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EDITORIAL COMMENT

Endothelial Function Under Pressure*

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In the study entitled "Men Born in 1914," a reduction of pulse-wave amplitude during reactive hyperemia was found to be predictive of long-term cardiovascular events (1). Of particular note is the fact that these observations were made many years before the whole concept of endothelium-dependent vasoreactivity and its mediators was elaborated (2). Therefore, this study was the first to subsequently demonstrate the association between vascular function and long-term clinical outcome. With a better understanding of the underlying molecular mechanisms and different techniques to examine endothelium-mediated vasoreactivity, subsequent studies confirmed the prognostic significance of endothelial dysfunction in both the coronary and the peripheral circulation (3–6).

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Impairment of endothelium-dependent vasorelaxation has become a marker of endothelial dysfunction, although endothelial dysfunction is, in fact, characterized by many additional vascular abnormalities. According to the response-to-injury theory, the currently prevailing pathogenetic concept of atherosclerosis, endothelial dysfunction is both an initial and integral part of the inflammatory-proliferative disease process in response to cardiovascular risk factors such as hypertension, hypercholesterolemia, diabetes mellitus, and smoking (7–9). Endothelial cell dysfunction is, therefore, both a consequence and a mediator of the pathophysiologic action of cardiovascular risk factors.

In this issue of the *Journal*, Ceravolo et al. (10) reported on the association between pulse pressure and acetylcholine (ACh)-stimulated forearm blood flow (FBF) in a cohort of patients with untreated essential hypertension, promoting pulse pressure as an independent risk factor for endothelial dysfunction. Blood pressure measurements were performed both during clinical visits as well as in an ambulatory monitoring setting, and pulse pressure was calculated as the difference between systolic and diastolic blood pressure. Endothelium-dependent and endothelium-independent FBF was measured during intra-arterial infusion of ACh and sodium nitroprusside, respectively. Using univariate and multivariate regression models, pulse pressure was found to be independently and most strongly associated with peak percent increase in FBF, accounting for one-third of the variation in ACh-stimulated FBF.

This article (10) is important not only because of the novelty of the findings, relating pulse pressure to endothelium-dependent vasorelaxation for the first time in humans, but even more so because of the potential implications of integrating these findings into clinical practice. Elevated systolic blood pressure and pulse pressure have been previously suggested to increase the risk of cardiovascular morbidity and mortality (11,12). However, recent subanalyses from multicenter trials such as the Multiple Risk Factor Intervention Trial questioned the independent prognostic value of pulse pressure (13).

Nevertheless, there are data available that underscore the parallelism between pulse pressure and other cardiovascular risk factors. For example, increase in pulse pressure reduced the vasorelaxation response of rabbit carotid arteries to ACh; the impairment in vasorelaxation was restored with superoxide dismutase treatment, indicating the involvement of oxidative stress (14). Furthermore, compared with laminar flow, oscillatory and pulsatile flow patterns are associated with an increase in endothelial oxidative stress, resulting in impairment of endothelial function (15–17). Thus, the pulsatile blood pressure component can affect the function of the endothelium, independently from the other blood pressure components.

Importantly, basal endothelial release of nitric oxide (NO) can, in turn, affect arterial stiffness or elasticity (18–21). By reducing NO bioavailability, an increase in pulse pressure might, therefore, become self-escalating. However, the initiating trigger for this vicious circle remains hard to define. If the primary culprit is endothelial dysfunction, cardiovascular risk factors in general should also increase pulse pressure by increasing arterial stiffness. Yet, neither hypercholesterolemia nor diabetes mellitus or smoking necessarily increases arterial stiffness (18,22,23). On the contrary in old spontaneously hypertensive rats, an increase in pulse pressure is usually subsequent to the development of endothelial dysfunction (24), and for instance, mechanical treatment of renovascular hypertension has been demonstrated to result in normalization of systemic endothelial function (8). The reciprocal relationship between pulse pressure and endothelial function is, furthermore, supported by the observation that antihypertensive drugs, such as angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, calcium channel blockers, beta-blockers, vasopeptidase inhibitors, and even diuretics have been shown to reduce pulse pressure but also to improve endothelial function, whereas drugs that improve endothelial function, such as 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, have been shown to reduce systemic blood pressure and pulse pressure, as well (25–27). The

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interaction between pulse pressure and endothelial dysfunction, therefore, seems to relate not to cardiovascular risk factors in general but rather uniquely to hypertension (28).

These considerations raise the question of whether pulse pressure, endothelial dysfunction, or both should be routinely studied during diagnostic clinical evaluation, at least of the hypertensive patient. Although blood pressure measurements and calculation of pulse pressure are usually readily available during the visit of the patient, 24-h blood pressure monitoring may prove to be more representative and accurate. Furthermore, blood pressure or pulse pressure measurements alone may not be sufficient to assess the cardiovascular risk of the patient, and specific evaluation of endothelial function may be required for this purpose. Further standardized studies will be required to determine the sensitivity and specificity of pulse pressure elevation for the assessment of endothelial dysfunction. The study by Ceravolo et al. (10) in this issue of the *Journal* is an important milestone on the way to developing a more effective diagnostic work-up of hypertensive patients and will need to be confirmed in larger-scale studies.

Taken together, a number of studies have underscored the association of long-term outcome with both endothelial function and pulse pressure. In the current study, Ceravolo et al. (10) provide further evidence for a direct association between pulse pressure and the function of the endothelial monolayer in hypertensive patients. As outlined by prior studies, this link might relate to a decrease in NO bioavailability, which results in both impairment in endothelial function and increased arterial stiffness. Therefore, it is not surprising to find that increased pulse pressure and endothelial dysfunction often coexist in hypertensive patients.

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