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The Real Offending Factor in Hypertension

Pressure or Flow?

Throughout the interesting paper by Al-Mashhadi et al. (1), accelerated atherosclerosis is explained by pressure. Indeed, as the authors eliminated humoral effects by this carefully designed model, only hemodynamic factors remain to account for the accelerated atherosclerosis. According to Ohm's law, pressure equals flow times resistance. Resistance can be excluded as a local element, but which of the other 2 factors exerts its effects on target organs is questionable. The focus to date has been on pressure because its measurement is technically easier. But the accumulated evidence may actually be related to flow, pressure being only a correlation. Some observations support this hypothesis (2).

Although frequently ignored, the pressure exerted on an arterial wall does not only include hydraulic pressure generated by the heart, but also includes hydrostatic pressure caused by gravity. Humans maintain upright posture and are more subject to the effects of hydrostatic pressure compared with the pigs used in this study. This has important implications. The study reports a mean pressure increase of 45 mm Hg in the upper body. In an upright human, a similar pressure increase occurs at the waist level simply due to the hydrostatic pressure. If the pressure itself is the causal factor for accelerated atherosclerosis, a craniocaudally increasing atherosclerosis pattern would be expected in humans. Likewise, a similar increase in cerebral arterial pressure occurs when the brain is lowered to the level of the heart, as occurs during sleeping, but supine position does not seem to have any effect on hypertensive cerebrovascular damage. Moreover, the model is very similar to coarctation of the aorta, in which upper-extremity hypertension has been shown to cause accelerated atherosclerosis (3). The similar findings in these 2 species lend support to the proposition that hydrostatic pressure is not a component of the real offending factor. On the other hand, the flow, or 1 of its iterations (such as shear stress), may be responsible for the seemingly "pressure-accelerated" atherosclerosis. Aortic constriction used in this model subjects the upper body to a higher flow because of the increased perfusion pressure. Therefore, the model unintentionally causes flow-based derangements and might have tested the real offending factor in hypertension.

Flow, not pressure, may be the real hemodynamic cause of the accelerated atherosclerosis in hypertension. This distinction is important to understanding the real pathophysiology and to developing treatment targets.

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Hypertension Aggravates Atherosclerosis

A Matter of Pressure Remodeling of Myofibroblasts or LDL Accumulation?

We read the paper by Al-Mashhadi et al. (1) that was recently published in the *Journal* (1). We have 3

questions regarding matters that confused us. 1) How does higher blood pressure promote the "LDL [low-density lipoprotein] accumulation?" Did the authors really observe this process in the similar pressure environment in vivo or in vitro? 2) If hypertension could press LDL into the subintima, is it easier for smaller molecules, such as water, sugar, and amino acids to be pressed into the subintima? According to the logic of this paper, is there a larger amount of water accumulation in the subintima for the much smaller molecules of water? 3) We all know that pressure in the aorta is greater than or equal to that of the coronary arteries. According to the logic of this paper, atherosclerosis of the aorta should not be milder than that of the coronary arteries. But in clinical practice, atherosclerosis of the coronary arteries is more serious than that of the aorta in the same patient. "Passive lipid accumulation" could not explain clinical practices. Recent studies showed that hypertension with higher hydrostatic pressure should promote myofibroblast transformation from other cells, such as fibroblasts, endothelial cells, and smooth muscle cells (2,3). There are many myofibroblasts in human atherosclerotic plaques, and the distribution of myofibroblasts is positively correlated with the thickness of atherosclerotic plaques (4,5). Therefore, we think that hypertension with higher hydrostatic pressure aggravates atherogenesis by promoting the pressure remodeling of myofibroblasts (2–5). These findings could explain the predisposing of sites of atherosclerosis in clinical practice that could not be explained by the traditional hypotheses (2–5).

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REPLY: Hypertension-Accelerated Atherogenesis

Barely Scratching the Surface

We thank Dr. Aslanger and Drs. Wang and Ge for their comments on our paper (1). Our responses to the main questions of their letters are provided below.

Drs. Wang and Ge pose the following question: "How does higher blood pressure promote the "LDL [low-density lipoprotein] accumulation"? Did the authors really observe this process in the similar pressure environment in vivo or in vitro?" We obtained postmortem histologic cross-sections from the left anterior descending coronary artery of hypertensive and normotensive normocholesterolemic Yucatan minipigs. Using immunohistochemistry, we observed increased accumulation of LDL in the deep intima in hypertensive compared with normotensive pigs. This clearly occurred in vivo even if it was only detected in postmortem analysis. As to how hypertension promotes LDL accumulation, we propose 2 hypotheses that fit the presented data: 1) the observed restructuring of the artery wall may hinder the passage of macromolecules through the arterial wall leading to the entrapment of LDL in the intima; and 2) increased vascular proteoglycan content may facilitate LDL retention as indicated by the correlation between LDL accumulation and Alcian Blue staining (1). As we discuss in the paper, these hypotheses need to be tested in future research.

Drs. Wang and Ge also ask: "Is there a larger amount of water accumulation in the subintima for the much smaller molecules of water?" We observed decreased insudation of plasma proteins into the artery wall and accumulation of LDL in the deep intima (1). Our interpretation was that restructuring of the artery wall enforced the barrier against filtration of macromolecules, leading to their accumulation locally in the intima. This does not necessarily apply