Endothelial Dysfunction and Hypertension: Cause or Effect?

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Endothelial dysfunction refers to impairment of endothelium-dependent vasodilatation and implies widespread abnormalities in endothelial integrity and homeostasis. The ability to assess endothelial function has been critical to advancing our understanding of the significance of this complex monolayer to cardiovascular (CV) disease. Early human translational approaches required invasive assessments in the coronary and brachial circulatory beds but had limited utility. Popularization of brachial reactivity testing using ultrasound by Celermajer et al,1 better known as flow-mediated dilatation (FMD), allowed more widespread clinical application by providing an estimate of conductance vessel NO bioactivity in response to a fixed hyperemic stimulus.

Although the link between endothelial dysfunction and adverse CV events was first described in studies performed in the human coronary circulation,2 the development of this noninvasive method led to widespread expectations that FMD could be used as a risk prediction tool and as a surrogate endpoint for novel therapies. Numerous studies demonstrated significant association between impaired FMD and CV risk factors. Although studies in those with CV disease have shown prognostic association with lower FMD predicting worse long-term outcomes,2 the real promise of FMD as a noninvasive tool was in demonstrating predictive use in community-based population cohorts.

In the largest of just 3 studies addressing this question, Yebouh et al3 examined 3026 subjects free of CV disease from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort. They demonstrated that, at 5 years, after multivariate analysis, each SD increase in FMD conferred a hazard ratio of 0.84 for incident CV events. Importantly, FMD also improved net reclassification of risk when compared with the Framingham risk score. Two further studies in more selected populations, including the Cardiovascular Health Study of elderly subjects and a study by Rossi et al4 on >2000 postmenopausal women, support these findings by demonstrating significant association between impaired FMD and CV outcomes. Thus, there now appears to be convincing evidence that impaired FMD is associated with a risk of adverse CV events on the basis of a cumulative cohort of >9000 community participants.

An important question is how abnormal FMD, a specific measure of depressed NO bioavailability in the conductance vessels, predicts future risk of atherosclerotic events, including myocardial infarction and death. Experimental data with endothelial denudation and models where the endothelial NO synthase gene is deleted have highlighted the propensity for inflammation, atherosclerosis development, plaque instability, and progression. Other mechanisms include a hypercoagulable state from platelet adhesion and aggregation, increasing the risk of thrombosis. Thus, the traditional viewpoint states that conventional risk factors, along with a host of other insults and genetic propensity, precipitate endothelial dysfunction. An alternative and somewhat controversial hypothesis is that a primary defect in the endothelial NO activity in fact acts directly or indirectly to increase the risk of developing traditional risk factors, such as hypertension and insulin resistance. In this issue of Hypertension, Shimbo et al5 present results from a longitudinal study designed to address this very question.

Using the MESA cohort, the authors first confirmed findings from other studies and demonstrated a cross-sectional association between FMD and hypertension prevalence in 3500 middle-aged participants of varying ethnicities.5 After excluding those with baseline hypertension, they further examined 1869 of these subjects for incident hypertension over a median of 4.8 years. Although the association between low FMD and incident hypertension was significant, both as an ordinal and continuous trait, this did not withstand multivariate adjustment for important confounders. To overcome the inherent limitations of a binary definition of hypertension (>140/90 mm Hg or clinician diagnosed), the authors also performed secondary analyses to explore the association with sustained hypertension (hypertension at several clinic visits), as well as with a clinically meaningful rise of >10 mm Hg systolic or >5 mm Hg diastolic blood pressure between visits. Even with these analyses, results remained insignificant, as they did when they studied the incidence of prehypertension. The authors concluded that, “impaired endothelial function does not play a major role in the development of hypertension.”

The study is, on the whole, well designed and is the largest study of its type published to date. A few limitations, however, need to be noted. First, although the ethnic diversity of the cohort is a strength, it may also be a weakness given the potential confounding introduced by a higher incidence of hypertension in black participants in particular. Although this study found black race to be a predictor of low FMD, as well as a higher incidence of hypertension, a previous study...

