Arterial Stiffness and Endothelial Function
Key Players in Vascular Health

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Functional assessment of the blood pressure waveform helps us to obtain an estimation of the arterial stiffness or its converse, arterial elasticity. Several epidemiological studies have clearly demonstrated that arterial stiffness is a significant predictor of cardiovascular disease incidence in the general population. There is clear evidence now that decreased arterial elasticity or increased arterial stiffness in normotensive and prehypertensive subjects induces increased risk for the development of arterial hypertension. In vitro and in vivo experiments have shown that the vascular endothelium plays a crucial role in vascular tone and consequently in arterial stiffness. However, there are no data available regarding the endothelial pathways involved in the adaptation of arterial mechanics during changes in blood flow.

The elegant study by Bellien et al in this issue of *Hypertension* studied the endothelial pathways involved in the adaption of arterial mechanics during changes in blood flow. Besides identifying the “endothelial-derived relaxing factor” nitric oxide (NO) as important in this biological process, a unique aspect found in their study was the “endothelial-hyperpolarizing factor” EDHF. Endothelium-dependent relaxation/vasodilation in response to neurohumoral mediators and physical forces, such as the shear stress caused by blood flow, is generally attributed to the release of NO and/or prostacyclin. However, NO and prostacyclin cannot fully explain these endothelium-mediated vasodilator responses. The relaxations observed in the presence of NO synthase and cyclooxygenase inhibitors are often associated with hyperpolarization of the vascular smooth muscle cells and were first attributed to EDHF. The acronym “EDHF” turned out to be confusing because it seemed to imply that a single diffusible substance mediates this type of endothelium-dependent relaxation. In fact, in addition to NO itself, numerous endothelium-derived factors, including carbon monoxide, hydrogen sulfide, reactive oxygen species, peptides, and arachidonic acid metabolites derived from the cyclooxygenase, lipoxygenase, and cytochrome P450 monoxygenase pathways can hyperpolarize the underlying smooth muscle cell.

The nonlinear elastic response of arteries implies that their mechanical properties depend strongly on blood pressure. Thus, dynamic measurements of both the diameter and pressure curves over the whole cardiac cycle are necessary to characterize the arterial elastic behavior properly. In this study, the echotracking device NIUS02 was used to measure the cross-sectional compliance as a means of evaluating deformability of the arterial chamber, the incremental elastic modulus was used to evaluate the arterial stiffness and the midwall stress was calculated as means of evaluating the arterial wall loading conditions. This apparatus uses a radiofrequency signal and is sufficiently precise to determine change in arterial diameter as low as 1 μm across the cardiac cycle. It is possible to determine the pressure–diameter curve of the artery, thus to determine arterial stiffness for any given blood pressure. A major advantage of this methodology is that local arterial stiffness is directly determined from the change in pressure that drives the change in volume, ie, without using any model of the global circulation. This technique for measuring local arterial stiffness is not well known and is little used because it requires a high degree of technical expertise and takes longer to perform than do global techniques, such as measurement of pulse-wave velocity. Local measurement of arterial stiffness is largely indicated for mechanistic analyses in pathophysiology, pharmacology, and therapeutics and does not appear to be suited for epidemiological studies.

The major findings of Bellien et al were that local inhibition of both NO and EDHF pathways in vivo in humans fully prevents the decrease in smooth muscle tone and wall stiffness of the radial artery during hand skin heating. These observations showed the major role of these endothelium-derived factors in the adaptation of peripheral conduit artery mechanics to changes in blood flow. Their results were the first demonstration of the role of a cytochrome-related EDHF in the adaptation of peripheral conduit artery mechanical properties to an increase in flow in humans. Beyond their human studies, Bellien et al studied the detailed mechanism of action of pharmacological inhibitors of the EDHF pathway using in vitro coronary vascular studies in wild-type FVB mice. This vascular model was chosen based on their previous experiments demonstrating the model is characterized by prominent NO-independent, EDHF-mediated relaxations.

The endothelial cells are the interface between the blood and the vascular wall and are involved in many physiological functions in the cardiovascular system. They maintain the balance between vasodilation and vasoconstriction. In the past, EDHF was considered as a diffusible substance which mediated endothelium-dependent relaxation. However, NO and other endothelium-derived relaxing factors can hyperpo-
larize the underlying smooth muscle cells. Hyperpolarization decreases Ca$^{2+}$/H$^{+}$ influx, by reducing the open probability of Cav channel–dependent activation of the sarcoplasmatic reticulum, which is a powerful means to produce the relaxation of vascular smooth muscle cells.7

Another pathway for relaxing vascular smooth muscle cells does not involve the synthesis and the release of a factor. This pathway is associated with the hyperpolarization of both endothelial cells and vascular smooth muscle cells (EDHF-mediated responses) and also contributes to endothelium-dependent relaxations. These responses involve an increase in the intracellular Ca$^{2+}$/H$^{+}$ concentration of endothelial cells and a subsequent hyperpolarization of these cells.8 Then, the underlying smooth muscle cells can be evoked by direct electric coupling through myoendothelial junctions and/or the accumulation of K$^{+}$/H$^{+}$ ions in the intercellular space between the two cell types. The Figure illustrates these mechanisms in a simplified manner.

The next step in this line of research is to translate these findings into clinical practice. It is generally accepted that atherosclerotic disease is associated with a decrease in NO synthesis and/or loss of its biological activities. Further research is necessary to explore whether alterations in the EDHF pathway also contributes to these endothelial dysfunctions or, conversely, compensates for the loss of NO bioavailability.

Alterations of EDHF-mediated responses have been described with aging, hypertension, atherosclerosis, diabetes, hypercholesterolemia, and heart failure.9

Some therapeutic interventions, such as angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, can restore the EDHF-mediated responses.10

The improvement or restoration of EDHF responses has not yet been the focus of any pharmaceutical development effort. At this moment, there is an urgent need to further explore the importance of the endothelium-dependent hyperpolarization and to elaborate on electrophysiological measurements and pharmacological tools.

It would be interesting also to study the effect of EDHF-mediated response on small versus large arteries beyond the effect of NO.

In conclusion, since the discovery of NO as pioneer molecule in the endothelium-mediated regulation of vascular tone, the EDHF pathway has been revealed as an alternate mechanism for endothelial-mediated vascular control. Further research is necessary to understand the crosstalk between these 2 pathways with the ultimate aim to target therapy for maintaining vascular health.

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References

Figure. Diagram depicting 2 pathways leading to vasodilation and reduced arterial stiffness. A, Hyperpolarization of the endothelial cell resulting from shear stress. B, Production of EDHF and NO induced by an agonist. Pathways A and B may occur simultaneously.
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