donor source and NO synthetase produce NO, which stimulates the smooth muscle guanylate cyclase. Vasodilation follows. Sodium nitroprusside or nitroglycerine, directly applied to smooth muscle cells, also causes vasodilatation.5

Insulin’s Role
Insulin-mediated vasodilation in skeletal muscle appears to amplify insulin’s ability to stimulate skeletal muscle glucose uptake in insulin-sensitive man. In insulin-resistant states (obesity, hypertension, and non–insulin-dependent diabetes mellitus), insulin-mediated vasodilation is blunted and endothelium-dependent vasodilation is impaired. Endothelial dysfunction is thus an integral aspect of insulin resistance, independent of hyperglycemia. It may worsen insulin resistance, increase vascular reactivity, and accelerate macrovascular disease. Insulin plays a key role in terms of healthy endothelium stimulating NO and smooth muscle cell vasodilatation.5

The table indicates exactly what changes one can expect to see in the diabetic or hypertensive person.6 All these atherogenic traits can cause problems in the high-risk patient. This demonstrates the importance of healthy endothelium in maintaining cardiovascular health and avoiding problems associated with abnormal endothelial function.

Summary
Nitroglycerine was first used as a vasodilator with no understanding of its mechanisms. Today its mechanisms have been elucidated, as have the links between hypertension and diabetes that are so common. Although many organizations have pushed to encourage physicians to control hypertension in the diabetic patient, we now see the link at the endothelial surface. We have moved forward from nitroglycerine to look at newer compounds that may use a NO synthetase mechanism to enhance NO formation within the vasculature. Understanding endothelial vasculature will be imperative as these new agents are developed.

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<th>Increased</th>
<th>Reduced</th>
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<tr>
<td>Plasma levels of von Willebrand factor</td>
<td>Prostacyclin release</td>
<td>Fibrolytic activity</td>
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<td>Expression, synthesis, and plasma levels of</td>
<td>Release of endothelium-derived relaxing</td>
<td>Plasmin degradation of glycosylated fibrin</td>
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<td>endothelin-1</td>
<td>factor (NO) and responsiveness to NO</td>
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<td>Endothelial cell procoagulant activity</td>
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NO = nitric oxide.

REFERENCES

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