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reported an association with endothelium-independent smooth muscle vasodilatation with nitroglycerin in this ethnic subset, a test not performed in the MESA population. Second, although the authors have found that correction for age and other risk factors abolished the association between a lower FMD and incident hypertension, in clinical practice, a single test like FMD that predicts the risk of future hypertension would indeed be valuable. Third, it is important to note that FMD measurement is not necessarily a fixed phenomenon and may improve or worsen over time with a host of factors, such as exercise, diet, weight gain, medication use, and so forth. Thus, the question remains whether subjects with impaired FMD at baseline could have improved over time and, thus, prevented the development of hypertension. Recent studies are useful examples, where subjects with low FMD at 2 time points or with a further decline in FMD endured worse outcomes during follow-up. Fourth, these findings may not disprove the hypothesis that endothelial NO deficiency will result in hypertension because FMD is only measuring conductance vessel function, and it is likely that microvascular NO activity is a more critical determinant of vascular tone and hypertension. Finally, hypertension is a complex multifactorial disease, where the initiating injury may be in the kidney, central nervous system, blood vessels, or a combination of the above. FMD in the brachial artery may, thus, not be a predictor for all of these precipitating causes.

Importantly, the results of the current study are at variance with the only other large-scale study addressing this question. In 952 postmenopausal women free of risk factors including hypertension, Rossi et al found that the incidence of hypertension over 3.6 years of follow-up was 5.77-fold higher in those in the lowest FMD quartile compared with the highest or a 16% increase in risk per unit of FMD. Here the authors concluded that, “endothelial dysfunction may be a significant cause of the development of hypertension.” Interestingly, this group also reported a higher incidence of type 2 diabetes mellitus in this population with depressed FMD during follow-up. So what might we conclude given these 2 contrasting findings in relatively large cohorts? Shimbo et al note that the association with incident hypertension was borderline and may yet reach statistical significance in a larger cohort. However, the stark discrepancy between the strength of the relationship in the 2 studies makes this unlikely. There are some significant differences in the 2 study cohorts beyond sex and risk factors that may also contribute to the differing results. The range of FMDs between the lowest and highest quartiles was greater in MESA than in the study by Rossi et al, where the lowest quartile in the latter study had FMD values similar to the third quartile of MESA. Also, the incidence per 1000 person-years in those in the best FMD quartile was 50.8 in MESA and 10.4 the postmenopausal women study, indicating a much higher risk population being studied in MESA.

Results of the current study support the more traditional and widely accepted viewpoint that hypertension is a cause rather than a consequence of endothelial dysfunction. An acute increase in blood pressure precipitates endothelial dysfunction, and multiple well-controlled clinical investigations have confirmed a specific endothelial NO abnormality in hypertensives, both in the microcirculation and conductance vessels. Moreover, the Cardiovascular Risk in Young Finns Study found that abnormal blood pressure in youth tended to predict future impaired endothelial function. Yet, we also know that intravenous infusion of NO synthase antagonists in normotensive subjects increases systemic blood pressure. Similarly, blood pressure in endothelial NO synthase knockout mice is higher than in control mice, whereas hypertensive subjects also appear to have more NO synthase 3 gene mutations, and normotensive offspring of hypertensive patients demonstrate impaired endothelial dysfunction. All of these observations suggest that, indeed, endothelial NO deficiency could result in higher blood pressure. But, in contrast to these findings, we also know that endothelial NO deficiency can be precipitated by a variety of nonhypertension-related insults that increase vascular oxidative stress, such as hypercholesterolemia. In these conditions, for example, in the apolipoprotein E knockout mouse, where profound endothelial dysfunction occurs from a hypercholesterolemic diet, blood pressure is not elevated. Thus, it appears that hypertension can (but may not necessarily) result from endothelial dysfunction. In this context, the MESA population had multiple risk factors that accounted for a lower FMD, and only some of these subjects were presumably prone to become hypertensive. In contrast, the relatively healthy postmenopausal women in the study by Rossi et al had a greatly increased risk of incident hypertension in the presence of endothelial dysfunction. Thus, FMD may reflect the risk of incident hypertension in populations with a low risk factor burden. A subgroup analysis of the low risk cohort in MESA would, thus, be valuable addition to the discussion.

Although these studies are focused on FMD as a determinant of vascular endothelial function, it should be remembered that the endothelium releases other vasodilators, in particular, endothelium-derived hyperpolarizing factor, particularly from the microcirculation, that compensates in states of NO deficiency. Moreover, NO-dependent vasodilator tone at rest and during mental stress appears to be primarily from neuronal NO release in the human forearm. Also, other vascular assessments that test global vascular function, including smooth muscle reactivity and arterial stiffness, are also predictors of future risk of hypertension, and perhaps a more integrated vascular assessment that also focuses beyond the endothelium may be more successful in prediction.

In summary, FMD has become a widely used tool for exploring vascular biology in clinical studies. Recent longitudinal studies have provided much needed validity to the prognostic value of this noninvasive test. The study by Shimbo et al adds further valuable insight and contributes to our understanding of the relationship between hypertension and endothelial dysfunction.

Disclosures

None.

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